25 April 2024
EMA/256238/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

JERAYGO

International non-proprietary name: Aprocitentan

Procedure No. EMEA/H/C/006080/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABPM	Ambulatory blood pressure monitoring
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event(s) of special interest
AI	Accumulation index
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AUC0-∞	Area under the plasma concentration vs time curve from 0 h to infinity
AUC0-t	Area under the plasma concentration-time curve from zero to time t of the last measured concentration above the limit of quantification
AUCτ	Area under the plasma concentration-time curve during one dosing interval
BCRP	Breast cancer resistance protein
b.i.d.	Twice daily
BMI	Body mass index
BP	Blood pressure
CAC	Central Adjudication Committee
CCB	Calcium channel blocker
CFU	Colony Forming Units
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology
Cmax	Maximum plasma concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CQA	Critical Quality Attribute

CSR	Clinical study report
CT	Computed tomography
CV	Cardiovascular
CYP	Cytochrome P450
ΔΔQTcF	Placebo-corrected change from baseline corrected for heart rate according to Fridericia's formula
DB	Double-blind
DB-WD	Double-blind withdrawal
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EMR	Electronic medical records
ePV	Estimated plasma volume
EOS	End of study
EOT	End of treatment
ERAs	Endothelin receptor antagonists
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ET	Endothelin
ETA	Endothelin receptor type A
ETB	Endothelin receptor type B
E/V/M	Eye-opening / verbal response / motor response
FDA	Food and Drug Administration (US)
FAS	Full analysis set
FT-IR	Fourier Transform Infrared Spectroscopy
FU	Follow-up
GC	Gas Chromatography
Hb	Hemoglobin

HCTZ	Hydrochlorothiazide
HDPE	High Density Polyethylene
hERG	Human ether-a-go-go-related gene
HI	Hepatic impairment
HMG-CoA	3-hydroxy-3-methylglutaryl co-enzyme A
HTN	Hypertension
ICH	International Council for Harmonisation
IR	Infrared
ISH	International Society of Hypertension
ISS	Integrated Summary of Safety
IU	International Units
i.v.	Intravenous(ly)
LC	liquid chromatography
LDPE	Low density polyethylene
LLOQ	lower limit of quantification
LSLV	Last subject, last visit
LSM	Least squares mean
MACE	Major adverse cardiovascular event
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mFAS	Modified Full analysis set
MRI	Magnetic resonance imaging
MR-proANP	Mid-regional pro-atrial natriuretic peptide
MS	mass spectrometry
mSAF	Modified safety analysis set
NOEL	No-observed-effect level
Non-STEMI	Non-ST (segment) elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
o.d.	Once daily

PE	Polyethylene
PD	Pharmacodynamic
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
p.o.	Orally
PPB	Plasma protein binding
PPS	Per-protocol set
p.r.n.	When required
PSD	Particle size distribution
PT	Preferred Term
QC	quality control
QCH	quality control high
QCL	quality control low
QCM	quality control medium
qd	once daily
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QTPP	Quality target product profile
RAS	Renin-angiotensin system
RCT	Randomized controlled trial
RH	Relative Humidity
RHT	Resistant hypertension
RI	Run-in
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions
rSAF	Restricted safety analysis set
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SB	Single-blind
SBAT	Standardized background antihypertensive therapy

SBP	Systolic blood pressure
SD	Standard deviation
SGLT2	Sodium-glucose cotransporter-2
SiDBP	Sitting diastolic blood pressure
SiSBP	Sitting systolic blood pressure
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SPRINT	Systolic Blood Pressure Intervention Trial
SOC	System Organ Class
SRFI	Severe renal function impairment
t½	Terminal half-life
T3	Triiodothyronine
T4	Thyroxine
TAMC	Total Aerobic Microbial Count
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
Tmax	Time to reach maximum plasma concentration
TSH	Thyroid-stimulating hormone
TQT	Thorough QT
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
UACR	Urine albumin-to-creatinine ratio
uAOBPM	Unattended automated office blood pressure measurement
UHPLC	ultra-high performance liquid chromatography
ULN	Upper limit of the normal range
US	United States
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
Vz/F	Apparent volume of distribution
WD	Withdrawal
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Idorsia Pharmaceuticals Deutschland GmbH submitted on 30 January 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for JERAYGO, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 February 2022.

The applicant applied for the following indication: *"JERAYGO is indicated for the treatment of resistant hypertension in adult patients in combination with other antihypertensive medications."*

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is:

composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0356/2019 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active Substance status

The applicant requested the active substance Aprocitentan contained in the above medicinal product to be considered as a new active substance in comparison to macitentan previously authorised in the European Union as Opsumit, as the applicant claimed that Aprocitentan differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 July 2015	EMEA/H/SA/3110/1/2015/III	Angeles Alonso, Markku Pasanen
12 October 2017	EMEA/H/SAH/086/1/2017/III	Angeles Alonso, Peter Mol

The Scientific Advice pertained to the following non-clinical and clinical aspects:

EMEA/H/SA/3110/1/2015/III - Non-clinical and clinical development

- The proposed non-clinical data package and in particular agreement on using non-clinical safety data of macitentan for risk assessment of aprocitentan regarding reproductive toxicity and carcinogenicity.
- The proposed definition of resistant hypertension (RHT); the overall clinical programme to support an MAA in the proposed indication; the proposed primary endpoints for the dose-finding study (AC-080A201) and the phase 3 programme.

EMEA/H/SAH/086/1/2017/III - Non-clinical and clinical development

- The proposed non-clinical data package and, in particular, agreement on waiving reproductive toxicity and carcinogenicity studies.
- The proposed safety database; the patient population to be enrolled in the phase 3 programme; the design of Phase 3 studies (AC-080A301 and AC-080A302) and, in particular, the comparator, duration of treatment including the run-in and double-blind period, safety monitoring, efficacy endpoints, and statistical methodology; the design of the open-label, long-term extension study (AC-080A303); appropriateness of the design of the AC-080A304 study in Type 2 diabetes mellitus with diabetic nephropathy, with respect to the comparative setting, population, safety monitoring, efficacy endpoints and statistical methodology, to support the MAA as well as provide additional evidence of patient benefit in a population that overlaps, and interacts with, the RHT target population; appropriateness of the design of AC-080A305 study in chronic kidney disease stages 3 and 4, with respect to the population, efficacy endpoints and statistical methodology, to support the MAA as well as provide additional evidence of patient benefit in a population that overlaps, and interacts with, the RHT target population; adequacy of the clinical development programme for the indication of treatment of RHT.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Margareta Bego

The application was received by the EMA on	30 January 2023

The procedure started on	23 February 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 May 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	29 May 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 May 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 June 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 October 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	24 November 2023
The CHMP agreed on a list of outstanding issues in writing/or in an oral explanation to be sent to the applicant on	14 December 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 March 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	20 March 2024
The CHMP agreed on a 2nd list of outstanding issues in writing/or in an oral explanation to be sent to the applicant on	21 March 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	2 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the 2nd List Outstanding Issues to all CHMP and PRAC members on	12 April 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to JERAYGO on	25 April 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	25 April 2024

2. Scientific discussion

2.1. Problem statement

Aprocitentan (Jeraygo film-coated tablets 12.5 mg and 25 mg) is an orally active dual ETA/ETB endothelin receptor antagonist selected for clinical development in resistant hypertension (RHT), which has not been previously authorised as a medicinal product.

The MAA is submitted under Article 8(3) of Directive 2001/83/EC as a complete and independent application. Eligibility for the Centralised Procedure was granted by the CHMP on 24 February 2022, under Article 3(2)(a) - New Active Substance of Regulation (EC) No 726/2004.

2.1.1. Disease or condition

The therapeutic indication wording proposed by the applicant in section 4.1 of SmPC was as follows:

"Jeraygo is indicated for the treatment of resistant hypertension in adult patients in combination with other antihypertensive medications."

The following indication was approved at the end of the procedure:

"JERAYGO is indicated for the treatment of resistant hypertension in adult patients in combination

with at least three antihypertensive medicinal products (see section 5.1)."

2.1.2. Epidemiology

Hypertension (HTN) is a leading cause of CV disease and mortality worldwide [GBD 2017 Risk Factor Collaborators 2018]. An estimated 1.3 billion people have HTN [NCD-RisC 2021], of whom approximately 10% have difficult-to-control HTN [Noubiap 2019, Williams 2018].

2.1.3. Aetiology and pathogenesis

Hypertension is divided into a primary (formerly and still also currently referred to as 'essential') and secondary forms. Secondary hypertension originates from specific causes and can be detected in only a small fraction of hypertensive patients. Primary hypertension covers the remaining large fraction of the hypertensive population, and its origin depends on the complex interaction between a genetic background, a large number of environmental factors and the aging process." (2023 ESH guidelines for the management of arterial hypertension of the ESH, Journal of Hypertension 2023; 41:p 1874-2071).

2.1.4. Clinical presentation, diagnosis

HTN is generally defined as difficult to control, or "treatment-resistant", if BP is not controlled despite the administration of at least 3 antihypertensive medications at appropriate doses. For a subject to fulfil this definition, pseudo resistant hypertension (RHT) linked to e.g. white coat effect, inappropriate BP measurement or medical inertia (insufficient efforts to optimize therapy) should have been excluded, as well as curable secondary causes of HTN [Carey 2018, Williams 2018]. By a multi-step screening and exclusion

process the pivotal study 301 aimed to exclude such patients but failed to a considerable proportion in this regard. Patients with RHT are more likely to be older and to have higher body mass index than patients with non-RHT. They are more likely to have albuminuria, reduced renal function, and self-reported medical histories of coronary heart disease (CHD), heart failure, stroke, and diabetes mellitus.

2.1.5. Management

Difficult-to-control HTN patients per definition fail to achieve BP control target on a triple therapy consisting of mechanistically complementary antihypertensive agents, commonly including a long-acting calcium channel blocker (CCB), a renin-angiotensin system (RAS) blocker (angiotensin converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]), and a diuretic [Carey 2018, Williams 2018]. All 3 must be prescribed at maximum or maximally tolerated (i.e., optimal) doses and at the appropriate dosing interval. Of note, beta-blockers can be considered at any stage in patients with complicated HTN especially if associated with heart failure, angina pectoris, post-MI, or atrial fibrillation [Mancia 2022].

The guidelines, as well as HTN textbooks, consistently emphasize that the use of a diuretic is critically important in difficult-to-control HTN as it is considered from a physiology-pathology standpoint a volume-dependent HTN (i.e. inverse to the renin and/or sympathetic-dependent HTN) [Carey 2018, Unger 2020, Whelton 2018]. If blood pressure (BP) remains uncontrolled on a thiazide diuretic, it is recommended to switch to a long-acting thiazide-like diuretic (i.e. chlorthalidone or indapamide) due to their effect on nocturnal BP and additional antihypertensive benefit. In patients with Chronic Kidney Disease (CKD) grade 3b to 5, a loop diuretic is usually preferable since thiazide-like agents progressively lose their efficacy as renal function declines.

There is no consensus on the choice of a fourth agent for those patients who still have uncontrolled BP. Most guidelines recommend a steroidal MRA, spironolactone or eplerenone, as fourth-line therapy following the PATHWAY-2 study [Williams 2015].

2.2. About the product

Aprocitentan (ACT-132577) is a potent, orally active, dual ETA/ETB endothelin receptor antagonist. The first endothelin receptor antagonist, bosentan, was approved more than 20 years ago for the treatment of PAH and was followed by macitentan and ambrisentan for that indication. Aprocitentan would be the first of its class to become an approved treatment for systemic arterial HTN.

2.3. Type of Application and aspects on development

An initial CHMP Scientific Advice procedure took place in 2015.

The advice concerned the non-clinical programme, definition of RHT, aspects of endpoints and the statistical approach in the clinical studies, and the design of the phase 2 dose finding study AC-080A201. It was adviced to investigate dose finding also in the target group of patients with RHT "the safety profile can be different in these patients dependent on the volume overload. As for any vasodilator drug, fluid retention may be an adverse reaction. This is why a dose selection balancing the beneficial vasodilation against this fluid retention would be more sensitive in the actual target population." This advice was not followed.

Regarding the phase 3 programme it was stated: "a new antihypertensive agent can only be considered

acceptable for registration after assessment of the potential detrimental effect on mortality and cardiovascular morbidity. More commonly, MACE endpoints are recommended for phase III study which makes a 12 week study inadequate in respect of this part of the assessment"

This advice was not followed.

It was stated: "In addition to an assessment of overall safety data in multiple organ systems, it is essential to, as far as possible, exclude that the new drug increases the risk of damage in any of the target organs normally affected by elevated BP (in particular the cardiovascular system and the kidneys)."

In this regard the clinical development programme does not meet the requirement. Reference was made to the requirements for an application based on one pivotal trial.

A second CHMP Scientific Advice procedure took place in 2017.

The advice concerned the non-clinical programme and the design of the at that time two pivotal studies 301 and 302 that were proposed which, at that time, included three arms over 3 months, placebo, 12.5 mg and 25 mg aprocitentan with the only difference in the background therapy between the studies. Some inclusion criteria (e.g. renal cut off) were different to the finally conducted study 301. The primary efficacy endpoint in both studies is the change from baseline to Week 12 in SBP. Conducting a placebo controlled trial over 3 months was considered feasible by the Applicant at that time, the CHMP considered a shorter period of e.g. 4 – 8 weeks possibly sufficient to demonstrate efficacy. The CHMP strongly recommended to generate comparative data against an active control like spironolactone in patients with preserved renal function or alpha blockers like doxacosin over at least 6 months. It was stated:" an active comparator arm might be the only way in which interpretable long term safety data can be generated." For efficacy it was agreed that durability of an effect could be assessed by a randomized withdrawal design.

It was mentioned that in addition to the development programme as proposed, a survey was ongoing. Additionally, the efficacy and safety of ACT-132577 was to be investigated in two critical populations overlapping with RHT: type 2 DM patients with DN of 3 months duration, and hypertensive patients with CKD stage 3 to 4 of 1 month duration. These studies were also discussed in the Scientific advice but were not included in the dossier.

In that advice the CHMP referred to the need for long term data allowing an assessment of cardiovascular safety. It was stated: "The 4th revision of the hypertension guideline (EMA/CHMP/29947/2013/Rev. 4) states: "It is expected that the drug development programme, containing all relevant clinical and non-clinical data, adequately characterizes the cardiovascular safety profile enabling an evaluation of the cardiovascular safety in the marketing authorisation application (MAA). This refers in particular to products with a new mechanism of action or products belonging to a drug class for which the cardiovascular safety profile is not yet established or questioned, e.g. in case of a detrimental effect on another cardiovascular risk factor." Therefore, MACE plus (including heart failure) needs be collected and adjudicated. Any correlation between BNP and fluid retention needs to be studied." For contextualization clinical data with another ERA were cited: "The experience with the selective endothelin-A receptor antagonist darusentan raises concern. It was tested in RHT and reduced BP but also caused fluid retention/oedema and caused numerically more MACE than placebo. ... in the 14-week study with darusentan in patients with RHT (n=379 patients, 132 on placebo) fluid retention occurred in 27% of the darusentan treated patients compared with 14% given placebo. All of five cardiovascular serious adverse events which occurred in the darusentan arms (2 MI due to heart failure, 1 case of atrial fibrillation and 1 case of heart failure) were judged to be fluid related (Lancet 2009;374:1423-31)." Further, long term safety data coming from patients with PAH treated with macitentan were not considered appropriate for an extrapolation due to differences in patient populations. Not planning

for generating meaningful outcome data was not endorsed by the CHMP.

The plan how to identify patients with real RHT was endorsed by the CHMP as were the standardized triple background therapy,

The Phase 3 program consisting of 2 confirmatory studies, as originally planned, was discussed with the EMA and HTA bodies (from Germany, France, UK) in the context of a parallel EMA/HTA Scientific Advice procedure in 2017. The revision of this program, following the interaction with the FDA, occurred after the CHMP meeting and therefore was not discussed with the CHMP. The Applicant stated that the feedback from CHMP was considered and implemented in the final design of Study 301 (ID-080A301) as far as possible in the frame of a single global study. However, key elements considered necessary as the generation of controlled long term data over at least 6 months was not followed.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film coated tablets containing 12.5 mg or 25 mg of aprocitentan as active substance.

Other ingredients are:

Tablet core: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

Film coat: poly(vinyl alcohol), hydroxypropyl cellulose, triethyl citrate, talc, colloidal hydrated silica, titanium dioxide, iron oxide red (E172), iron oxide yellow (E172) and iron oxide black (E172).

The product is available in a white, opaque, HDPE bottle with child-resistant closure and induction seal liner, containing silica gel desiccant and also in perforated unit dose blisters in aluminium cold-form film with desiccant and aluminium push-through lidding foil as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of aprocitentan is *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-sulfamide corresponding to the molecular formula $C_{16}H_{14}Br_2N_6O_4S$. It has a relative molecular mass of 546.2 g/mol and the following structure:

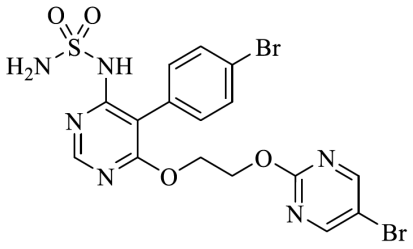


Figure 1: active substance structure

The chemical structure of aprocitentan was elucidated by a combination of elemental analysis, infrared spectroscopy (FT-IR), ultraviolet spectrophotometry, nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C NMR) and mass spectroscopy. The solid-state properties of the active substance were studied by X-ray powder diffraction (XRPD), differential scanning calorimetry, thermogravimetric analysis and dynamic vapour sorption.

The active substance aprocitentan is a white to off-white powder which is practically insoluble in water and acidic aqueous conditions and very slightly soluble in water at higher pH values. Aprocitentan is not hygroscopic and has a non-chiral molecular structure.

Polymorphism has been observed for aprocitentan. It has been demonstrated that the different polymorphic forms can be differentiated by XRPD and that the proposed manufacturing process consistently produces the desired polymorphic form in the final crystallisation step. The polymorphic form is routinely controlled in the active substance specification (desired polymorphic form is specified).

The active substance is designated as a new active substance based on safety and efficacy considerations. As regards quality aspects (chemical structure), the active substance is considered a derivative of macitentan and not a structurally new active substance (see Appendix 1 of the CHMP AR for further details).

2.4.2.2. Manufacture, characterisation and process controls

Aprocitentan is manufactured by one manufacturing site and a further site is responsible for micronisation of the active substance.

Aprocitentan is synthesised in four main steps (chemical transformations) using well defined starting materials with acceptable specifications. After synthesis, aprocitentan is micronised to give the active substance.

Class I solvents or metal catalysts are not used during the synthesis.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

Potential and actual impurities are well discussed with regards to their origin and characterised. Two actual organic impurities are detected in the active substance. These two impurities are adequately controlled with a suitable limit in the active substance specification. The fate and purge of all intermediates and other impurities is discussed in sufficient detail. A (Q)SAR assessment has been presented which includes a mutagenicity assessment of the starting materials and also their specified and potential impurities. In addition, the mutagenic potential of impurities (actual and potential), intermediates and reagents has been assessed. No risk has been identified and all organic impurities are classified as non-mutagenic (Class 5 according to ICH M7).

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. Previously investigated manufacturing processes are described (SM 1.1, SM 2.1, SM 2.2) and the differences to the proposed commercial manufacturing process are detailed. Process SM 1.1 was used to manufacture the early toxicology and clinical batches. Process SM 2.1 was used to manufacture phase 1 and 2 clinical

batches. Minor updates in work up procedures led to process SM 2.2, which was used for phase 3 clinical batches and to manufacture stability batches. SM 2.3 is the proposed commercial manufacturing process. The main difference between the processes are changes made to solvents used for work-up. Batches manufactured with process SM 2.2 and SM 2.3 show a similar impurity profile. The control strategy for the solvents used is demonstrated by batches manufactured *via* process SM 2.3. The quality of the active substance used in the various phases of the development is considered to be comparable to that produced by the proposed commercial process.

The active substance is packaged in low-density polyethylene (LDPE) bags (inner bag) which are placed in a second LDPE liner (outer bag). The bags are closed appropriately with a twist-tie or equivalent. The primary packaging material complies with Commission Regulation (EU) 10/2011, as amended. The secondary packaging protects the active substance from exposure to light.

2.4.2.3. Specification

The active substance specification includes tests for appearance (visual), identification (IR, HPLC), sulphated ash (Ph. Eur.), water content (Karl Fischer), polymorphic form (XRPD), residual solvents (GC), related substances (UHPLC), assay (UHPLC) and particle size distribution (laser diffraction).

The active substance specification is acceptable and in line with the requirements set out in Ph. Eur. 2034 (substances for pharmaceutical use) and in ICH Q6A. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Based on the proposed maximum daily dose of 25 mg / day, the reporting threshold for impurities is 0.05%, the identification threshold is 0.10% and the qualification threshold is 0.15%. The limit for the specified impurity exceeds the qualification threshold. Depending on the storage condition, the specified impurity was observed to increase on stability, and it is considered a degradation product. The limit of the specified impurity is toxicologically qualified and is set in line with batch data. The limit is acceptable. Appropriate specifications have been set for the second specified impurity. The limits for residual solvents are acceptable and the omission of microbiological testing is justified by data.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay, identification and impurities testing has been presented.

Batch analysis data from four batches of the active substance manufactured according to the proposed commercial process and at commercial scale are provided (two of the batches originate from the same non-micronised batch and are therefore seen as one batch). The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability studies were performed on three micronised registration batches of the active substance. These batches were manufactured using manufacturing process SM 2.2 (see also above chapter on manufacture, characterisation and process controls). Manufacturing process SM 2.2 is similar to the proposed commercial manufacturing process SM 2.3 and the pharmaceutical quality of active substance produced by the two process is comparable. Therefore, those batches are acceptable as stability batches.

Stability data from three commercial-scale batches of active substance from the proposed manufacturer stored in a container closure system identical to that intended for the market for up to 36 months under long term conditions (5 ºC) and for up to 36 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. The following parameters were tested*:* appearance, water content, related substances, and assay. The analytical methods used were the same as for release and are stability indicating. Polymorphism and particle size distribution were tested on selected samples and no change was observed.

An out-of-specification result was obtained for a specified impurity after 36 months in 1 batch under accelerated conditions (25 ºC / 60% RH). All other tested parameters were within the specified limits.

Photostability testing following the ICH guideline Q1B was performed on one development batch and one batch used in Phase 3 clinical trials. Degradation was observed as related substances were detected above the qualification threshold and total impurities were observed above the specification limit. Based on these results it can be concluded that protection from light is needed during storage to prevent degradation.

Results under stressed conditions were also provided from one batch both in the solid state and in solution. Samples in the solid state were exposed to heat, heat and humidity, light, and oxidative conditions. Samples in solution were exposed to different aqueous buffers from acidic to alkaline pH, light, and oxidative conditions. In the solid state, aprocitentan was not stable in dry heat (100 °C) and showed an increase in total impurities in moist heat (60 °C / 80% RH). Degradation upon exposure to light was also observed. In solution, degradation occurred under high and low pH conditions. Exposure to light as well as to oxidative conditions in solution also led to degradation.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored between 2–8 °C and protected from light.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Jeraygo finished product presents as a round biconvex film-coated tablet with a diameter of 6 mm. The finished product is available in two strengths: 12.5 mg and 25 mg. The film-coated tablet containing 12.5 mg aprocitentan is yellow to orange, debossed with "AN" on one side and plain on the other side. The film-coated tablet containing 25 mg aprocitentan is pink, debossed with "AN" on one side and "25" on the other side.

The aim of formulation development was to develop an immediate-release oral film-coated tablet, containing either 12.5 mg or 25 mg of aprocitentan which is suitable for once daily dosing.

The active substance aprocitentan is characterised by low aqueous solubility across the pH range of the gastrointestinal tract (pH 1.2–6.8) in aqueous buffer systems and by high permeability across cell membranes. As further discussed above, several polymorphic forms of the active substance are known. All studies to date have shown that the desired polymorphic form is kinetically favoured over other forms. The proposed commercial active substance manufacturing process consistently delivers the desired form. This desired form has been used in the finished product throughout development and has been shown to be stable and processable including in commercial-scale manufacturing. Aprocitentan has been demonstrated to be chemically stable if exposed to light and to oxygen under ambient conditions. At higher temperatures, higher

relative humidity, and under intense exposure to light, an increase of a degradation product (hydrolysis product as further discussed above) was observed.

The impact of the particle size of the active substance on the finished product was studied and no impact was observed in the investigated range. From the results of the study on the impact of the particle size distribution on the manufacturing of the finished product and also from the bioequivalence clinical study (ID-080-110, D-22.208) it can be concluded that there is not impact of the PSD on the manufacturing processability and robustness or on the bioavailability of aprocitentan in the studied range. The PSD of aprocitentan is routinely controlled in the active substance specification.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of the ferric oxide colourants used for film-coating which comply with the NF. There are no novel excipients used in the finished product formulation. Lactose is an excipient with a known physiological effect and is thus also listed in section 2 of the SmPC. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

A rationale for the selection of each excipient is provided and the functionality is described. No formal compatibility studies between the active substance and excipients have been performed, however based on the results of stability studies (see chapter below), no incompatibilities are expected, and no further data is required.

The information provided on formulation development is considered adequate. A summary describing the development of the formulation, including the definition of a quality target product profile (Table 5) as well as the identification of quality attributes which are critical for the proposed formulation was provided.

Table 1: finished product QTPP and Critical Quality Attributes

Quality Target Product Profile		Drug Product Critical Quality Attribute
Drug Product Attribute	Target	
Route of Administration	Oral	Appearance
Dosage Form	Film-coated tablet, round shaped with debossing	Appearance
Dosage Strength	12.5 and 25 mg of aprocitentan	Appearance, Identification, Assay, Content Uniformity
Purity	Sufficiently low level of impurities/degradation products, complying with the ICH requirements	Chromatographic Purity
Drug Release Profile	Immediate release	Dissolution
Microbial Purity	Sufficiently low level of microbial burden, complying with the ICH requirements	Microbial Purity
Container Closure System	HDPE bottle with child-resistant closure and desiccant and blisters	
Stability	Minimum 24 months shelf life at room temperature	Appearance, Assay, Chromatographic Purity, Dissolution, Water Content, Microbial Purity

The main challenge of formulation development was the low solubility of the active substance in aqueous media at acidic pH (<10 µg/mL). For Phase 1 and Phase 2 clinical trials, capsules containing a dry granulate

were developed in four strengths (5, 25, 50, and 100 mg). Subsequently and in line with the QTPP, immediate-release film-coated tablets were developed. During formulation development, the tablet weight and the concentration of the active substance, the amount of lubricant, the amount of binder and the ratio of microcrystalline cellulose to lactose monohydrate in the granulate were optimised. The final 12.5 mg and 25 mg film-coated tablets proposed for marketing differ only in the debossment and film-coating colour from the formulations used for the (pivotal) Phase 3 clinical trials.

The qualitative composition of the two strengths is the same with the exception of the film coating, however the quantitative composition differs and is not proportional.

The development of the dissolution method has been described and the discriminatory power of the dissolution method has been demonstrated. The dissolution method proposed for routine QC testing uses a paddle apparatus (USP, Ph. Eur., JP) with a rotation speed of 50 rpm in 900 mL of 0.05% (w/v) CTAB (Cetrimonium bromide) and 0.5% (w/v) polysorbate 20 (Tween® 20) in phosphate buffer pH 6.8 at 37 °C. The selected dissolution apparatus, rotation speed, medium pH and medium volume are in line with Ph. Eur. recommendations and are acceptable. The selection of surfactants and their concentration in the dissolution medium have been adequately justified. The discriminatory ability of the proposed dissolution method has been evaluated for different active substance particle-size distributions (PSD), changes in the formulation (variation in the amount of binder), changes to process parameters (amount of granulation water used, tablet hardness) as well as changes observed during stability studies. Considering the proposed dissolution specification limit, the discriminatory ability of the proposed method was demonstrated for changes in active substance PSD, changes in process parameters and changes observed in stability studies. Batches used in clinical trials were re-tested with the proposed dissolution method and results support bioequivalence of the batches used in clinical studies. Finally, a comparison of batches used in Phase 3 clinical trials with commercial batches is also presented. The information is sufficient.

The development of the manufacturing process is described in sufficient detail. Adhering to the defined QTPP, three conventional solid technologies to manufacture an immediate release film-coated tablet were explored. Tablets containing 5 mg, 12.5 mg, 25 mg and 50 mg aprocitentan were manufactured to support the clinical strategy for Phase 3 clinical trials. During manufacturing process development, dissolution was tested to assess the criticality of different steps and parameters of the manufacturing process. Critical process parameters and steps with an impact on the CQAs of the finished product were identified (see chapter below) and suitable target set-points and proven acceptable ranges (PAR) were set.

Two primary packaging formats are proposed: a HDPE bottle with child-resistant closure and induction seal liner, containing silica gel desiccant and perforated unit dose blisters in aluminium cold-form film with desiccant and aluminium push-through lidding foil.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site, with further sites involved for testing, packaging, and release.

The manufacturing process consists of nine main steps: blending, granulation, drying, milling, blending, lubrication, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

The manufacturing process is described in sufficient detail and the batch formula is provided. The process steps identified as critical are drying, compression, film-coating, and packaging. There are no intermediates

in the process. A process validation scheme has been presented and is considered acceptable. The process will be validated on 3 consecutive batches of each tablet strength before commercialisation. Based on batches manufactured so far, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release specifications shown in **Error! Reference source not found.** include appropriate tests for this kind of dosage form: appearance (visual), identity (LC and UV), water content (Karl Fischer), uniformity of dosage units by content uniformity (Ph. Eur.), content of aprocitentan (LC), degradation products, individual unspecified impurities and total impurities (all LC), dissolution (in house) and microbial purity (Ph. Eur.).

The specification for the finished product (12.5 mg strength and 25 mg strength) is acceptable and includes all parameters necessary for the dosage form. Adequate justification for the proposed specification limits has been provided. The limit for one specified impurity exceeds the qualification threshold of 0.5% (based on a maximum daily dose of 25 mg / day) and the specified impurity was therefore covered by a toxicity study. The limit of this specified impurity is toxicologically qualified and is set in line with batch data. The specification limits for dissolution were tightened during the procedure in response to an initially raised major objection.

During the procedure, a major objection was also initially raised on the nitrosamine risk assessment. In response, a risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed as requested considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The potential presence of elemental impurities in the finished product has been assessed for both strengths following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay, identification and impurities testing has been presented.

Batch analysis results are provided for 3 commercial-scale batches of each strength (12.5 mg and 25 mg) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.4.3.4. Stability of the product

Stability data from 3 commercial-scale batches of finished product stored for 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Both strengths (12.5 mg and 25 mg) were studied in both packaging options proposed for marketing (3 batches of each combination). The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing (blisters and bottles, respectively). Intermediate conditions (30 °C/75% RH) were also studied. Samples were tested for appearance, water content, content of aprocitentan, degradation products, individual unspecified impurities and total impurities, dissolution, and microbial purity. The analytical procedures used are stability indicating. An increase in water content, an impurity, and total impurities was observed but all results remained within specification.

In addition, one batch of each strength (12.5 mg and 25 mg) was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant differences between the control sample and the samples exposed to light were detected and all results remained within specification.

Forced degradation studies were also conducted on one batch (12.5 mg strength). The lower strength tablet was studied as worst-case formulation for degradation due to the higher matrix to active substance ratio. Samples of the bulk finished product were exposed to combined heat and humidity stress (open dish). The main degradation product detected was and when exposed to heat/humidity conditions the formation of this hydrolysis product is accelerated (6.11 % after 12 days).

Based on available stability data, the proposed shelf-life of 30 months as stated in the SmPC (section 6.3) is acceptable in combination with the storage conditions 'Store in the original package (HDPE bottle or blisters) in order to protect from moisture (no special temperature storage conditions are required)' and 'Keep the HDPE bottles tightly closed in order to protect from moisture' as stated in section 6.4 of the SmPC.

2.4.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Two major objections initially raised during the procedure (on the dissolution limit and on the nitrosamine risk assessment) were resolved during the procedure. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Aprocitentan (ACT-132577) is an orally active, dual endothelin (ET) receptor antagonist (ERA) of both the ETA and ETB receptors. Aprocitentan is being developed for use in adult patients with resistant hypertension in combination with other antihypertensive medications. The ET system is involved in the control of vascular tone, and its dysregulation plays a role in hypertension and especially in salt-sensitive/volume-dependent forms of hypertension.

Aprocitentan has the same chemical structure as the main pharmacologically active metabolite of macitentan (Opsumit®, ACT-064992) with a similar pharmacological mode of action. Opsumit® is approved for the treatment of pulmonary arterial hypertension. Some aspects of the nonclinical, notably toxicological, characterization of aprocitentan were derived from the macitentan program, given that the main active metabolite of macitentan contributed, with approximately 50% of the systemic drug exposure, to the results of the macitentan studies in animals. The assessment of embryofetal development (EFD), pre- and postnatal development, and carcinogenicity for aprocitentan was done based on studies performed with macitentan, in alignment with CHMP scientific advice given. However, based primarily on pharmacological data obtained for aprocitentan during the development, the full aprocitentan-specific EFD programme was decided to be performed and the results were submitted during this MAA.

Paediatrics: A full paediatric waiver has been granted for aprocitentan film-coated tablets for the treatment of hypertension (procedure: EMEA-001978-PIP02-19).

2.5.2. Pharmacology

Aprocitentan is an active metabolite of the authorised drug macitentan. The latter is indicated for pulmonary arterial hypertension (PAH) whereas aprocitentan was developed for systemic hypertension. Aprocitentan is an endothelin antagonist, and binds to the human endothelin-A-receptor (ETA) with around 300-fold affinity that to the endothelin-B-receptor (ETB). Since aprocitentan is intended for use in resistant hypertension, which cannot be sufficiently controlled with existing combination of antihypertensive drugs,the primary PD programme mainly aimed to demonstrate the additional benefit of aprocitentan on top of the common combination of antihypertensive substances in established rat models of hypertension.

Safety pharmacology studies revealed the expected effect on blood pressure, and in-vitro studies revealed inhibtion of the cardiac hERG potassium channel at concentrations above the intended therapeutic concentrations. However, it is difficult to compare an in-vitro concentration with plasma levels, and there were hints that aprocitentan caused a slight prolongation of the QTc interval in the human TQT study.

2.5.2.1. Primary pharmacodynamic studies

The applicant conducted non GLP in-vitro studies to determine binding and activation of the endothelin receptors ETA and ETB. Aprocitentan has a higher affinity to ETA than to ETB. The in-vivo studies were mainly conducted in two rat models of hypertension, the DOCA-salt rat and the Spontaneously Hypertensive Rat (SHR). Most in-vivo studies aimed to demonstrate an additive or synergistic effect of aprocitentan when given along with other common antihypertensive drugs. Synergism was detected when aprocitentan was combined with blockers of angiotensin (angiotensin receptor antagonist or ACE inhibitors). The individual primary PD studies conducted are tabulated below.

Type of study	Test system	Report Number
In vitro		
Inhibition of ET-1 binding	Recombinant CHO cells expressing ET_A and ET_B receptors	B-07.246
Functional inhibition of ET receptors and evaluation of receptor binding mode	Human pulmonary artery smooth muscle cells and CHO-K1 cells	B-12.108
Inhibition of ET_A and ET_B receptor-mediated contraction	Rat isolated aorta and trachea	B-05.057
In vivo		
Acute effect on plasma ET-1 concentrations in normotensive rats	Wistar rats	B-14.017
Acute effect on blood pressure and heart rate in conscious hypertensive rats	Hypertensive (DOCA-salt, Dahl-S and spontaneously hypertensive) rats	B-14.016
Chronic effect on blood pressure, heart rate, kidney and heart in hypertensive rats	DOCA-salt hypertensive rats	B-16.033
Effect on blood pressure and heart rate in combination with valsartan in hypertensive rats	DOCA-salt hypertensive rats	B-15.067
Effect on blood pressure and heart rate in combination with valsartan in hypertensive rats	Spontaneously hypertensive rats	B-14.051
Effect on blood pressure and heart rate in combination with enalapril in hypertensive rats	DOCA-salt hypertensive rats	B-18.042
Effect on blood pressure and heart rate in combination with enalapril in hypertensive rats	Spontaneously hypertensive rats	B-18.043
Effect on blood pressure and heart rate in combination with amlodipine in hypertensive rats	DOCA-salt hypertensive rats	B-18.068
Effect on blood pressure and heart rate in combination with amlodipine in hypertensive rats	Spontaneously hypertensive rats	B-18.069
Effect of spironolactone in combination with valsartan on blood pressure and heart rate in hypertensive rats	Spontaneously hypertensive rats	B-19.002
Effect of aprocitentan in combination with triple antihypertensive therapy on blood pressure and heart rate in hypertensive rats	DOCA-salt hypertensive rats and spontaneously hypertensive rats	B-22.047

Key findings are presented in more detail below.

In-vitro studies were conducted to characterise receptor binding, receptor activation (measured as increase in intracellular Ca^{2+}) and functional effects in smooth muscle preparations (rat aorta and rat trachea). The results are summarised in the following table. From the studies in CHO cells, a clear preference of aprocitentan for the endothelin recepor subtype A (ETA) become obvious.

Table 1 of pharmacol written summary: Activity of aprocitentan on endothelin receptors in vitro:

System	Assay	Variable	ETA	ETB	Report Number
CHO cells expressing human ET_A or ET_B	Inhibition of ET-1 binding	IC_{50}	3.4 nM (n = 4)	987 nM (n = 4)	[B-07.246]
CHO cells expressing human ET_A or ET_B	Inhibition of ET-1-induced increase in cytosolic Ca^{2+}	K_b	5.5 nM (n = 5)	319 nM (n = 4)	[B-12.108]
Rat isolated aorta denuded of endothelium	Inhibition of ET-1-mediated contraction	pA2	6.7 (n = 3)	N/A	[B-05.057]
Rat isolated trachea denuded of epithelium	Inhibition of sarafotoxin S6c-mediated contraction	pA2	N/A	5.5 (n = 3)	[B-05.057]

CHO = Chinese hamster ovary; ET-1 = endothelin-1; IC_{50} = concentration causing 50% inhibition; K_b = equilibrium dissociation constant of a ligand determined by means of a functional assay; N/A = not applicable; pA2 = negative logarithm of the molar concentration of antagonist that causes a 2-fold shift to the right of an agonist concentration-response curve.

In-vivo effects of aprocitentan were determined in normotensive Wistar rats, demonstrating a clear, dose-dependent increase in plasma endothelin-1, 6 hours after administration of a single dose.

Blood pressure (BP) lowering was studied in rat models of hypertension. In total, three rat models of hypertension were used, DOCA-salt (DOCA = deoxycorticosterone acetate) and Dahl salt-sensitive (Dahl-S) rats as well as spontaneously hypertensive rats (SHR):

- DOCA-salt: The animals receive the mineralocorticoid DOCA (deoxycorticosterone acetate) together with a high-salt diet (0.6-1% NaCl in the drinking water). In addition, unilateral nephrectomy can be performed in this model to further increase hypertension.

- Dahl-S: Inbred rat strain developing hypertension when placed on a high-salt diet. The increase in mean arterial pressure is attributed to sodium retention, and can be prevented by the use of diuretics.

- SHR: A rat strain that was obtained by breeding Wistar-Kyoto rats with high blood pressure. Hypertensive development is connected to the kidney. Transplanting a kidney from SHR to a normotensive Wistar rat increases blood pressure in the recipient.

The applicant assumed that the effect of endothelin antagonists is larger in salt- and volume dependent hypertension models such as DOCA and Dahl than in SHR. Blood pressure lowering was least pronounced in the SHR model; the magnitude of BP reduction was similar in the two other models.

A wider range of physiological parameters was studies in the DOCA-salt rat. Aprocitentan increased renal blood flow, decreased renal vascular resistance, reduced the weight ratio of the left ventricle (including septum) to total heart and decreased plasma NT-proBNP levels. Not all changes reached the level of statistical significance.

A series of in-vivo studies in the SHR and DOCA-salt model investigated the BP-lowering effect of aprocitentan when administered together with other antihypertensive agents. It turned out that aprocitentan acted synergistically with angiotensin blockers (ARB and ACEi) but not with other agents. The results are summarised in the following table for mean BP; similar results were obtained for systolic and diastolic BP.

Table 3 Summary of single-dose combination studies with aprocitentan, or spironolactone, and other antihypertensive drugs on blood pressure in hypertensive rats (data from studies B-14.051, B-15.067, B-18.042, B-18.043, B-18.068, B-18.069, and B-19.002):

SHR			DOCA-salt rat		
	Aprocitentan 100 mg/kg	**Spironolactone** 300 mg/kg		**Aprocitentan** 10 mg/kg	**Spironolactone** 300 mg/kg
Valsartan 10 mg/kg	A: −662 ± 52	S: −441 ± 35	**Valsartan** 30 mg/kg	A: −543 ± 111	S: −270 ± 69
	V: −407 ± 61	V: −543 ± 50		V: −31 ± 52	V: −28 ± 17
	A+V: −1958 ± 248 a	S+V: −933 ± 78		A+V: −887 ± 146 a	S+V: −389 ± 71
Enalapril 3 mg/kg	A: −838 ± 82	S: −634 ± 121	**Enalapril** 10 mg/kg	A: −775 ± 98	S: −304 ± 86
	E: −168 ± 41	E: −230 ± 58		E: −27 ± 32	E: −37 ± 25
	A+E: −1504 ± 162 a	S+E: −1013 ± 81		A+E: −939 ± 176	S+E: −319 ± 76
Amlodipine 2 mg/kg	A: −1044 ± 68	S: −813 ± 13	**Amlodipine** 3 mg/kg / 1 mg/kg b	A: −685 ± 142	S: −275 ± 103
	Am: −177 ± 46	Am: −262 ± 108		Am: −148 ± 62	Am: −97 ± 25
	A+Am: −1074 ± 144	S+Am: −682 ± 205		A+Am: −1011 ± 119	S+Am: −491 ± 68

a indicates a synergistic effect on ABC.
b 3 mg/kg was used with aprocitentan and 1 mg/kg was used with spironolactone.
Data represent the ABC (in mmHg·h) determined after single-dose administration, alone and in combination. Negative values indicate a reduction in blood pressure from baseline values. Data are expressed as mean ± SEM. The letter represents the compound tested. A = aprocitentan; ABC = area between the curves; Am = amlodipine; E = enalapril; S = spironolactone; SEM = standard error of the mean; SHR = spontaneously hypertensive rats; V = valsartan.

The applicant also demonstrated (see figure below) that aprocitenan further reduced BP in the DOCA-salt model when given as add on to a clinically used triple combination of anti-hypertensive drugs, amlodipine (a calcium channel blocker), valsartan (an angiotensin II type 1 receptor antagonist) and hydrochlorothiazide (a thiazidic diuretic).

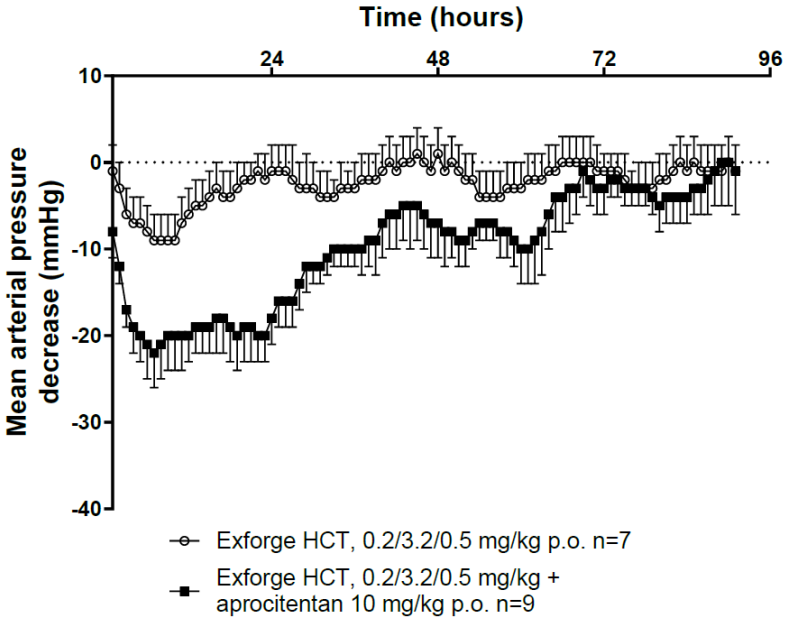


Figure 6 of PD written summary: The effect of Exforge HCT® and its combination with aprocitentan on mean arterial blood pressure in conscious DOCA-salt rats. Exforge HCT is a combination of amlodipine, valsartan

and hydrochlorothiazide; the selected dose was 0.2, 3.2, and 0.5 mg/kg for amlodipine, valsartan, and hydrochlorothiazide, respectively.

2.5.2.2. Secondary pharmacodynamic studies

One study was performed to address secondary PD, an in-vitro screen for off-target binding. Aprocitentan was screened at a concentration of 10 µM in 53 radioligand binding assays to assess its potential to inhibit other known receptor systems or enzymes. Aprocitentan did not show greater than 50% inhibition in any of these assays.

2.5.2.3. Safety pharmacology programme

The safety pharmacology studies conducted are tabulated below.

Type of study	Test system	Report Number
Effect on hERG potassium channel	Stably transfected HEK293 cells	T-18.063
Cardiovascular telemetry study	Beagle dog	T-14.029
Irwin profile test	Wistar rat	T-14.027
Respiratory function evaluation by whole body plethysmography	Wistar rat	T-14.028

All studies are GLP compliant.
Aprocitentan dose-dependently inhibited hERG current in vitro (see figure below). The IC50 was 28.6 µM and the IC20 was 7.2 µM. In comparison, Cmax was 3.57 µg/mL in the clinical study AC-080-101, corresponding to 6.53 µM, in steady state after a dose of 25 mg aprocitentan.

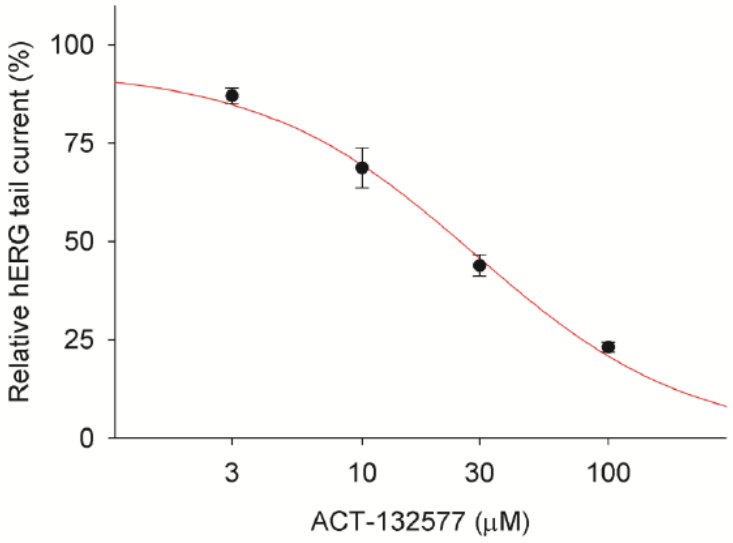


Fig. III of Report B-18.063: Inhibition curve for ACT-132577.

In the dog telemetry study, decrease in blood pressure (BP) and increase in heart rate (HR) was observed after a single oral dose of aprocitentan. The maximal effect on BP and HR is shown in the figure below. No ECG changes were observed, particularly no change in the duration of the HR-corrected QT interval (QTc).

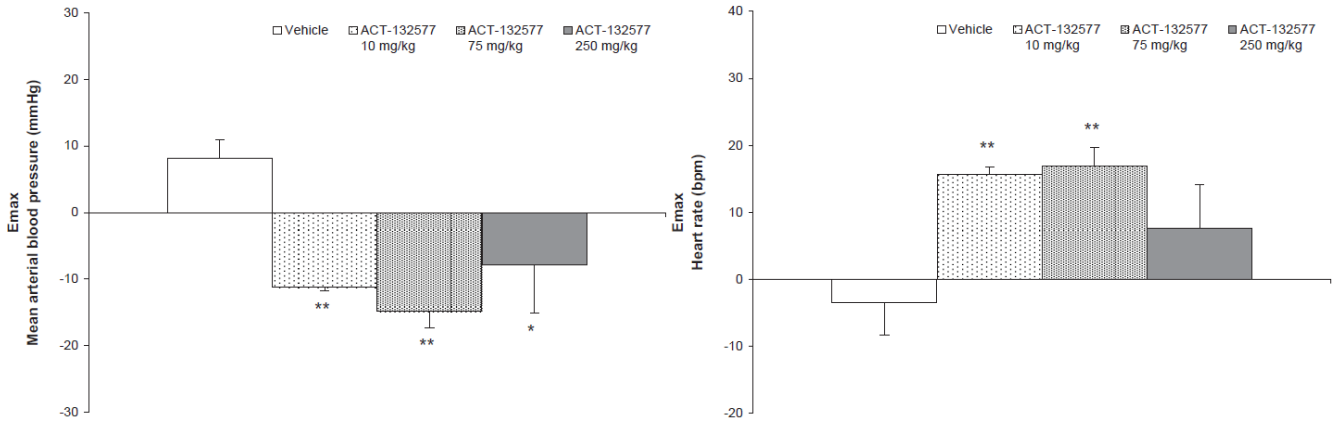


Figure: Effect on mean arterial blood pressure (left) and heart rate (right) in the conscious beagle dog treated with vehicle or ACT-132577 by oral route.

No effects of aprocitentan were observed on CNS (Irwin test) and on respiratory function in rats.

2.5.2.4. Pharmacodynamic drug interactions

PD interactions with other anti-hypetensive agents was studied within the frame of the primary PD programme (see above).

2.5.3. Pharmacokinetics

PK studies were performed addressing biavailability, plasma protein binding, tissue distribution, use of drug transporters, metabolism and quantitative excretion of radiolabelled aprocitentan. The enzymes responsible for formation of the main metabolites were identified to a large extent. Inhibition and induction of drug-metabolising enzymes and drug transporters were studied to address DDI.

Methods

Bioanalytical methods using LC-MS/MS were established for the quantification of aprocitentan in mouse plasma over a concentration range of 100–200,000 ng/mL. For quantification in rat and dog plasma, methods were validated over the concentration range of 1–200,000 ng/mL. For quantification in rabbit plasma, methods were developed and validated for two concentration ranges, i.e., 10–20,000 ng/mL and 100–200,000 ng/mL. Stability of aprocitentan in plasma was demonstrated for at least one year, covering the maximal storage period of samples from the different studies.

Oral bioavailability

Oral bioavailability was 41% in rats and 92% in dogs, see table below. Note that exposure was around 6-times higher with the sodium salt of aprocitentan than with the free acid in the rat toxicology study T-14.011. Thus, bioavailability is probably higher with the sodium salt than with the free acid, and this could be related to solubility.

Table 2 of PK written summary: Pharmacokinetic parameters of aprocitentan in Wistar rats and Beagle dogs after single oral administration

Species	Wistar rat (n = 6, male), Beagle dog (n = 4, male)		
Administration	Rat: 3 mg/kg; suspension in 7.5% gelatin Dog: 3 mg total dose in capsules (0.22–0.33 mg/kg)		
Rat [B-05.130]			
Design	**Parameter**	**Geometric mean**	**Range**
Free acid, suspension in 7.5% gelatin, fed state	AUC0–last (ng·h/mL)	16,300	12,900–19,300
	Cmax (ng/mL)	708	465–1040
	tmax (h)	8.0 [a]	6.0–24
	F (%) [b]	41	–
Dog [B-13.249]			
Free acid, micronized, hard gelatin capsules, fasted state	AUC0–last (ng·h/mL)	9100	5710–20,900
	Cmax (ng/mL)	766	588–1180
	tmax (h)	2.7 [a]	2.0–3.0
	F (%) [c]	92	71–118
Free acid, micronized, gastro-resistant capsules, fasted state	AUC0–last (ng·h/mL)	8860	5080–22,800
	Cmax (ng/mL)	737	508–1260
	tmax (h)	3.2 [a]	3.0–4.0
	F (%) [c]	88	71–105

a Median
b,c Oral bioavailability calculated with reference to the AUC0–inf at an intravenous dose of (b) 0.5 mg/kg (6660 ng·h/mL) / (c) 0.3 mg/kg (12,000 ng·h/mL).

Dose proportionality

In DOCA-salt rats, exposure (AUC) and Cmax increased fairly proportionally with dose up to a dose of 30 mg/kg. At higher doses, 100 mg/kg and 300 mg/kg, the increase in AUC and Cmax was less than proportional. The ratios AUC per dose and Cmax per dose markedly decreased.

Sex differences

Plasma levels in female rats were 20–60% higher than those of males. No consistent sex difference in aprocitentan PK has been observed in the dog.

Accumulation

In rats and dogs, no accumulation of aprocitentan was observed when given for 28 days. In contrast, exposure decreased from Day 1 to Day 28, particular at higher doses in the rat study (see table below). The applicant assumes that this could be due to the induction of metabolising enzymes. For details see DDI section below.

Table 5 of PK written summary: Exposure in male rats and dogs after multiple oral administration

Species	**Dose (mg/kg/day)**	**AUC0–24 (µg·h/mL)**		**Day 28/Day 1 Ratio c**
		Day 1	Day 28	
Rat a [T-14.023]	10	114	90.9	0.8
	50	552	232	0.4
	250	3890	1870	0.5
Dog b	75	1980 (1810–2280)	1390 (1010–1880)	0.7

[T-14.022]	250	2520 (1900–3160)	2610 (1970–3480)	1.0
	1000	4540 (3650–5400)	3770 (3250–4170) d	0.8

a Data presented are geometric means of n = 3/group (composite profiles) in rats.
b Data presented are geometric means and range of n = 4/group in dogs (individual profiles).
c Calculated using mean exposures from both dosing occasions.
d Data from Day 14 as dose was reduced to 500 mg/kg/day thereafter.
AUC0-24 = area under the plasma concentration vs time curve from 0 to 24 h post dosing.

Plasma protein binding

Binding of aprocitentan to plasma proteins was determined using equilibrium dialysis and 14C-radiolabeled aprocitentan (ACT-132577B) in a concentration range of 0.1–300 µg/mL.

Table 6 of PK written summary: Plasma protein binding of aprocitentan

Species	Fraction bound (%)	Free fraction (%)
Mouse	99.0	1.0
Rat	98.7	1.3
Rabbit	99.9	0.1
Dog	98.3	1.7
Human	99.5	0.5

Blood partitioning

The blood/plasma ratio was around 0.6 in all species tested, indicating no relevant uptake of aprocitentan into red blood cells.

Aprocitentan as transporter substrate

The data from Study B-17.068 indicate that aprocitentan is a substrate of P-gp/MDR1.

Tissue distribution

The liver, kidney cortex, lung, pituitary, thyroid, and myocardium were among the organs with the highest exposure. At 72 h post dose, drug levels in most tissues had fallen below the limit of quantification. At 10 days after dosing, only the liver and kidney cortex contained quantifiable levels of radioactivity. There was no significant retention of radioactivity in the uveal tract/retina, pigmented skin, or meninges of the brain in pigmented rats.

Excretion into milk

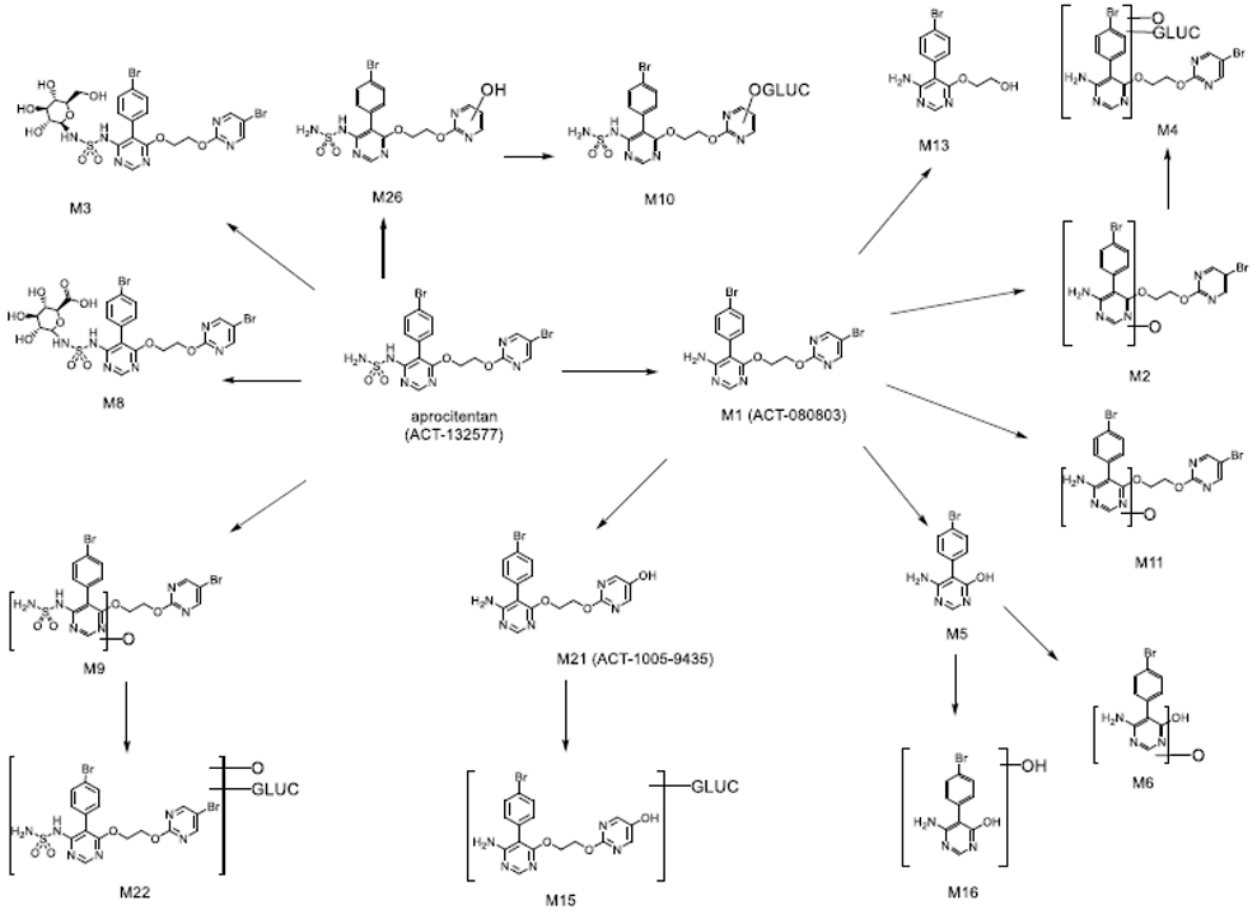
Milk excretion was investigated only as part of the macitentan program. The active metabolite of macitentan, aprocitentan was consistently observed in plasma and milk samples across all collection times after oral administration of ^{14}C-labeled macitentan. However, the amount of the metabolite aprocitentan was not quantified; only total radioactivity, including parent compound and further metabolites, was provided.

Metabolites

A total of 15 aprocitentan metabolites were structurally characterized: M1–M6, M8–M11, M13, M15, M16, M21 and M22. Aprocitentan was metabolized along five pathways, i.e., hydrolysis of the sulfamide moiety to the corresponding aminopyrimidine M1, N-glucosidation and N-glucuronidation of the sulfamide to M3 and M8, oxidative debromination of the pyrimidine to form M26 followed by glucuronidation to M10, and N-oxidation of the pyrimidine sulfonamide moiety to form M9 and subsequent glucuronidation to M22 [Figure 1]. M26 was identified indirectly in a separate study as the aglycon of M10, based on its formation after β-

glucuronidase treatment [B-14.034]. The structure of M26 was, therefore, proposed as a product of oxidative debromination of aprocitentan on the bromopyrimidine moiety.

Metabolites M2, M5, M11, M13 and M21 were identified as secondary metabolites of M1 resulting from oxidative processes. M2 bears the oxygen atom in the central pyrimidine moiety. Subsequent glucuronidation of M2 on the bromophenyl aminopyrimidine moiety produces M4. M5 results from combined hydrolysis of the sulfamide and cleavage of the ethylene glycol linker followed by further oxidation to M16 and M6. M11 results from N-oxidation of the aminopyrimidine. M13 is the product of oxidative cleavage of the ethylene glycol linker at the distal oxygen atom. Metabolite M21 results from initial oxidative debromination of the aminopyrimidine and subsequent glucuronidation to M15.



Species comparison of metabolic profile

The metabolism of aprocitentan was slow in all species. Incubation with human liver microsomes led to formation of two products, i.e., the hydrolysis product M1 and its oxidative product M2. These two products were consistently observed with liver microsomes of all animal species used in this study [Table 7]. Rat and dog microsomes produced an additional metabolite, M5, the cleaved hydrolysis product of M1 on the ethylene glycol linker. Microsomal enzymes, and more specifically cytochrome P450s, do not catalyze the hydrolysis of aprocitentan in liver microsomes as M1 formation was equally prominent in control experiments in the absence of the enzymes. Metabolites M5, M9, and M20 were observed with animal liver microsomes but not in humans.

Table 7 Cross-species comparison of metabolic profiles of ACT-132577B (i.e. radiolabelled aprocitentan) in incubations with liver microsomes and hepatocytes; data from Study B-14.033

Species	Test system	M1	M2	M3	M4	M5	M6	Σ metabolites	native aprocitentan
Human	Liver microsomes	4.3	2.1	ND a	ND	ND	ND	6.4	94
	Hepatocytes a	3.8–15	3.0–7.6	4.0	3.6	1.7–2.1	4.5	15–21	79–85
Rat	Liver microsomes	5.1	1.4	ND	ND	1.5	ND	10 b	90
	Hepatocytes	5.8	1.8	2.6	2.0	5.3	3.9	32 c	68
Dog	Liver microsomes	4.7	1.7	ND	ND	1.3	ND	9.3 d	91
	Hepatocytes	6.8	8.4	ND	ND	5.5	ND	23 e	77
Cynomolgus monkey	Liver microsomes	3.7	2.8	ND	ND	ND	ND	8.0 f	92
	Hepatocytes	3.9	3.9	ND	ND	ND	ND	18 g	83
Rabbit	Liver microsomes	5.6	2.3	ND	ND	ND	ND	7.9	92
	Hepatocytes	4.3	ND	ND	ND	ND	ND	4.3	96
Mouse	Liver microsomes	5.1	2.1	ND	ND	ND	ND	7.2	93
	Hepatocytes	3.8	13	1.4	5.3	1.9	ND	27 h	73
Controls	Without microsomes	9.3	ND	ND	ND	ND	ND	9.3	91
	Microsomes w/o NADPH	6.4	ND	ND	ND	ND	ND	6.4	94
	Without hepatocytes	8.7	ND	ND	ND	ND	ND	8.7	91

All values are expressed as percent of total chromatogram radioactivity; metabolites with an abundance of < 0.1% are not listed.
a Data are from three different batches of human hepatocytes; range indicates the presence of a metabolite in more than one hepatocyte batch.
b Includes the non-human metabolite M9 (2.0%)
c Includes the non-human metabolites M8 (6.9%) and M9 (3.6%)
d Includes the non-human metabolite M20 (1.6%)
e Includes the non-human metabolite M14 (2.3%)
f Includes the non-human metabolite M20 (1.5%)
g Includes the non-human metabolite M19 (5.9%) and M28 (3.8%)
h Includes the non-human metabolite M11 (1.2%)
NADPH = nicotinamide adenine dinucleotide phosphate; ND = not detected.

Metabolising enzymes

The human UGT enzymes involved in the formation of the glucoside M3 were identified using recombinant UGT enzymes expressed in baculovirus-transfected Sf9 cells. Aprocitentan was incubated with recombinant UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B4, UGT2B7, UGT2B10 and UGT2B15.

UGT1A1 and UGT2B7 were shown to catalyze the formation of M3. As turnover in these experiments was low, no quantitative information is available on the individual contribution of both UGT isoforms on total glucosidation capacity.

The hydrolysis product M1 was observed as the major product in all experiments. As M1 was similarly present in experiments without UGT enzyme or UDPG co-factor, it is likely the product of chemical rather than enzyme-mediated hydrolysis.

Excretion

After a single oral dose of radiolabelled aprocitentan in two rats, about half of the radioactivity was found in the bile, the remainder in urine and faeces; see table below. Overall, nearly the entire administered radioactivity was recovered within 72 hours.

Table 3 of Report B-14.034(shortened): Radioactivity recovered from bile, urine, feces, cage wash and debris after oral dosing of ACT-132577B (aprocitentan) to two male, bile duct-cannulated Wistar rats

	Radioactivity (% of dose)	
rat #	BD 108993	BD 109133
bile 0-72 h	47.6	51.6
urine 0-72 h	21.8	9.31
feces 0-72 h	18.6	29.6
cage wash 0-72 h	0.15	0.14
debris 0-72 h	0.03	0.02
total	**88.2**	**90.7**

Inhibition of drug metabolising enzymes by aprocitentan

This was studied in human liver microsomes and recombinant human P450.
The test substances were incubated with human liver microsomes or recombinant human P450 enzymes for up to 50 minutes at 37 °C. Analysis of samples by LC-MS/MS or HPLC. The following table lists the test substrates used, the obtained IC50 and Ki values along the study from which the results were derived. The lowest IC50 (i.e. strongest inhibition) was observed for CYP3A4, followed by CYP2C19. There were no hints for time-dependent inhibition.

P450	Substrate	IC50 (µM)	Ki (µM)	Report No.
CYP1A2	Phenacetin-O-Deethylation	>50	ND	B-05.130
CYP2A6	Coumarin 7-Hydroxylation	>100	ND	B-05.130
CYP2B6	(S)-Mephenytoin N-Demethylation	>100 a	ND	B-05.130
CYP2C9	Diclofenac 4'-Hydroxylation	31	11	B-05.130
CYP2C8	Paclitaxel 6α-Hydroxylation	23	ND	B-12.103
CYP2C19	(S)-Mephenytoin 4'-Hydoxylation	15	ND	B-05.130
CYP2D6	Dextromethorphan O-Demethylation	>100 b	ND	B-05.130
CYP2E1	Chlorzoxazone 6-Hydroxylation	>100 c	ND	B-05.130
CYP3A4	Midazolam 1'-Hydroxylation	7.3	ND	B-05.130
CYP3A4	Testosterone 6β-Hydroxylation	11	6.3	B-05.130

a 32% inhibition at 100 µM.
b 16% inhibition at 100 µM.
c 42% inhibition at 100 µM.

Inhibition of human UGT isoforms by aprocitentan

The potential of aprocitentan to elicit UGT1A1 or UGT2B7-mediated DDI was studied in vitro using recombinant human UGT enzymes expressed in baculovirus-transfected Sf9 cells and aprocitentan concentrations up to 100 µM. Incubation of test substances with recombinant human UGT enzymes for 20 minutes at 37 °C. Analysis of samples by LC-MS/MS. The test substrates used and the results obtained are shown in the table below. Inhibition of UGT1A7 and UGT2B7 was observed. IC50 values are indicated.

UGT enzyme	**Substrate**	**IC50 (µM)**
UGT1A1	Estradiol 3-β-glucuronidation	23
UGT2B7	3'-azido-3'-deoxythymidine 5-β-glucuronidation	43

Inhibition of drug transporters by aprocitentan

The following test systems were used: Caco-2 cells; recombinant or transfected CHO cells, MDCK cells, HEK293 cells, human membrane vesicles, or human CHO Flp In™ cells. Incubation of test substances in vitro was done for up to 2 hours at 37 °C. Analysis of samples by LC-MS/MS or scintillation counting. The table below shoes the test substrates and summarises the results. Strongest inhibition (lowest IC50) waas observed for OAT3, followed by OAT1 and BCRP.

Transporter	Test System	Substrate	IC50 (µM)	Report
OATP1B1	CHO cells	atorvastatin acid	19	B-20.030
OATP1B3	CHO cells	atorvastatin acid	27	B-20.030
OAT1	HEK293 cells	p-aminohippuric acid	4.7	B-13.097
OAT3	HEK293 cells	furosemide	1.5	B-13.097
OCT1	HEK293 cells	1-methyl-4-phenylpyridinium iodide	> 100	B-13.097
OCT2	HEK293 cells	1-methyl-4-phenylpyridinium iodide	> 100	B-13.097
P-gp	Caco-2 cells	digoxin	> 70	B-13.098
BCRP	MDCK cells	cladribine	5.7	B-13.097
MATE1	HEK293 cells	metformin	> 100	B-13.097
MATE2K	HEK293 cells	4-(4-dimethylaminostyryl)-N-methylpyridinium	> 100	B-13.097
BSEP	Human BSEP-expressing membrane vesicles	taurocholic acid	50 a	B-05.044
NTCP	Human NTCP-expressing CHO Flp InTM cells	taurocholic acid	14	B-05.044

a 16.5% binding to BSEP vesicles was calculated in report B-13.099.
b 30–35% inhibition at 70 µM
BCRP = breast cancer resistance protein; BSEP = bile salt export pump; CHO = Chinese hamster ovary; Flp InTM = CHO cells expressing a single stably integrated FRT site at a transcriptionally active genomic locus; HEK = human embryonic kidney; IC50 = concentration that elicits 50% inhibition; LC-MS/MS = liquid chromatography coupled to tandem mass spectrometry; MATE = multidrug and toxin extrusion protein; MDCK = Madin-Darby canine kidney; NTCP = sodium-dependent taurocholate co-transporting polypeptide; anion transporting polypeptide; OCT = organic cation transporter; P-gp = permeability glycoprotein.

Induction of CYP enzymes by aprocitentan in human hepatocytes

Aprocitentan activated the transcription factor PXR, which is invovled in CYP induction, with EC50 values of 7.2–8.7 µM in a reporter gene assay.

In human hepatocytes, aprocitentan elicited concentration-dependent increases in CYP3A4 mRNA and enzyme activity. CYP3A4 activity was increased by up to 3.9-fold and CYP3A4 mRNA was increased by up to 6.7-fold at the highest concentration of 10 µM. No relevant changes in CYP1A2 and CYP2C9 activity up to 10 µM was observed.

Upregulation of P450 and UGT enzymes in rats and dogs

Data are taken from the 4–wk toxicology studies T-14.023 (rat) and T-14.022 (dog). Aprocitentan exposure in the rat decreased after repeated dosing in the 4-week toxicity study. This observation may indicate induction of drug-metabolizing enzymes. Therefore, expression levels of mRNA for rat cyp3a1, cyp2b1, cyp2b2, ugt1a1, ugt1a6 and ugt2b1 and dog cyp3A12 were quantified using real-time polymerase chain reaction. Aprocitentan doses tested were 0, 10, 50 and 250 mg/kg in the rat and 0, 75, 250 and 1000 mg/kg

in dogs. The latter dose was reduced to 500 mg/kg during the study due to poor taolerability; see toxicology section.

All tested CYP and UGT mRNAs became induced by aprocitentan treatment in a dose-dependent manner. The magnitude of induction (fold-change vs. control) widely differed, from around 6-fold (ugt1a6) to around 4000-fold (cyp2b1 in females) in the rat. Canine cyp3a12 was induced around 4-fold by 250 mg/kg aprocitentan.

Summary of DDI data

- Aprocitentan inhibited CYP2C and CYP3A4 with IC50 or Ki values in the range of 6–31 µM
  Among the P450 enzymes, the strongest inhibition was observed on CYP3A4, using midazolam as a probe substrate, with an IC50 of 7.3 µM
- Aprocitentan inhibited UGT1A1 and UGT2B7 with IC50 values of 23 µM and 43 µM, respectively.
- Aprocitentan inhibited several drug transport proteins, in particular OAT1, OAT3 and BCRP with IC50 values in the range of 1.5–5.7 µM.

Aprocitentan upregulated CYP3A4 mRNA expression in human hepatocytes and activated the human PXR in a reporter-gene assay.

2.5.4. Toxicology

Study design and testing strategy was based on the ICH M3(R2) guideline and other applicable ICH nonclinical safety guidelines. All pivotal safety studies were performed in accordance with GLP regulations. Most of the early dose range-finding or pilot studies were performed as non-GLP studies, but in GLP accredited laboratories and according to their standards.

The general toxicity profile of aprocitentan was characterized in repeat-dose toxicity studies in rats and dogs with treatment durations of up to 26 weeks in the rat and 39 weeks in the dog. Repeat-dose toxicity studies included recovery groups. In addition, male and female fertility studies, and in vitro and in vivo genotoxicity studies were conducted. Toxicokinetic evaluations were included in most *in vivo* studies.

Toxicity studies were conducted using clinically relevant route of administration (oral). The species selection (rat, dog) is justified by the pharmacodynamic characteristics and metabolism (based on *in vitro* data) similarities between these species and humans.

The assessment of embryo-foetal development, pre- and postnatal development, carcinogenicity and phototoxicity was based on studies performed with macitentan (Opsumit®), in alignment with CHMP scientific advice (EMA 2015, EMA 2017; see Introduction). However, the aprocitentan-specific EFD programme was ultimately decided to be performed to potentially characterize NOAEL value for teratogenicity. The full study reports became available during this MAA procedure

2.5.4.1. Single dose toxicity

No single-dose studies were conducted by the applicant. Effects of a single dose can be derived from the repeat-dose toxicity studies and from the pharmacodynamics studies.

2.5.4.2. Repeat dose toxicity

A listing of the conducted repeated-dose toxicity studies is provided in the table below. The pivotal studies were conducted in rats and in dogs.

Table 1 of Toxicol Written Summary: Overview of toxicity studies performed with aprocitentan

Study type [Reference]	**GLP**	**Route**	**Species (sex)**	**Treatment duration**	**Doses (mg/kg/day)**
Repeat dose					
Dose range-finding [T-14.011]	N	Oral	Wistar rats (M & F)	2 weeks	0, 100, 300, and 1000
Subacute [T-14.023]	Y	Oral	Wistar rats (M & F)	4 weeks + 4-week recovery	0, 10, 50, and 250 [a]
Chronic [T-14.036]	Y	Oral	Wistar rats (M & F)	26 weeks + 9-week recovery	0, 10, 50, 100, and 250 [a]
Chronic [T-16.021]	Y	Oral	Wistar and Sprague Dawley rats (M)	26 weeks + 9-week recovery	0, 10, 50, and 250 [a]
Maximum tolerated dose [T-14.020]	N	Oral	Beagle dogs (M & F)	3 days ascending 7 days fixed	100, 300, and 1000 1000
Subacute [T-14.022]	Y	Oral	Beagle dogs (M & F)	4 weeks + 4-week recovery	0, 75, 250, 1000/500
Subchronic [T-14.072]	Y	Oral	Beagle dogs (M & F)	13 weeks + 9-week recovery	0, 5, 25, 50, and 250
Chronic [T-15.053]	Y	Oral	Beagle dogs (M & F)	39 weeks + 13-week recovery	0, 5, 25, and 75/50

The results of the repeated-dose studies are compiled in the table below.

Toxicity was assessed based on mortality, clinical observations, body weight, food consumption, ophthalmology, electrocardiography, clinical pathology (hematology, coagulation, clinical chemistry, and urinalysis), and organ weight, macroscopic observations at necropsy, and microscopic evaluation.

Administration of the sodium salt of aprocitentan (ACT-132577E) in rats resulted in higher exposure than the free acid. Therefore, all toxicity rat studies, with the exception of the 2-week dose range-finding study, were performed with ACT-132577E, whereas all dog studies were performed with aprocitentan, which is the free acid that is also used in humans.

Study ID	**Species/Sex/ Number/Group**	**Dose mg/kg/day; Route**	**Duration**	**Major findings**

T-14.011	Wistar rats/ M&F /n = 5/sex/dose level (treatment period) satellite animals n ≤ 6/sex/dose level for toxicokinetics single administration of aprocitentan and ACT-132577E at dose levels of 100 and 1000 mg/kg was administered to 2 male rats each to compare exposures	0 (vehicle), 100, 300, and 1000 mg/kg/day; oral gavage	2 weeks oral toxicity study	**Macroscopic pathology & Histology:** <u>Liver:</u> -Weight ↑ (≥100) -Centrilobular hepatocellular hypertrophy (≥100; dose-dependent increase in incidence and severity) -Hepatocellular focal necrosis (1F 300 & 2F 1000)
T-14.023	Wistar rats/ M&F n = 10/sex/dose level (treatment period) n = 5/sex/dose level (recovery period) satellite animals (n = 6/sex/dose level except control group) for toxicokinetics	0 (vehicle), 10, 50, and 250 mg/kg/day; oral gavage	4 weeks oral toxicity study, 4 weeks recovery period	**Laboratory values**: -HB ↓ (F 250) -HCT ↓ (F 250) -Platelet count ↑ (≥10) -Calcium ↑ (≥10) -Cholesterol ↑ (M≥10; F250) -Protein ↑ (M≥10) -Globulin ↑ (≥10) -Creatinine ↑ (M 250) -GGT ↑ (F 250) -Urea ↓ (F≥10) -ASAT ↓ (≥10) -ALP ↓ (M≥10; F≥50) -Bile acids ↓ (M≥10) **Macroscopic pathology & Histology:** <u>Liver:</u> -Weight ↑ (≥10; dose dependent) -Centrilobular hepatocellular hypertrophy (≥10; dose dependent) -Hepatocellular focal necrosis (1M&1F 250) <u>Testes:</u> -Dilation of seminiferous tubules (≥50) At the end of treatment, the laboratory values were largely reversible. In the liver minimal fatty change was still present at slightly higher incidences at 250 mg/kg/day after 4 weeks of recovery. Other changes were fully reversible.

T-14.036	Wistar rats/ M&F /n = 20/sex/dose level (treatment period) 5 /sex / dose level (recovery period) satellite animals n = 9/sex/dose level for toxicokinetics	0(vehicle), 10, 50, 100 and 250 mg/kg/day; oral gavage	26 weeks oral toxicity study, 9 weeks recovery period	**Clinical observations**: -Body weight gain ↓ (250) **Laboratory values**: -HB ↓ (250) -Alanine aminotransferase ↑ (M 250) -Cholesterol ↑ (F≥100) -Total Protein ↑ (F≥50) -Globulin ↑ (F≥100) -Calcium ↑ (M 250) **Macroscopic pathology & Histology:** <u>Liver:</u> -Dark (≥10) -Weight ↑ (M≥10; F≥50) -Size ↑ (M 10/ F 50) -Hydropic hepatocyte degeneration (250) -Increased apoptosis (250) -Hepatocellular hypertrophy (M≥10/ F≥50) <u>Thyroid glands:</u> -Weight ↑ (≥100) -Size ↑ (≥100) -Follicular hypertrophy (M≥10/F≥50) -Follicular hyperplasia (≥50) -Follicular adenomas (2M 100; 3M 250; 1F 250) <u>Kidney:</u> -brownish pigment (F≥10; M≥50) -Weight ↑ (F≥100) At the end of treatment, brownish pigment finding was partially reversible in females and fully reversible in males, other changes were full reversibility.

T-16.021	Wistar (W) and Sprague Dawley (SD) rats/ male/ n = 20/strain/dose level (treatment period) n=5 /strain/ dose level (recovery period) satellite group n = 9/strain/dose level for toxicokinetics	0 (vehicle), 10, 50, and 250 mg/kg/day; oral gavage	Supplemental 26 weeks oral toxicity study 9 weeks recovery period	At the same dose levels, exposure to aprocitentan (based on AUC0-24) was not different between Wistar and Sprague Dawley rats. **Clinical observations (both strains):** <u>≥50:</u> -Hypersalivation -Abnormal foraging -Pedalling -Sneezing -Raised tail <u>250:</u> -Body weight ↓ **Laboratory values**: TSH ↑ (250 W; all dose level SD) W&SD 250: -Increase in chloride levels ↑ -Total protein ↑ -Globulin ↑ -Triglycerides ↓ -Cholesterol ↑ **Macroscopic pathology & Histology:** **<u>Liver:</u>** <u>Dose dependent; both strains:</u> -Weight ↑ -Size ↑ -Hepatocellular hypertrophy ↑ <u>Both strains, 250</u> -Hepatocellular degeneration/necrosis <u>Few rats, both strains, 250:</u> -Multinucleated hepatocytes **<u>Thyroid glands:</u>** - Size ↑ (W 250) -Weight ↑ (W&SD 50) - Follicular cell hypertrophy (dose dependent) -Focal follicular cell hyperplasia (2 SD 250) **<u>Testes:</u>** -Tubular dilation (≥50) -Tubular degeneration/atrophy (250) At the end of treatment, there was full reversibility for most changes. In the liver and the testes, the changes were largely but not fully reversible.
T-14.020	Beagle Dog/ n = 1/sex/group	100, 300, 1000, oral (Capsule)	3 days oral toxicity study, 4 days wash out	**Clinical observations** -Food consumption ↓ (M ≥300) -Body weight ↓ (M≥300) **Laboratory values**: -HB/RBC/PCV ↓ (both sex/all dose level) -Cholesterol ↓ (1000)

	Beagle Dog/ n = 2/sex/group (treatment period)	1000; oral (Capsule)	7 days oral toxicity study	**Clinical observations:** -Food consumption ↓ (1F 1000) -Body weight ↓ (1F 1000) **Laboratory values** (all doses)**:** -HB/RBC/PCV ↓ -Cholesterol ↓ -Globulin ↓ -Albumin ↓ -Total protein ↓ **Macroscopic pathology & Histology:** Heart (right heart atrium/coronary groove) - coronary peri-arteritis/arteritis (all)
T-14.022	Beagle Dog/ n = 4/sex/group (treatment period) 2 /sex /control and high-dose groups (recovery period)	0(vehicle), 75, 250, 1000/500***; oral (Capsule)	4 weeks oral toxicity study Systemic exposure: Day 1 (all dose groups), 15 (only 1000/500 dose group), 20 (0, 75, 250), and 28 (all dose groups) 4 weeks recovery period	**Mortality** (1000): -1M/1F sacrificed day 16 (poor clinical condition) -Severe body weight loss -Low food consumption -Decreased activity -Slow movements **Clinical observations** (1000/500): -Food consumption ↓ -Body weight ↓ -Body temperature ↑ (Two F) **Laboratory values:** -HB/RBC/PCV ↓ (both sex/all dose level) -Fibrinogen ↑(F 1000/500) -Cholesterol ↓ (both sex/all dose level) -Total protein ↓ (M 75 & F ≥ 250) -Albumin ↓ (M 75 & F ≥ 250) -A:G ratio ↓ (250, 1000/500) -ALP ↑ (F 250; M&F 1000/500) **Macroscopic pathology & Histology:** Liver: -Weight ↑ (all sex & dose) -Size ↑ (F 250; M&F 1000/500) -Centrilobular hepatocellular hypertrophy (F 250; M&F 1000/500) Heart (right heart atrium/coronary groove) **-**Coronary peri-arteritis/arteritis (one M/group 75, 250, 1000/500) **Testes**: -Tubular dilation (M 1000/500) At the end of treatment, there was full reversibility for all changes.

T-14.072	Beagle Dog/ n = 4/sex/group (treatment period) 2 /sex /control and high-dose groups (recovery period)	0(vehicle), 5, 25, 50, 250; oral (Capsule)	13 weeks oral toxicity study, Systemic exposure Day 1 and Week 13 9 weeks recovery period	**Clinical observations** (250): -Noisy respiration (M≥25; F≥50) -Subdued/sluggish behaviour (250) -Mild tremors (250) -Thin appearance (250) -Food consumption ↓ (250) -Body weight ↓ (250) **Laboratory values:** <u>Haematological Effects</u> HB↓ (F≥50; M250) RBC↓ (F≥50; M250) PCV↓ (F≥50; M250) RABS↑ (F≥50; M250) RDW↑ (F≥50; M250) HDW↑ (F≥50; M250) PLT↓ (250) PCT↓ (M 250) MPV↑ (250) PDW ↑ (F 250) FIB ↑ (F≥50; M 250) <u>Clinical Chemistry Effects</u> HALP ↑ (250) CHOL ↓ (F≥50; M≥25) HHDL ↓ (25) HDLN ↑ (25) PLPC ↓ (50) ALB ↓ (F≥50; M≥250) GLOB ↑ (F≥50; M≥250) A\G RATIO ↓ (F≥50; M≥250) CAL ↓ (250) HCRE ↓ (250) **Macroscopic pathology & Histology:** <u>Liver:</u> -Weight ↑ (all dose groups) -Size ↑ (≥25) -Hepatocellular hypertrophy (F 25, dose-dependent increase in incidence and severity /M 250) <u>Heart:</u> -Right: intra-/extramural, atrium / coronary groove: Peri-/arteritis (M 25; M&F 250) -Right / Left: intra-/extramural, atrium / coronary groove: Intimal thickening (M≥25) <u>Testes:</u> -Tubular dilation (M≥25) -Tubular degeneration (M 250) <u>Nasal cavity level 3 (≥5, dose-dependent increase in incidence and severity):</u> -Congestion -Vascular dilation <u>≥25, dose-dependent increase in incidence and severity:</u> -Submucosal edema -Goblet cell proliferation -Hyperchondrosis -Hyperostosis <u>Spleen:</u> -Extramedullary hemopoiesis (One F250) <u>Bone marrow:</u> -Granulopoiesis (One F 50; Two M 250; One F 250)

				At the end of treatment, there was a trend towards reversibility in platelet counts. After the recovery period, there was one male still affected by Hepatocellular hypertrophy at 250 mg/kg/day. Full reversibility for all other changes.
T-15.053	Beagle Dog/ n = 4/sex/group (treatment period) n=3/sex/ control and high-dose groups (recovery period)	0(vehicle), 5, 25, 75/50****; Oral (Capsule)	39 weeks oral toxicity study Systemic exposure Day 1 and Week 39 13 weeks recovery period	**Clinical observations**: -Noisy respiration (≥25) -Body weight ↓ (75/50) -Food consumption ↓ (75/50) -subdued/sluggish behaviour, halitosis, pale body/ears (75/50) **Laboratory values**: -HB/RBC/PCV ↓ (75/50) -HALP ↓ (F 25; F&M 50/75) - CHOL ↓ (F 25; F&M 50/75) -ALB ↓ (F 25; F&M 50/75) -A:G ratio ↓ (50/75) **Macroscopic pathology & Histology:** <u>Liver (≥25, dose-dependent increase in incidence and severity):</u> -Weight ↑ -Size ↑ -Hepatocellular hypertrophy <u>Nasal cavity level 3 (dose-dependent increase in incidence and severity):</u> -Submucosal edema, congestion (≥5) -Goblet cell proliferation (≥25) -Hyperchondrosis (≥25) -Hyperostosis (≥25) -Connective tissue ↑ (≥75/50) <u>Testes (M):</u> -Tubular dilation (≥5) -Tubular degeneration (≥25) Reversal was evident for all parameters at the end of the recovery phase.

In the main results, the doses and, if necessary, the sex are given in brackets () without the unit mg/kg/day.
***= dose level was reduced on Day 15 from 1000 to 500 mg/kg/day - consequence of clinical signs: body weight loss, reduced food consumption, decreased activity, elevated body temperature, 1 M and 1 F dog were excluded from experiment on day 14 as consequence of deterioration of their clinical condition. Histopathological evaluations showed that these two animals were affected by idiopathic canine polyarteritis (Beagle pain syndrome), which is considered dog specific.

****= dose level was reduced on Days 163 and 165 (females and males, respectively) from 75 to 50 mg/kg/day - consequence of clinical signs: hunched posture, pale or thin appearance, and subdued/sluggish behaviour

Abbreviations: A:G ratio= Albumin:Globulin ratio; ALB = Albumin; CAL= Calcium; CHOL = Total cholesterol; F= female; FIB= Fibrinoge; GLOB= Globulin; HALP = Alkaline phosphatase; HB=hemoglobin; HCRE=Enzymatic Creatinine; HDLN= Non High Density Lipoprotein Cholesterol; HHDL= High Density Lipoprotein Cholesterol; HDW= Haemoglobin Distribution Width; M=male; MPV= Mean Platelet Volume; PCT= Platelet Crit; PCV= Packed Cell Volume (=haematokrit); PDW= Platelet Distribution Width; PLPC= Phospholipid C; PLT= Platelets, RABS= Absolute Reticulocytes; RBC=red blood cells; RDW= Red Cell Distribution Width; SD= Sprague Dawley rats; W= Wistar rats

The pivotal studies, i.e. one 26-wk rat study and the 39-wk dog study are presented in more detail in the following.

Rat 26-week study plus 9-wk recovery (T-16.021)

Based on the unusual occurrence of thyroidal follicular hyperplasia and adenomas in the first 26-week rat study, this additional 26-week study was performed to assess the thyroid function and histopathology in more detail. This study was conducted with ACT-132577E in male Wistar and Sprague Dawley rats (n = 20/strain/dose level) at dose levels of 0 (vehicle), 10, 50, and 250 mg/kg/day [T-16.021]. A 9-week recovery group (n = 5/strain/dose level) and a satellite group (n = 9/strain/dose level) for toxicokinetics were included in the study.

At the same dose levels, exposure to aprocitentan (based on AUC0-24) was not different between Wistar and Sprague Dawley rats.

Relevant findings are described in the following.

Clinical signs

Hypersalivation, associated with abnormal foraging, pedalling, sneezing and/or raised tail was observed after dosing mainly in animals treated at 50 and 250 mg/kg/day, for both strains. These observations occurred early after dosing and were transient. Therefore, the applicant regarded them as related to poor palatability of the drug formulation.

Haematology and coagulation

Only minor changes were observed, in line with the results of the other rat studies.

Serum chemistry

The following changes were observed in the high-dose (250 mg/kg) group:

- Increase in chloride levels, up to 11%
- Increase in total protein (up to 10% above control) and globulin (up to 17% above control)
- Decrease in triglycerides (largest change, -65%)
- Increase in total cholesterol, up to around 60%.

The applicant noted that all values were within or close to the historical range.

Furthermore, due to the observed histological thyroid changes, the applicant determined plasma TSH levels. In the SD rats, there was a largely dose-dependent increase over control in all dose groups, up to 3.0-fold. In Wistar rats, TSH increase was only observed in the high-dose (250 mg/kg) group and was up to 3.6-fold above control level.

Macroscopic pathology

In both strains, organ weight changes that correlated with microscopic findings consisted of a dose-dependent increase in liver weight in all test item treated groups and thyroid gland weight at doses ≥50 mg/kg/day at the end of the treatment period.

Recovery: The liver and thyroid gland weight changes were fully reversible.

Histology

Liver

Hepatocellular hypertrophy was observed in nearly all animals treated with aprocitentan but not in vehicle controls. Hepatocellular damage (degeneration or necrosis) was found in high-dose animals only. Centrilobular fat deposition was found in many animals including controls with no clear dose-dependency. See table below.

Table: Incidence and Mean Severity of Main Findings in the Liver – Terminal Sacrifice

	Strain 1 – Wistar				Strain 2 – Sprague Dawley			
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8
Dose (mg/kg/d)	0	10	50	250	0	10	50	250
	20 M	21* M	22* M	20 M	21* M	20 M	20 M	20 M
Hepatocellular hypertrophy	0	12/1.1	21/1.7	20/3.1	0	17/1.2	20/1.9	20/3.2
Fatty change, centrilobular	10/1.1	20/1.2	18/1.7	15/1.9	5/1.0	14/1.1	14/1.2	7/1.0
Hepatocellular degeneration/necrosis	0	0	0	5/2.0	0	0	0	8/1.6
Multinucleated hepatocytes	0	0	0	4/1.0	0	0	0	3/1.0

*: Including premature deaths/sacrifices in recovery or satellite groups.
Recovery: The changes were largely but not fully reversible.

Thyroid

Hypertropy of follicular cells was observed in al dose groups but not in controls. Incidence and severityincreased with aprocitentan dose. Hyperplasia of the follicular cells was observed in two high-dose animals only; see table below.

Table: Incidence and Mean Severity of Main Findings in the Thyroid Glands – Terminal Sacrifice

	Strain 1 – Wistar				Strain 2 – Sprague Dawley			
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8
Dose (mg/kg/d)	0	10	50	250	0	10	50	250
	20 M	21* M	22* M	20 M	21* M	20 M	20 M	20 M
Follicular cell hypertrophy	0	7/1.0	14/1.3	19/1.6	0	6/1.0	12/1.0	20/1.5
Focal follicular cell hyperplasia	0	0	0	0	0	0	0	2/1.5

*: Including premature deaths/sacrifices in recovery or satellite groups.
Recovery: The changes were fully reversible.

Testes

Tubular degeneration/atrophy was observed in some control animals of both strains, but the incidence markedly increased with aprocitentan, most pronounced in the high-dose groups. Tubular dilation wa sobserved in the mid- and high-dose group; see table below.

Table: Incidence and Mean Severity of Main Findings in the Testes - Terminal Sacrifice

	Strain 1 – Wistar				Strain 2 – Sprague Dawley			
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8
Dose (mg/kg/d)	0	10	50	250	0	10	50	250
	20 M	21* M	22* M	20 M	21* M	20 M	20 M	20 M

Tubular dilation	0	0	6/1.0	8/1.0	0	0	6/1.0	12/1.0
Tubular degeneration/atrophy	2/1.0	1/2.0	4/1.0	7/1.9	1/2.0	4/1.8	4/1.3	12/1.4

*: Including premature deaths/sacrifices in recovery or satellite groups.

Recovery: The changes were largely but not fully reversible.

Dog 39-week study plus recovery (T-15.053)

A 39-week oral (capsule) toxicity study was conducted with aprocitentan in Beagle dogs (n = 4/sex/group) at dose levels of 0 (vehicle), 5, 25, and 75/50 mg/kg/day [T-15.053]. The 39-week treatment period was followed by a 13-week treatment-free period in 3 dogs/sex from the control and high-dose groups. Systemic exposure was assessed on Day 1 and Week 39.

Assessment of toxicity was based on the standard parameters, i.e. mortality, clinical signs, body weight, food consumption, rectal temperature, ophthalmologic observations, ECG, blood pressure, clinical pathology (hematology, coagulation, clinical chemistry, and urinalysis), organ weight, macroscopic observations at necropsy, and microscopic evaluation.

The relevant findings are prsented in the following.

Clinical observation

ACT-132577-related adverse clinical observations included noisy respiration, subdued/sluggish behavior and thin appearance. In addition halitosis and pale body/ears were noted.

Noisy respiration was detectable in the mid- (25 mg/kg) and high-dose (75/50 mg/kg) group; most animals in these groups were affected.

The other clinical signs were observed mostly intermittently and fewer animals were affected, predominantly in the high-dose group.

Body weight, food consumption

Compared with concurrent controls, decreased intake was most apparent during the first few weeks of the dosing phase among both sexes administered 75/50 mg/kg/day. Body weight gain was decreased accordingly.

ECG, blood pressure

No effect on ECG or hemodynamic parameters was noted following administration of ACT-132577, compared with baseline and control values, based on data collected during Day 2 and Weeks 26 and 39 at approximately 3 hours postdose.

Haematology, coagulation

In the high-dose group, predominantly in females, slight reductions (up to 16%) in the number of red blood cells, haemoglobin and related parameters were observed. For details, see table below.

Text Table 4.2: Notable Haematological Effects
Difference from pretreatment (Group mean)

		75/50 mg/kg/day	
Parameter	Interval	Male	Female
HB	Day 177/179	↓ 9.6%	↓ 15%
	Day 268	NE	↓ 16%

RBC	Day 177/179	↓ 8.4%	↓ 13%
	Day 268	NE	↓ 13%
PCV	Day 177/179	NE	↓ 12%
	Day 268	NE	↓ 10%
RDW	Day 177/179	NE	↑ 11%
	Day 268	NE	↑ 6.9%

HB = Hemoglobin; NE = No effect; PCV = Packed cell volume; RBC = Red blood cells; RDW = Red cell distribution width

Recovery: The above changes were reversible.

Clinical chemistry

In the high-dose group and in females of the mid-dose group, a decrease in total cholesterol, albumin and albumin:globulin ratio was observed. Alkaline phosphatase was decreased at the beginning of the study and was increased at the end of the study. Details are shown in the table below.

Text Table 4.3: Notable Clinical Biochemistry Effects
Difference from pretreatment (Group mean)

		25 mg/kg/day		75/50 mg/kg/day	
Parameter	Interval	Male	Female	Male	Female
HALP	Day 85	NE	↓ 37%	↓ 56%	↓ 49%
	Day 177/179	NE	NE	↑ 63%	↑ 77%
	Day 268	NE	NE	↑ 88%	↑ 127%
CHOL	Day 177/179	NE	↓ 35%	↓ 56%	↓ 53%
	Day 268	NE	↓ 26%	↓ 44%	↓ 56%
ALB	Day 177/179	NE	↓ 7.9%	↓ 11%	↓ 14%
	Day 268	NE	↓ 11%	↓ 11%	↓ 16%
A:G RATIO	Day 177/179	NE	NE	↓ 24%	↓ 26%
	Day 268	NE	NE	↓ 24%	↓ 26%

A:G = Albumin:Globulin; ALB = Albumin; CHOL = Total cholesterol; HALP = Alkaline phosphatase; NE = No effect

Recovery: The above changes were reversible.

Macroscopic pathology

Absolute and relative (organ/brain and organ/body weights) liver weights were slightly increased at ≥25 mg/kg/day (both sexes). Enlarged liver lobes and/or mottled livers were observed at 25 mg/kg/day (males only) and at 75/50 mg/kg/day (both sexes). These lesions were associated with an increased incidence of hepatocellular hypertrophy at ≥ 25 mg/kg/day in both sexes.

Recovery: The weight increase was reversed after the recovery period.

Histology

Liver

A dose-dependent increase in the incidence of hepatocellular hypertrophy was observed. In the control and low-dose group no animals were affected; see table below.

Text Table 4.4: Incidence and Mean Severity of Main Findings in Liver

Dose (mg/kg/day)	Control		5		25		75/50	
Finding / Groups	1		2		3		4	
Total Affected / Mean Severity	(4) M	(4) F	(4) M	(4) F	(4) M	(4) F	(4) M	(4) F
Liver: Hepatocellular hypertrophy	0	0	0	0	1/1.0	3/1.0	4/1.0	4/1.0

Recovery: Hepatocellular hypertrophy was found to be reversible.

Nasal cavity

Various histological findings were reported in several parts of the nasal cavity. Most effects were dose-dependent in respect to incidence and severity. Congestion and submucosal oedema were already observed in the low-dose group. At higher doses, signs of prliferation of several structores (goblet cells, connective tissue, cartilage and bone) were found. For details, see table below.

Text Table 4.5: Incidence and Mean Severity of Main Findings in Nasal Cavities

Dose (mg/kg/day)	Control		5		25		75/50	
Finding / Groups	1		2		3		4	
Total Affected / Mean Severity	(4) M	(4) F	(4) M	(4) F	(4) M	(4) F	(4) M	(4) F
NC: Congestion	0	0	0	1/1.0	4/1.5	3/1.3	4/1.3	3/1.7
NC: Submucosal edema	0	0	1/1.0	3/1.3	4/1.3	4/1.8	4/2.0	4/2.5
NC: Goblet cell hyperplasia	0	0	0	0	2/1.0	3/1.3	2/1.5	4/1.3
NC: Increased connective tissue	0	0	0	0	0	0	1/1.0	2/1.5
NC: Hyperchondrosis	0	0	0	0	1/1.0	0	1/1.0	2/1.0
NC: Hyperostosis	0	0	0	0	1/1.0	1/1.0	1/1.0	2/1.0
NC: Inflammation, chronic	0	0	0	0	0	0	0	1/2.0

NC = Nasal Cavities

Recovery: All changes reversed after the 13 week treatment-free period.

Testes

Tubular dilation in the testes was observed in nearly all males treated with aprocitentan in any dose. The severity of this finding was dose-dependent. In the mid- and high-dose group, also tubular degeneration occurred; see table below.

Text Table 4.6: Incidence and Mean Severity of Main Testicular Findings

Dose (mg/kg/day)	Control	5	25	75/50
Finding / Groups	1	2	3	4
Total Affected / Mean Severity	(4) M	(4) M	(4) M	(4) M
Testes: Tubular degeneration	0	0	2/1.5	3/1.7
Testes: Tubular dilation	0	4/1.0	4/1.5	3/2.0

Recovery: After the treatment-free period, no findings were noted in the testes.

2.5.4.3. Genotoxicity

The genotoxic potential of aprocitentan was examined in a standard test battery comprised of in vitro bacterial (study T-14.025) and mammalian (study T-14.026) cells and in vivo micronucleus test (study T-15.006). Aprocitentan was negative in all tests.

2.5.4.4. Carcinogenicity

Carcinogenicity studies have not been conducted with aprocitentan, but were assessed from the carcinogenicity studies with macitentan. These studies have been performed in B6C3F1 mice and Wistar rats. The waiver for a test item-specific carcinogenicity study has been discussed during the initial and follow-up scientific advices (EMEA/H/SA/3110/1/2015/III; EMEA/H/SAH/086/1/2017/III) and agreed by the CHMP on the grounds of the same chemical structure as the major metabolite of macitentan and on the grounds of sufficient estimated systemic exposure to aprocitentan (at least 50%) both in rats and mice following the administration of macitentan. No special issues are noted during the MAA as well, therefore, the recommendation given in the scientific advice can be confirmed.

Carcinogenicity studies with macitentan in both species revealed no oncogenic potential with relevant systemic exposure to the major metabolite, being up to 26 (52)-fold in mice (averaged for males and females) and 4.2

(10.8) and 7.2 (18.5)-fold in male and female rats, respectively, above the human exposure at a dose of 25 mg aprocitentan.

2.5.4.5. Reproductive and developmental toxicity

An overview of the performed reproductive toxicity studies is provided in the tables below.

The list of aprocitentan-specific studies includes:

Study type [Reference]	GLP	Route	Species (sex)	Treatment duration	Doses (mg/kg/day) NOAEL*
Fertility					
Male fertility (T-16.001)	y	Oral	Wistar rats (M)	10 weeks before mating	0, 10, 50, **250***
Female fertility (T-16.002)	Y	Oral	Wistar rats (F)	2 weeks before mating – GD7 (up to 5 weeks in total)	0, **10***, 50, 250
Embryo-foetal development					
Preliminary EFD study in rat (T-22.029)	Y	Oral	Wistar rats (F)	GD6 – GD17	0, 0.3, 1, **3***, 10
Definitive EFD study in rat (T-22.030)	Y	Oral	Wistar rats (F)	GD6 – GD17	0, 1, 3, **10***
Preliminary EFD study in rabbit (T-22.027)	Y	Oral	Himalayan rabbits (F)	GD7 – GD19	0, 0.25, 0.75, **2.5***
Definitive EFD study in rabbit (T-22.028)	Y	Oral	Himalayan rabbits (F)	GD7 – GD19	0, 0.25, 0.75, **2.5***

The reproductive and developmental studies with macitentan, which were submitted to derive aprocitentan data are the following:

Study type [Reference]	GLP	Route	Species (sex)	Treatment duration	Doses (mg/kg/day) NOAEL*
Embryo-foetal development					
Preliminary EFD study in rats (T-05.008)	Y	Oral	Wistar rats (F)	GD6 – GD17	0, 150, 450, 1500 (*NOAEL not established)
Definitive EFD study in rats (T-12.804)	Y	Oral	Wistar rats (F)	GD6 – GD17	0, 3, 10, 150 (*NOAEL not established)
Preliminary EFD study in rabbits (T-05.029)	Y	Oral	New Zealand White rabbits (F)	GD7 – GD19	0, 2.5, 12.5, 25 (*NOAEL not established)
Pre- and postnatal development					
PPND (T-09.617)	Y	Oral	Wistar rats (F)	GD17 – PND20	0, 10, 50, 250 (*NOAEL not established)

Fertility

Rats were used to examine effects of aprocitentan (sodium salt) on male (study T-16.001) and female (study T-16.002) fertility (gonadal function, mating behaviour, reproductive performance and early pregnancy). Male fertility was assessed during 10-week treatment period. This duration is based on the duration of full spermatogenic cycle, since there were testis-related findings observed in repeat-dose toxicity studies (see above). In addition, thyroid hormone assessment was made in male fertility study as a further follow-up on thyroid hypertrophy findings. TK evaluation was included in both studies.

In male rats, drug-related dilation of seminiferous tubules was observed at 250 mg/kg/day (considered as non-adverse). There were no effects observed on sperm parameters, reproductive performance, male reproductive organs (with exception of seminiferous tubules), or early embryonic survival in the male fertility study in rats up to the highest tested dose of 250 mg/kg/day (NOAEL), providing a high safety margin of 25.9 (66.9) based on total (free) exposure. TSH levels were increased in the 50 and 250 mg/kg/day groups, while T3 and T4 levels were comparable among all groups. Dose-dependent increase in centrilobular hepatocellular and thyroid follicular cell hypertrophy were evident in all groups, consistent with DME induction.

Female mating performance, oestrous cycle, ovary weights, and post-implantation parameters were not affected by treatment with aprocitentan up to 250 mg/kg/day. However, minimally increased incidence of pre-implantation loss and reduced corpora lutea numbers were observed at higher doses, with a NOAEL of 10 mg/kg/day, resulting in an exposure-based safety margin to the MRHD of 2.3 (8.6). Slightly increased pre-implantation loss was noted with ambrisentan as well (Volibris EPAR).

Embryo-foetal development (EFD)

Macitentan showed clear dose-dependent teratogenic effects in rats and rabbits. In both species, there were cardiovascular and mandibular arch fusion abnormalities. The observed effects are class effects of ET receptor antagonists. ERAs are considered as well-known and powerful teratogens during early pregnancy due to the role of endothelin in neural crest cell migration and/or proliferation in the developing embryo. Disruption of this process produces serious craniofacial and cardiovascular malformations typical to those noted at all dose levels in all macitentan EFD studies. A NOEL for embryo-fetal development was not established for macitentan.

Based on the studies conducted with macitentan, aprocitentan could be considered teratogenic in animals. In line with other ERAs, a pregnancy contraindication is included in the SmPC for aprocitentan. During the MAA procedure, the contraindication was applied on WOCBP, as well, in line with other ERAs.

Although initially asking for a Segment II studies waiver, the applicant ultimately decided to conduct an aprocitentan-specific studies to potentially characterize NOAEL value, since there were some hints from pharmacological differences (*in vitro* and *in vivo*) between aprocitentan and macitentan that the two substances might have different effects on EFD. A full EFD programme of aprocitentan, which includes four studies in total in rats and rabbits (one DRF preliminary and one main study for each species), was completed during this MAA procedure. Aprocitentan was purposefully assessed in a dose range that resulted in exposure around human exposure at MRHD [T-22.027, T-22.028, T-22.029, and T-22.030]. Doses that result in higher exposures were not assessed. Embryotoxicity and teratogenicity were not observed in the dose range tested, i.e., 1–10 mg/kg/day in rats and 0.25–2.5 mg/kg/day in rabbits. The achieved exposures provided safety margins of 2 and 14 (based on total concentrations), and 6 and 3 (based on free concentrations) in rats and

rabbits, respectively. The safety margins for teratogenicity in rats and rabbits may suggest that an inadvertent use of aprocitentan at MRHD in early pregnancy may not be associated with induction of teratogenicity in human foetuses. As the principal potential of ERAs to induce teratogenicity is acknowledged, these results do not change previous recommendations about appropriate contraceptive measures to be used by women of childbearing potential and the use of aprocitentan is contraindicated during pregnancy.

Pre- and postnatal development (PPND)

The potential effect of aprocitentan on PPND was derived from study performed with macitentan. Aprocitentan is considered to have contributed to the observed effects in this study since exposures in terms of $AUC_{0\text{-}24h}$ were similar for macitentan and its major metabolite. All pups which were breast-fed by the dams were also exposed to macitentan and its major metabolite ACT-132577. A number of adverse effects on fertility and development of offspring were described for macitentan:

- in F0 females, post-natal loss (leading to decreased birth and viability indices) was slightly increased at all dose levels, while breeding loss (resulting in a decreased weaning index) was increased at 250 mg/kg/day;
- in F1 pups, there was change of the liver shape, reduced testes and epididymides size at 50 and 250 mg/kg/day observed at PND45-50 necropsy;
- the fertility index of F1 animals was decreased, and pre-implantation loss increased, resulting in a reduced number of implantation sites and live embryos at all dose levels;
- in several F1 animals used for the assessment of reproduction, signs of liver toxicity were noted at all dose levels (liver reduced in size, thickened, or thickened with enlarged lobes; hepatocytes of the periportal zone appeared enlarged, and bile duct hyperplasia and inflammatory foci were observed microscopically);
- in F1 males, the size of testes and epididymides was reduced in some animals at all dose levels, correlating with reduced organ weights. Histologically, the incidence of minimal/slight testicular tubular atrophy was increased in F1 males of the high-dose group.

Similar findings have been reported for other ERAs.

Aprocitentan partitioned into the milk of lactating rats (see PK section). Breastfeeding is not recommended during treatment with aprocitentan in the currently proposed PI for aprocitentan

2.5.4.6. Toxicokinetic data

Exposure (AUC) values at steady state as measured in the repeated-dose toxicology studies are tabulated below. Human therapeutic exposure is provided for comparison.

Table 2.6.7.3A from Toxicology Tabulated Summary: Toxicokinetics: Overview of toxicokinetic data from chronic studies performed at steady state. Steady state aprocitentan AUC (µg·h/mL) at end of treatment

	Rats		Dogs a	Humans a aprocitentan exposure
Daily Dose (mg/kg)	male	female		
0.2				34.7
0.4				69.5
5			374 g	
10	76.9 b, 105 c, 119 d, 107 e	138 b, 158 f		
25			1840 g	
50	448 b, 554 c, 474 d, 468 e	789 b, 788 f	2830 g	

75			3380 h	
100	1130 b	1870 b		
250	1710 b, 1460 c, 1440 d, 1800 e	3080 b, 4040 f		

a means of male and female
b 26-week rat study [T-14.036]
c 26-week rat study [T-16.021] (Wistar)
d 26-week rat study [T-16.021] (Sprague Dawley)
e fertility study in male rat [T-16.001]
f fertility study in female rat [T-16.002]
g 39-week dog study [T-14.020]
h 39-week dog study [T-14.020], Week 25 before dose reduction

2.5.4.7. Local Tolerance

N/A

2.5.4.8. Other toxicity studies

A phototoxicity study was conducted:

In vivo phototoxicity study in hairless rats (T-09.061)

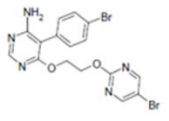
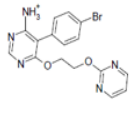
Phototoxicity of aprocitentan was estimated from *in vivo* phototoxicity study with macitentan. Sufficient exposure was achieved with the major metabolite at 60 mg/kg macitentan ($AUC_{0\text{-}24,total}$ 140 µg*h/mL; $AUC_{0\text{-}24,free}$ 1.82 µg*h/mL) to cover the human exposure at 25 mg of aprocitenatan per day ($AUC_{0\text{-}24,\ total}$ 69.5 µg*h/mL; $AUC_{0\text{-}24,free}$ 0.35 µg*h/mL). Macitentan was administered orally (gavage) to three groups of female hairless rats (Ico:OFA-hr/hr, n = 6/group) as single doses of 0 (vehicle), 15, and 60 mg/kg. A positive control group consisting of 6 females was administered a single dose of 2 mg/kg of 8-methoxypsoralen. Additional groups of satellite animals (n = 6/group, except 3 in the vehicle control group) were included for toxicokinetic determinations of macitentan and its major metabolite. Animals were narcotized with pentobarbitone. During narcosis, skin areas of approximately 2 cm^2 were exposed to increasing doses of suberythematogenic UVA irradiation.

No erythema formation was seen in animals receiving the vehicle or macitentan up to the high dose level of 60 mg/kg/day corresponding 24-fold the human exposure at 10 mg per day. In the positive control group, animals treated with 8-methoxypsoralen presented with erythema formation from the lowest irradiation dose, demonstrating the capability of the test system to detect phototoxic reactions.

2.5.5. Ecotoxicity/environmental risk assessment

Aprocitentan is not considered PBT compound. It is not a readily biodegradable. The calculated half-lives for aprocitentan are indicating that it is not persistent in water and total system, but its transformation products (ACT-80803 and WS1) are very persistent in water. Dissipation rates in sediment weren't determined due to insufficient decrease over the incubation period so persistence of aprocitentan and its transformation products in this system cannot be anticipated. Based on toxicity tests and PEC/PNEC ratios, there was no anticipated risk for ground water, microorganisms in STP or sediment compartment of environment following prescribed use of aprocitentan.

Summary of main study results

Substance (INN/Invented Name): Aprocitentan			
CAS-number (if available): 1103522-45-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Dow (pH 5) = 2.53 log Dow (pH 7) = 1.87 log Dow (pH 9) = 0.127	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Log D_{OW} (pH 5) = 2.53	Potentially not B
Persistence	DT50 or ready biodegradability	Transformation products TP ACT-080803: $DT_{50\ total\ system}$ (12 °C) = 281/ 385 d TP WS 1: ([pryamidinyl-]desbromo-ACT-080803): $DT_{50\ total\ system}$ (12 °C) > 180 d	**vP (transforma-tion products)**
Toxicity	*NOEC*	*open*	*T/not T*
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.125	µg/L	> 0.01 threshold Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Koc soil = 1771.9; 2247.8; 2904.4 Koc sludge = 174.4; 111.7	
Ready Biodegradability Test	OECD 301	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Parent (Aprocitentan) $DT_{50,\ water\ (20°C)}$ = 8.8/ 6.5 d $DT_{50,\ sediment\ (20°C)}$ = 24.5/ 16.9d $DT_{50,\ total\ system\ (20°C)}$ = 12.4/ 7.6d CO_2 = 0.6%/ 1.3% NER = 17.4%/ 28.1% (d 100) shifting to sediment = 16% / 14.1% (day 13) Transformation products > 10%: ACT-080803 (max. 59.1 %, d 28/ max. 75.6 %, d 28) $DT_{50,\ total\ system\ (20\ °C)}$ = 132d / 181 d WS 1: ([pryamidinyl-] desbromo-ACT-080803) (max 30.3 %, d 100/ max 9.4 %, d 28)	1) Calwich Abbey (silt) 2) Emperor Lake (sandy clay loam)  ACT-080803  WS1

		$DT_{50,\ total\ system\ (20\ °C)}$ = >180 d			
Phase IIa Effect studies					
Study type	**Test protocol**	**End-point**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *P. subcapitata*	OECD 201	NOEC	432	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	2670	µg/L	reproduction
Fish, Early Life Stage Toxicity Test/ *species*	OECD 210	NOEC	open	µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000000	µg/L	respiration
Phase IIb Studies					
Sediment dwelling organism, *C. riparius*	OECD 218	NOEC	260.4	mg/kg	Emergence rate, result normalised to 10% organic carbon

2.5.6. Discussion on non-clinical aspects

Pharmacology

In vitro primary pharmacodynamics studies were primarily conducted to characterize inhibitory properties of macitentan and its major active metabolite on both ET_A and ET_B receptors. Assuming that aprocitentan has the same chemical structure as major active metabolite of macitentan, the results from studies with macitentan referred to aprocitentan. In ligand-binding assays using CHO cells, aprocitentan inhibited binding of ET-1 to both ET_A and ET_B receptors, with mean IC_{50} values of 3.4 nM and 987 nM, respectively. Unbound C_{trough} measured in patients with resistant hypertension at therapeutic dose of 25 mg was approximately 25 nM (Study D-22.269), while unbound C_{max} and C_{min} in healthy subjects were 33 nM and 21 nM, respectively (Study D-15.519), suggesting that clinical exposures should be sufficient to inhibit ET_A, but not ET_B receptors. However, plasma protein binding of aprocitentan was above 98% in all species (Study B-07.077), and therefore the corrected IC_{50} for ET_B receptor was 94 nM, based on unbound concentrations. In intracellular calcium-release assays, aprocitentan inhibited ET-1-induced intracellular calcium increase, with K_b values of 5.5 nM on ET_A and 319 nM on ET_B. In addition, aprocitentan did not show prolonged receptor occupancy half-life. Functional assays were conducted ex vivo on isolated rat aorta (expressing ET_A) and rat trachea (expressing ET_B). Aprocitentan blocked ET-1-induced contraction in both organs, with the calculated pA_2 values of 6.7 at ET_A in rat aorta and 5.5 at ET_B in rat trachea. Taking into consideration the affinities of the agonists used i this study (ET-1 for ETA and sarafotoxin for ETB), an apparent K_b ($appK_b$) values were calculated using the Cheng-Prusoff equation. Unbound $appK_b$ was 3.5 nM for ET_A and 538 nM for ET_B. These values are in line with other experiments and confirm a high preference of aprocitentan for ET_A.

Based on a concentration-dependent rightward shift in the concentration-response curves following administration of aprocitentan and a slope similar to unity provided by Schild analysis, it was concluded that aprocitentan behaved as a competitive antagonist on ET receptors.

Another evidence of dual antagonism was provided in normotensive Wistar rats where ET-1 plasma concentrations were dose-dependently increased after single oral administration of aprocitentan. The same

effect was also observed in humans. An increase in ET-1 plasma concentration can be used as a marker of antagonism on ET_B receptor (Löffler 1993) because ET_B is involved in the removal of ET-1 from circulation. Taking into account corrected IC_{50} value and in vivo data, it could be concluded that ET_B receptors are at least partially blocked at clinical exposures and aprocitentan is considered a dual ET_A/ET_B endothelin receptor antagonist, with higher affinity for ET_A receptors.

The efficacy of aprocitentan was evaluated in conscious rats equipped with telemetry in three hypertensive models associated with elevated (DOCA-salt, Dahl-S rats) or normal (SHRs) ET system activity. Single oral administration of aprocitentan dose-dependently decreased MAP in all tested models, without increasing HR. Consistent with published data, maximal decrease in MAP was greater in DOCA-salt and Dahl-S rats than in SHRs. The maximal effective doses of aprocitentan in DOCA-salt rats were ≥10 mg/kg, whereas in SHRs were ≥100 mg/kg; thus, clearly demonstrating the correlation between ET system activity and efficacy of aprocitentan in reducing blood pressure. Based on similar exposures in normotensive and hypertensive rats, as well as previously demonstrated increase in ET-1 concentrations in normotensive rats, MAP reduction was probably achieved by inhibition of both ET_A and ET_B receptors, confirming the role of ET_B as part of the ET system-mediated vasoconstriction. There is no data on MAP changes in normotensive rats after administration of aprocitentan, however, blood pressure lowering effect was not observed with authorised dual endothelin receptor antagonists.

As the majority of patients with resistant hypertension already receive an angiotensin-converting-enzyme inhibitor (ACEi), an angiotensin receptor blocker (ARB), and/or a calcium channel blocker (CCB), the hemodynamic effects of the combination of aprocitentan with enalapril (ACEi), valsartan (ARB) or amlodipine (CCB) were assessed in hypertensive rats. Combination with a thiazide diuretic or a beta blocker was not studied. The selected dose of aprocitentan was equal to the maximally effective dose, while standard antihypertensive medicines were dosed to achieve a partial blood pressure decrease of 10-20 mmHg in appropriate hypertensive model. The aim was to show whether co-administration with aprocitentan might result in synergistic or additive effect on MAP decrease. Synergism was only assumed if there was a stistically significant difference between the sum of the individual actions of two compounds and the combined effect. Hence, some instances of synergism could be missed if e.g. statistical significance was not reached because of high variability. In both DOCA-salt rats and SHRs, aprocitentan administered in combination with angiotensin receptor blocker demonstrated synergistic effect in reducing MAP, while co-administration with angiotensin-converting-enzyme inhibitor showed either synergistic or additive effect. On the other hand, co-administration of aprocitentan with calcium channel blocker indicated possible antagonistic effect in SHRs. However, althoug the results numerically indicated antagonistic effects, statistcal significance was not reached so that antagonism could not be confirmed. Administration of spironolactone (the fourth line therapeutic option in patients with difficult-to-control hypertension) in combination with any of the tested compounds achieved only additive effect in both rat hypertensive models. Furthermore, based on area between the MAP-versus-time curves (ABC) values, aprocitentan in combination with standard antihypertensive therapy produced greater blood pressure reduction than spironolactone in combination with the same therapy.

In line with clinical trial, the hemodynamic effect of aprocitentan in combination with the triple antihypertensive therapy (Exforge HCT®) was assessed in conscious DOCA-salt rats. Co-administration of Exforge HCT® with aprocitentan decreased MAP to a greater extent than Exforge HCT® alone, indicating an additional effect of aprocitentan on top of standard background therapy. A slight and transient HR increase was observed following co-administration 2-7h post dosing, although Exforge HCT® alone did not affect HR, even at higher doses. There is no doubt that aprocitentan is able to produce an additive effect in combination with the triple antihypertensive therapy, however, dose of Exforge HCT® was selected to only partially

decrease blood pressure. Since the proposed indication is treatment of resistant hypertension, which is defined as hypertension that remains uncontrolled despite treatment with maximally tolerated doses of three antihypertensive medications of three different pharmacological classes (Judd 2014), the use of the intermediate dose is not fully supported. Considering that clinical efficacy of aprocitentan was assessed in patients with resistant hypertension treated with standard background therapy (Study D-22.269), data from nonclinical combination study are sufficient to demonstrate proof of concept.

Hypertension, and particularly difficult-to-control hypertension, is associated with a significant risk of end-organ damage. Chronic oral administration of aprocitentan at doses ≥10 mg/kg attenuated DOCA-salt induced increase in MAP without affecting HR. In addition, aprocitentan dose-dependently increased renal blood flow, decreased renal vascular resistance and tended to decrease left ventricular hypertrophy, as suggested by decrease in left ventricular relative weight and plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP). These results suggest possible end-organ damage protection, however, an interpretation is not convincing due to varying results and lack of dose-dependency. Aprocitentan did not improve urine, plasma and renal parameters or relative kidney weight, but managed to increase renal plasma flow and decrease renal vascular resistance, when compared to vehicle control. Kidney histopathology showed no effect on reducing inflammatory processes by aprocitentan. Taking into account that ET_B seems to have an important role in promoting natriuresis in the collecting ducts of kidneys (Dhaun and Webb 2019), blockade of ET_B is possibly associated with impaired natriuresis, which may explain unimproved urine, plasma and renal parameters following administration of aprocitentan. Equivocal findings were also demonstrated in the heart, suggesting that positive effects of chronic administration of aprocitentan on end-organ protection are questionable. Nevertheless, plasma concentrations of aprocitentan were more than 10-fold lower after repeated administration for 4 weeks, compared to single oral administration in DOCA-salt rats. Decrease in plasma concentrations was not observed after multiple-dose administration in humans.

Selectivity of aprocitentan for ET_A and ET_B was assessed in 53 binding and enzyme assays. Following administration of aprocitentan, inhibition greater than 50% was not achieved in any of the assays. Weak inhibition of kainate (30.5%) and leukotriene (28.4%) receptors was measured at 10 µM. Projected IC_{50} values for these targets are >50 µM, providing a margin of at least 14 706- and 51-fold against the binding affinity for ET_A and ET_B receptors, respectively. In addition, a wide margin of more than 1500-fold was observed compared to unbound clinical exposures. Based on provided calculations, aprocitentan is considered selective for ET_A and ET_B receptors at the recommended dose of 25 mg.

The core battery of GLP-compliant safety studies was conducted to evaluate vital organ systems in vitro and in vivo after oral administration of aprocitentan in rats (gavage) and dogs (capsules). In male Wistar rats, the Irwin profile test was performed and aprocitentan had no effect on a battery of behavioral and physiological variables covering the main central and peripheral nervous system functions. Similarly, aprocitentan did not alter respiratory parameters in conscious, freely moving male Wistar rats, confirmed by whole body plethysmography. The potential of aprocitentan for QT-prolongation was assessed in vitro by measuring hERG inhibition in HEK293 cells. At concentrations up to 10 µM, aprocitentan had no relevant effect on hERG channels (inhibition <50%). At 30 µM and 100 µM, inhibition was ≥50%. After construction of concentration-response curve, an IC_{50} of 28.6 μM was determined, which is more than 1150-fold above clinically measured unbound concentrations. Aprocitentan decreased blood pressure and increased heart rate in conscious telemetry equipped normotensive beagle dogs. These non-dose-dependent effects were observed at doses from 10 mg/kg up to 250 mg/kg. Blood pressure lowering effect was also observed with macitentan in normotensive dogs, but not in normotensive rats, suggesting different levels of ET-1 contribution to the vascular tone between species. Decrease in blood pressure was not considered adverse due to expected pharmacological effect of aprocitentan and greater involvement of the ET system in the maintenance of blood

pressure in dogs. Although statistically significant differences ($p \leq 0.05$) in corrected QT interval duration, compared to time-matched vehicle values, were detected at the intermediate dose of 75 mg/kg aprocitentan, these changes were of small amplitude (did not exceed 12 ms for group mean values) and without dose-dependency. Based on Day 1 exposure values from the 4-week toxicity study in the dog (Study T-14.022), unbound C_{max} at 75 mg/kg was approximately 3330 nM, which is 130-fold higher than clinically measured concentrations. According to results from the hERG study and dog cardiovascular safety study, aprocitentan is not expected to induce QT-prolongation at clinically recommended dose. In terms of proposed indication, this nonclinical conclusion should be confirmed in clinical settings.

Pharmacodynamic drug interaction assessment was included in primary pharmacodynamics section to evaluate the efficacy of aprocitentan in lowering blood pressure when administered in combination with standard antihypertensive therapies.

Pharmacokinetics

The pharmacokinetic profile of aprocitentan has primarily been characterized in rat and dog. The same animal species were used in general toxicology program. In vivo investigations on the absorption, distribution, and metabolism of aprocitentan were complemented by a battery of in vitro assays. Bioanalytical methods were developed and validated for all relevant species to comply with regulatory requirements. Plasma concentrations were determined by using liquid chromatography coupled to tandem mass spectrometry, while liquid scintillation counting was used for the quantification of total radioactivity in studies with ^{14}C-radiolabeled aprocitentan.

Pharmacokinetic parameters were evaluated following single oral or intravenous administration in male Wistar rats and male beagle dogs. Free acid form of aprocitentan was used in these experiments. Bioavailability was around 90% after single oral administration in beagle dogs and comparable exposures were demonstrated between dogs and humans, suggesting almost complete absorption. Bioavailability was approximately 41% and T_{max} around 8h after single oral administration in Wistar rats. Taking into account differences in body surface area between species, exposures in rats were lower than those in humans, indicating slow and incomplete absorption. However, PK data from PD studies showed similar exposures between hypertensive/normotensive rats and humans. Aprocitentan showed dose-linearity up to 30 mg/kg in hypertensive DOCA-salt rats after single administration, covering therapeutic dose range. Although gender-related differences in exposure to aprocitentan were observed after repeated dosing in rats, these changes were not noticed in dogs and humans. Notably, overall exposure values were significantly higher in rat toxicity studies, compared to PK and PD studies. As mentioned earlier, PK and PD studies were conducted by using free acid form, while toxicology program was performed by using sodium salt form of aprocitentan. Consequently, the extent of absorption and exposure levels in rats are possibly regulated with solubility and/or dissolution of aprocitentan.

The volume of distribution at steady state, as a general measure of tissue distribution, was in the range of total body water volume in both rats and dogs, indicating significant partitioning of aprocitentan into tissues. This was supported by the presence of a second peak at timepoints later than 1h after intravenous administration in all concentration-time curves, suggesting possible redistribution of aprocitentan from tissues back to circulation. Tissue distribution was investigated with ^{14}C-radiolabeled aprocitentan in rats by using whole-body autoradiography. In line with calculated volume of distribution, total radioactivity was widely distributed into most tissues. The highest radioactivity, except the gastrointestinal mucosa, was measured in liver, bile ducts, kidneys, urinary bladder, blood, lung, pituitary, thyroid, heart, prostate and lacrimal glands at the first sampling point after 8h. In general, tissue levels of radioactivity were lower than those in blood. Exposures in most tissues, excluding liver, kidneys and GIT, were below or near the limit of

quantification at 72h post dose, indicating maintained decrease of radioactivity from tissues. Measurable levels of radioactivity were only present up to 10 days in previously mentioned excretory organs, suggesting the involvement of both biliary and renal elimination pathways. Pigmented and albino rats showed comparable elimination of radioactivity from uveal tract/retina, skin or meninges of the brain, confirming the absence of relevant binding of aprocitentan to melanin. Aprocitentan was present up to 48h in milk samples of lactating rats following oral administration of macitentan. Protein binding of aprocitentan was in the range from 98.3 to 99.9% across species. In the case of highly protein bound compounds, exposure values and safety margins in toxicity studies should be calculated by using unbound concentrations, in accordance with ICH S3A guideline (CPMP/ICH/384/95). The mean blood/plasma ratios were in the range of 0.54–0.69 across species, indicating limited partitioning of aprocitentan into red blood cells.

In vivo metabolism was investigated in bile-cannulated rats following oral and intravenous administration of ^{14}C-radiolabeled aprocitentan. Unchanged aprocitentan was the main entity circulating in rat plasma exceeding 92% of total radioactivity, followed by M1 as the only metabolite at a relative level of about 5%, irrespective of administration route. Interestingly, no absorption was demonstrated after oral administration of M1 in non-bile-cannulated rats. In feces of bile-cannulated rats, unchanged aprocitentan and metabolite M1 were detected. An increase in M1 production was observed after incubation of aprocitentan with fecal homogenates and the occurrence was also confirmed in the absence of hepatocytes, suggesting that M1 is produced by non-enzymatic hydrolysis in the gut. The presence of M1 in rat plasma is probably due to instability of aprocitentan, rather than systemic absorption of M1 from the gut. This was supported by greater amounts of M1 in feces, compared to plasma levels. Unchanged aprocitentan was not present in rat urine, while approximately 10% was detected in rat bile, indicating an extensive metabolism of aprocitentan. None of the metabolites in urine exceeded 6% of total radioactivity, while M8, M9, M10 and M3 were the most notable metabolites in bile. M8, M10 and M3 represent conjugates of aprocitentan with glucose or glucuronic acid and might be potential targets for enterohepatic recirculation. However, only a minor degree of enterohepatic recirculation was demonstrated by using macitentan in the tandem bile duct-cannulated rat model, without any clinical relevance. Following intravenous administration, excretion in bile was predominantly represented, suggesting the formation of conjugative metabolites from aprocitentan as the main elimination pathways. On the other hand, excretion in bile after oral administration was limited by unabsorbed amount of aprocitentan, as well as the extent of M1 formation in the gut. As a result, higher percentage of excretion in urine and feces was observed compared to intravenous administration.

Metabolic profiling studies were performed by using high performance liquid chromatography combined with ultraviolet, mass spectrometry, and/or ^{14}C-radiodetection. Five metabolic pathways were described: 1) hydrolysis to M1, 2) N-glucosidation to M3, 3) N-glucuronidation to M8, 4) oxidative debromination to M26 followed by glucuronidation to M10, 5) N-oxidation to M9 followed by glucuronidation to M22. According to the measured radioactivity, all these pathways were represented in rats, while hydrolysis to M1 and glucosidation to M3 were the two main elimination pathways in humans. Metabolites of aprocitentan were formed by oxidation, hydrolysis and glucuronidation. The enzymes responsible for glucuronidation were identified, UGT1A1 and UGT2B7. The applicant assumes that hydrolysis occurs in part spontaneously, i.e. without involvement of enzymes, and in part by cytosolic hydrolases, which could not be identified. The applicant pointed out that drug-drug interactions (DDI) based on these hydrolases were not yet described and therefore are unlikely.

In addition, cross-species comparison of metabolic profiles was conducted in vitro after incubation of ^{14}C-radiolabeled aprocitentan with liver microsomes or hepatocytes from different species. Metabolites M1 and M3, as well as secondary and tertiary metabolites M2, M4, M5 and M6 were detected in human hepatocytes. All these metabolites were observed in rat hepatocytes, while M1, M2 and M5 were also present in dog

hepatocytes. Therefore, the selection of rat and dog as relevant species for toxicology program is considered appropriate. Several minor human-specific metabolites were detected in the human ADME study (Study D-18.105), that were not observed in vitro. M29 was detected in human plasma, but at levels below relevant threshold of 10% of total radioactivity. A1 and A3-A5 were excreted at low levels in human urine and/or feces and represented secondary or tertiary metabolites, for which a precursor was observed in nonclinical species. From the nonclinical point of view, these human-specific metabolites are not of toxicological concern and no further characterization is required.

Although no dedicated excretion balance studies were conducted, information on the excretion of aprocitentan after intravenous and oral dosing was generated as part of the metabolic profiling study in bile-cannulated rats. Overall recovery exceeded 88% of total radioactivity at 72h post oral dosing, indicating almost complete excretion and adequacy of study design. Biliary excretion was the main route of excretion, accounting for 70-78% of total radioactivity after intravenous and 48-52% after oral administration of ^{14}C-labeled aprocitentan. Renal excretion represented less than 22% of total radioactivity, regardless of the administration route. Radioactivity in feces after oral administration likely represented unabsorbed fraction of aprocitentan, supported by unchanged aprocitentan and gut metabolite M1 as the most prominent entities.

According to results from the ADME study, renal excretion is the main elimination pathway in humans. Interestingly, the percentage of unchanged aprocitentan detected in urine and feces was comparable between humans and rats, indicating a similar extent of metabolism across species. However, biliary excretion was the main route of excretion in rats. The main reason for observed differences in excretion between rats and humans is the molecular weight (MW) cut-off for biliary excretion. This value is approximately 325 ± 50 for rats and 500 ± 50 for humans (Millburn 1967, Millburn 1970). Since aprocitentan has a molecular weight of 546.2, it is expected that unchanged entity and metabolites would result in higher percentage of biliary excretion in rats, compared to humans. A similar situation was also observed with macitentan, a structurally related endothelin receptor antagonist.

Aprocitentan was able to inhibit and/or induce several CYP enzymes, UGT enzymes and transporter proteins. The most pronounced effect was observed for CYP3A4 (inhibition and induction). A clinical DDI study revealed no relevant net effect of aprocitentan on the PK of midazolame (a CYP3A4 test substrate); midazolam AUC increased by 14% when administered along with aprocitentan. However, separating the consequences of CYP3A4 induction from the effects of CYP3A4 inhibition is important for situations in which aprocitentan is discontinued. In this case, CYP3A4 inhibition is terminated virtually immediately whereas the CYP3A4 expression level remains elevated for a longer time. This could lead to a transient decrease in the plasma level of midazolam or other CYP3A4 substrates. However, the slight increase in midazolam plasma level during steady state would blunt any potential transient decrease so that this is not considered as concern.

Toxicology

Apart from expected exaggerated pharmacology findings and findings previously reported for the same class of agents (dual ERA antagonists), no other noteworthy outcomes were identified. In the rat and dog repeat-dose toxicity studies with aprocitentan, the heart (dog), testes (rat, dog), liver (rat, dog), thyroid (rat), and nasal cavity (dog) were identified as the main target organs. Additionally, a slight and reversible changes in haematology parameters were observed in all dog toxicity studies. Increased kidney weight with increased appearance of a brown pigment in tubular epithelia of the outer cortex was reported in one rat 26-week study.

Regarding tolerability of aprocitentan, the administration of the highest aprocitentan doses resulted in slight to even marked body weight loss in some animals (especially females) that was occasionally accompanied

with reduced food consumption requiring food supplementation across all studies in both species. However, when the no-effect dose level (NOEL) on body weight/body weight gain and food consumption in conjunction to clinical signs across rat and dog pivotal repeat-dose toxicity studies is compared to the aprocitentan total or free exposure in relation to human exposure at the 25 mg once daily dosing (maximal recommended human dose, MRHD), it can be stated that aprocitentan was well tolerated up to high multiples of human exposure (i.e. up to 100-fold the human exposure (free) in dogs and up to 63-fold in rats at MRHD).

Periarteritis/arteritis of coronary arteries is considered a dog-specific finding, since no heart findings were observed in rats and it is known from the literature that dogs are prone to hemodynamically induced vascular changes. Exaggerated pharmacology of aprocitentan on ET_A receptors (inhibition of vasoconstriction), marked hypotension, sustained vasodilatation in the coronary vascular bed and reflex tachycardia may alter flow dynamics and lead to increased shear stress and tension on the coronary wall with subsequent microscopic trauma. However, no blood pressure lowering effect could be identified in any of the dog repeat-dose toxicity study during cardiovascular examination performed usually 3h post-dosing (the time point at which the effect on BP was observed in safety pharmacology study). This might be attributed to the impreciseness and low sensitivity of the blood pressure measuring method used (forelimb or tail cuff) as well as to the frequency and duration of measurement (once or twice during the experiment). In addition, the excitement of the animals during manual measurements might have masked the precise assessment of blood pressure. In contrast, the reduction of blood pressure is clearly identified in a dedicated safety pharmacology assessment in dogs, which included telemetry devices with continuous recording 24 h before and after dosing.

Dilation of seminiferous tubules, a pharmacological effect of aprocitentan on smooth muscle cells, was seen in all toxicity studies performed in both species, with the exception of 26-week rat study T-14.036. The severity of this change was generally minimal, and all findings were fully reversible. As a consequence of such dilation, the propulsion of seminal fluid may be impaired. If this situation remains for a long time, the backlog of seminal fluid can lead to an increase of pressure to the germinal epithelium of the tubules, which can then eventually lead to signs of degeneration/atrophy of tubular epithelium. While tubular dilation is a functional change considered not to be adverse, degeneration is considered as an adverse effect. Since degeneration/atrophy of testicular tubules is also a well-known background finding in male rats (with the mean background incidence around 5-6%, but the incidence may be higher than 30% based on Harlan 2014 report compiled from 80 13-week studies), there may be challenges in determination of the relationship of the observed degeneration to the drug treatment. In initial assessment of the data, the assessor was of opinion that the determination of the relationship between tubular degeneration as a drug-related (dilation induced) or background finding was not uniformly addressed across the rat studies. However, based on detailed assessment of NOAEL values in repeat-dose toxicity studies and the fertility study, in which the principle of dose-dependence and the correlation of the number of tubular dilations with the tubular degenerations was followed, the NOAELs obtained in each study is considered to be adequate. Moreover, animals in fertility study presented with normal sperm counts according to histology and seminology examinations, indicating that aprocitentan does not influence spermatogenesis.

Nasal cavity findings have been observed in animals treated with ERAs. Changes in the nasal cavity (enlarged turbinates characterised by submucosal hyperostosis and/or hyperchondrosis associated with congestion, vascular dilation, oedema, and goblet cell proliferation) were seen in dogs at doses $\geq$ 25 mg/kg/day in the 13- and 39-week studies performed with aprocitentan. These histological findings might be related to the clinical observation of noisy respiration in some treated dogs. All changes were fully reversible after the recovery period. In studies performed with macitentan, nasal cavity changes were noted in carcinogenicity study in mice as well. These findings in mice are related to local vasodilator effects of macitentan formulation on nasal mucosa during the dosing procedure (e.g., reflux of the formulation, withdrawal of the tube). The

absence of nasal cavity findings in rat toxicity studies performed with aprocitentan and macitentan are uniform and might be related to the lower incidence of reflux of the formulation into the nasal cavities or less sensitivity to such effects in comparison to mice.

Increased kidney weights at ≥100 mg/kg/day, with increased appearance of a brown pigment macroscopically and histologically characterized by brownish pigment in tubular epithelia of the outer cortex, localized mainly at proximal tubules at all dose levels, was an isolated finding of 26-week rat toxicity study T-14.036. An increased appearance of a brown pigment in the kidney was reported at all dose levels. Special stains for lipofuscin, hemosiderin, bilirubin, and bile salts did not provide a consistent characterization of the pigment. The morphology of the kidney was otherwise not altered and there was no evidence of tubular degeneration. The finding was partially reversible in females and fully reversible in males. The applicant states that no changes in kidney-related clinical chemistry parameters were observed. Therefore, this finding was considered as non-adverse and incidental. However, Opsumit (macitentan) EPAR describes similar kidney findings in 26-week repeat dose toxicity study in rats as well. A thorough review of clinical chemistry data potentially related to kidney function, organ weights and histopathological findings in macitentan and aprocitentan repeat-dose toxicity studies revealed no consistent pattern regarding kidney variables. Although it is intriguing that both substances caused such unexplainable histopathological kidney findings, each only in one isolated rat 26-week repeat-dose toxicity study, it can be agreed that, in the absence of any other consistent data describing kidney function, these findings might not indicate kidney toxicity. Moreover, when data from macitentan study were presented in more details, it could be seen that the hyaline droplets / pigment could be seen in control animals, as well. It is not clear at present if these findings might be related to the methodological tissue processing across different test facilities. It can be noted from the submitted documentation that necropsies and histological preparation in both studies in which this brown pigment was noted (macitentan T-05.045 and aprocitentan T-14.036) were conducted in the same test facility, while other rat studies in which this finding was not observed (including macitentan rat carcinogenicity study) were performed in other test facilities.

Systemic exposure to aprocitentan was monitored all non-pivotal and pivotal repeat-dose toxicity studies in rats and dogs. The pivotal rat studies were performed using sodium salt form of aprocitentan, based on the results of the 2-week rat pilot study T-14.011, where the administration of sodium salt form resulted in approximately 6-fold higher systemic exposure compared to treatment with free acid of aprocitentan. Dogs were dosed with aprocitentan (free acid). The exposures to aprocitentan were slightly higher in female than in male rats, while no sex differences were observed in dogs. Consistent with drug-metabolizing enzyme induction properties of aprocitentan, the exposures to aprocitentan were lower at the end of the treatment periods in comparison to those on the first day of administration in rats. In contrast to rat studies, there was no reduction of exposure at the end of the treatment period in dogs. In 39-week study, the week 39/day 1 exposure ratios were even slightly higher. These differences in rat and dog aprocitentan exposure while having similar liver findings (centrilobular hepatocellular hypertrophy) can be explained with the differences in metabolic pathways between rats and dogs and liver enzymes involved in metabolism. In the rat, aprocitentan repeated treatment led to a dose-dependent increase in the mRNA of CYP3A1, CYP2B1, CYP2B2, UGT1A1, UGT1A6, and UGT2B1, while dose-dependent CYP3A12 expression (up to 5 fold) was observed in dogs. In rats, the upregulation of CYP and UGT genes is in agreement with the observed decreases of aprocitentan exposure in rats over time. On the other hand, the single pathway observed in microsomes and hepatocytes of dogs was the formation of M1, which is not produced by P450 enzymes. Therefore, CYP3A12 induction is considered to be attributable to centrilobular hepatocellular hypertrophy, but is not expected to have an impact on aprocitentan exposure.

Rodent-specific thyroid effect of aprocitentan (thyroid follicular cell hypertrophy compatible to the increased liver metabolism and thyroid hormone elimination) is attributable to the species-specific thyroid hormone transport mechanisms. In humans, more than 99% of thyroid hormones are bound to thyroxine binding globulin (TBG), which protects T4 from degradation by UGTs. In dogs, thyroxine binding to TBG is less than in humans, but in rats there is almost no TBG expressed. Therefore, thyroid hormones are not bound to plasma globulins in rodents and are easily accessible for degrading enzymes.

Aprocitentan was negative in genotoxicity test battery (in vitro mutagenicity and chromosome aberration assay, micronucleus test in rats). Based on data estimated from macitentan carcinogenicity studies in rats and mice, aprocitentan can be considered not carcinogenic.

Aprocitentan did not affect male gonadal function, mating behaviour and fertility in rats up to the highest tested dose of 250 mg/kg/day (NOAEL) during 13-week treatment period. There was also no evidence of a male-mediated effect on early gestation of untreated females. Minimal dilation of the testes seminiferous tubules was observed in one 50 mg/kg/day and four 250 mg/kg/day males. Although increased incidence of tubular degenerations occurred as well in treated groups when compared to control (1 control animal, 2 animals at 10 mg/kg/day, 8 animals at 50 mg/kg/day, and 4 animals at 250 mg/kg/day), there was no dose-dependence in treated animals and no correlation with the tubular dilation number in the corresponding groups. Therefore, the effect was judged as non-treatment related and the NOAEL value for this study can be confirmed to be 250 mg/kg/day.

Female mating performance, oestrous cycle, ovary weights, and post-implantation parameters were not affected by treatment with aprocitentan up to 250 mg/kg/day. However, minimally increased incidence of pre-implantation loss and reduced corpora lutea numbers were observed at higher doses, with a NOAEL of 10 mg/kg/day, resulting in an exposure-based safety margin of 2.3 (8.6). Slightly increased pre-implantation loss was noted with ambrisentan as well (Volibris EPAR).

Based on studies performed with macitentan, aprocitentan is considered teratogenic in animals. Although initially planning to use aprocitentan-derived data from macitentan EFD studies and to rely on WoE approach based on biological plausibility and class-effect, the Applicant ultimately decided to conduct the aprocitentan-specific EFD programme. A full characterization of the teratogenic potential of aprocitentan in rats and rabbits is completed during this MAA procedure.

Results of a dose range-finding study in pregnant rats indicated that aprocitentan may not be teratogenic at approximately 2 (5)-fold the exposure at MRHD (T-22.029). Exposure of 140 µg*h/mL in terms of $AUC_{0\text{-}24h}$ in this preliminary study with aprocitentan 10 mg/kg/day was observed with negative teratogenicity result. In contrast, teratogenicity was previously observed in the study T-12.804 performed with macitentan at the aprocitentan exposure as low as 36.8 µg*h/mL. However, important feature of studies with macitentan is that they evaluated a combination of two potent ERAs (macitentan and its M6 metabolite) at similar exposures. First, macitentan levels increase in plasma, and then, when macitentan levels decline, M6 levels increase. Therefore, the endothelin system is maximally blocked for 24 hours. In contrast, only one ERA (aprocitentan) is present in the animals in studies with aprocitentan, which has distinct pharmacological properties from macitentan. The most important differences between macitentan and aprocitentan are the potencies on the ET_A receptor in different assays (slightly lower for aprocitentan) and their binding mode at the ET_A receptor, i.e., aprocitentan is surmountable by ET-1, whereas macitentan is not, due to its longer residence time at the receptor level. Moreover, the exposures of aprocitentan and macitentan at which desired pharmacological effect (i.e. blood pressure decrease) in *in vivo* animal model (DOCA-salt model) occurs are compared to the exposures eliciting teratogenicity. Additionally, when comparison is made for aprocitentan and macitentan exposures at which desired pharmacological effect (i.e. blood pressure

decrease) occurs in *in vivo* animal model (DOCA-salt model) to the exposures eliciting teratogenicity in EFD studies, it can be seen that macitentan shows teratogenicity already at doses/exposures that elicit half maximal pharmacological efficacy in DOCA-salt rats, while no teratogenicity was observed in a preliminary rat EFD study (T-22.029) with aprocitentan at doses/exposures that are 2.4-fold higher than the exposure that elicits maximal pharmacological efficacy of aprocitentan in DOCA-salt rats.

The absence of teratogenicity is clearly demonstrated in subsequent confirmatory study in rats (T-22.030) as well as in rabbits (studies T-22.027, T-22.028) up to exposures similar or slightly higher that exposure in humans at MRHD. The EFD programme of aprocitentan is carefully designed and thoroughly performed. It is evident that, unlike macitetnan, aprocitentan has no teratogenic potential at exposures relevant to desired pharmacological effect. It is acknowledged that the applicant considered to address the teratogenicity potential of aprocitentan more in relation to pharmacological differences between aprocitentan and macitentan than in relation to characterize "teratogenicity profile" of aprocitentan, i.e. to assess the actual risk than to identify a potential hazard. A potential hazard can already be anticipated based on biological plausibility and class effect. This is reflected by the high dose selection, which is not in line with the ICH S5 recommendations since is provides the exposure multiple only slightly above the MRHD. Therefore, the only conclusion provided by the EFD programme of aprocitentan is that aprocitentan, unlike macitentan and other marketed ERAs, is not teratogenic at exposures similar or slightly above human exposure at MRHD. However, it is not known which exposures may elicit adverse effects on embryo-foetal development (see required PI modifications).

ERAs are considered as well-known powerful teratogens during early pregnancy due to the role of endothelin in neural crest cell migration and/or proliferation in the developing embryo. Disruption of this process produces craniofacial and cardiovascular malformations typical to those noted at all dose levels in all macitentan EFD studies. Considering that macitentan studies are in fact combination toxicology studies and taking into account pharmacological differences between aprocitentan and macitentan presented above, the background for conducting stand-alone aprocitentan EFD studies is sufficiently justified with regard to 3R principles. Nevertheless, since the principal potential of ERAs to induce teratogenicity is acknowledged, these new results do not change previous recommendations (i.e., the contraindication during pregnancy and in WOCBP).

Aprocitentan partitioned into the milk of lactating rats (see PK section). Since aprocitentan PPND assessment was based on study performed with macitentan and the NOAEL could not be established, breast-feeding is a contraindication for aprocitentan use.

Regarding impurities, a small difference in impurity levels presented in table 2.6.7.4 of Module 2.6.7 (Toxiology tabulated summary) and Module 3.2.S.3.2, used to calculate the proposed specification limit, was noted during the assessment. The differences are attributed to the different units used, i.e. the results were given as weight % in module 3.2.S.3.2, (0.71% w/w of ACT-080803 and 0.19% w/w of ACT-730959, corresponding to the area % values given in the Certificate of Analysis no. 15015112 and presented in module 2.6.7, based on the correction factors (CFs) determined during method validation (ACT-080803 with CF of 1.13 and ACT-730959 with CF of 1.73).The specifications for actual impurities ACT-080803 and ACT-730959 are justified for an aprocitentan daily dose of up to 25 mg.

Regarding the assessment and control of mutagenic impurities based on ICH M7 guideline, some impurities (e.g. ACT-053052, ACT-284043, ACT-056482, ACT-283437, ACT-730960, ACT-080803) were commented to be negative in Ames test, with a link to a study report with Ames test conducted with aprocitentan only. The applicant submitted missing study reports during the procedure and the reports were assessed to be negative. All studies, with the exception of T-04.072 which relates to impurity ACT-080303, were GLP and

OECD guideline 471 compliant. Although the AMES test for ACT-080303 was not GLP and OECD compliant, no AMES test is actually necessary for this impurity according to ICH M7, since the substance has no *in silico* (Derek, Leadscope) alert for mutagenicity. Additionally, being a degradation product and a metabolite which represents 5% of the systemic aprocitentan exposure, ACT-080803 was present in many batches that were tested in toxicity studies, including the micronucleus test and carcinogenicity studies. Furthermore, none of other impurities that were tested in GLP AMES tests (ACT-053052, ACT-284043, ACT-056482, ACT-283437, ACT-730960) had an *in silico* alert but were tested anyway due to suspicious structural properties or as a part of standard company's package.

Phototoxicity of aprocitentan was estimated from in vivo hairless rats phototoxicity study with macitentan (T-09.061). No relevant risk of phototoxicity for patients treated with aprocitentan at 12.5 or 25 mg per day can be expected.

Aprocitentan is not considered PBT compound. It is not a readily biodegradable. The calculated half-lives for aprocitentan are indicating that it is not persistent in water and total system, but its transformation products are very persistent in water. Dissipation rates in sediment weren't determined due to insufficient decrease over the incubation period so persistence of aprocitentan and its transformation products in this system cannot be anticipated. Based on toxicity tests and PEC/PNEC ratios, there was no anticipated risk for surface and ground water, microorganisms in STP or sediment compartment of environment following prescribed use of aprocitentan.

2.5.7. Conclusion on the non-clinical aspects

Primary PD studies clearly showed that aprocitentan can lower blood pressure in animal models, alone as well as add-on to other anti-hypertensive drugs. The toxicology studies revealed effects that are already known from other endothelin receptor antagonists. Particularly because aprocitentan is an active metabolite of the already approved compound macitentan, no unexpected findings occurred.

The marketing authorization for aprocitentan is approvable from non-clinical perspective, since major objections and other concerns were adequately answered.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Clinical pharmacology studies

Study	Study objectives
Bioequivalence study	
ID-080-110	To demonstrate bioequivalence between two batches of aprocitentan with different drug substance PSD and investigate safety and tolerability
Single- and multiple-ascending dose (including investigation of food, age, and sex effect) study	
AC-080-101]	To investigate single- and multiple-dose PK, PD, safety, and tolerability of aprocitentan and assess the effect of age, sex, and food on PK
Absorption, distribution, metabolism, and excretion study	
AC-080-104	To investigate the mass balance, PK, metabolism, safety, and tolerability of aprocitentan
Ethnic sensitivity study	
ID-080-107	To investigate the multiple-dose PK, safety, and tolerability of aprocitentan in Japanese compared to Caucasian subjects
Special population studies	
AC-080-105	To investigate the PK safety, and tolerability of aprocitentan in subjects with severe renal function impairment (inclusion criterion eGFR 15–29 mL/min/1.73 m^2) compared to healthy subjects (eGFR ≥ 90 mL/min/1.73 m^2)
ID-080-109	To investigate the PK safety, and tolerability of aprocitentan in subjects with moderate hepatic impairment (inclusion criterion Child-Pugh Grade B; score 7–9) compared to healthy subjects
Drug-drug interaction studies	
AC-080-103	To investigate the effect of aprocitentan on the PK, safety, and tolerability of the CYP3A4 substrate midazolam and its metabolite
AC-080-106	To investigate the effect of aprocitentan on the PK, safety, and tolerability of the BCRP substrate rosuvastatin
Pharmacodynamic mechanistic study	
AC-080-102	To evaluate the effect of aprocitentan on body weight and investigate safety and tolerability in healthy subjects on a high sodium diet
Safety study	
ID-080-108	To investigate the effect of therapeutic and supratherapeutic doses of aprocitentan on the QTc interval and investigate safety and tolerability

BCRP = breast cancer resistance protein; CYP3A4 = cytochrome P450 isoenzyme 3A4; eGFR = estimated glomerular filtration rate; PD = pharmacodynamics; PK = pharmacokinetics; PSD = particle size distribution; QTc = QT interval corrected for heart rate.

Phase 2 and Phase 3 studies providing efficacy and safety data

• **Study** • **[Doc No]**	• **Study objectives**	• **Number of randomized subjects**	• **DB treatment/ total daily dose**	• **Treatment duration**	• **Type of** • **control/blinding**
• **Dose-finding Phase 2 study**				• **Monotherapy**	
• Study 201	Efficacy, PK, and safety in adult subjects with HTN (grade 1 and 2)	N=490	• Aprocitentan 5 mg (N=82) • 10 mg (N=82) • 25 mg (N=82) • 50 mg (N=81) • Lisinopril 20 mg (N=81) • Placebo (N=82)	4–6-week SB placebo RI period 8-week DB randomized treatment period 2-week SB placebo WD period	Placebo and active reference DB
• **Phase 3 study**				• **Add-on therapy**	
• Study 301 (PRECISION)	Efficacy and safety and long-term efficacy and safety in adult subjects with HTN (grade 1 and 2) uncontrolled despite the use of 3 anti-HTN medications of different pharmacological classes	N=730	Aprocitentan 12.5 mg (N=243) 25 mg (N=245) • Placebo (N=242)	4-week SB placebo RI period 48-week randomized treatment period in 3 parts: • 4-week DB part 1 with aprocitentan 12.5 mg or 25 mg or placebo • 32-week SB part 2 with aprocitentan 25 mg • 12-week DB-WD part 3 with aprocitentan 25 mg or placebo	Placebo in part 1 and part 3. DB in part 1 and part 3, SB in part 2.

DB = double-blind; HTN = hypertension; N = number of subjects in the Full analysis set; RI = run-in SB = single-blind; WD = withdrawal.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Concentrations of aprocitentan were determined in human plasma using validated LC-MS/MS method at Actelion Pharmaceuticals Ltd, Switzerland. Bioanalytical method at Actelion site was satisfactorily validated with respect to precision, accuracy, sensitivity and selectivity, recovery, matrix effect, carryover and stability

in accordance with the relevant regulatory guidelines. Performed ISR analysis meet the acceptance criteria according to ICH M10 bioanalytical method guideline.

In study AC-080-101 endothelin-1 was measured by Algorithme Pharma, 575 boul Armand-Frappier, Laval, Quebec H7V4 B3, Canada using a commercially available luminescent immunoassay kit from Bio-Techne (Minneapolis, MN, USA). For study AC-080A201 the assay of ET-1 was organized through a central laboratory.

In DDI studies, concentrations of rosuvastatin, midazolam and 1-hydroxymidazolam were measured with a validated LC-MS/MS method. Performed ISR analysis meet the acceptance criteria according to ICH M10 bioanalytical method guideline.

In clinical study 301, valsartan concentrations were measured in urine samples using LC-MS method, in order to test patient adherence. Appropriate analytical method data were provided.

The binding of ACT-132577 to human plasma proteins using rapid equilibrium dialysis (RED) was determined at the Swiss BioQuant AG, Switzerland.

Absorption

Aprocitentan is practically insoluble in aqueous media over the physiological pH.

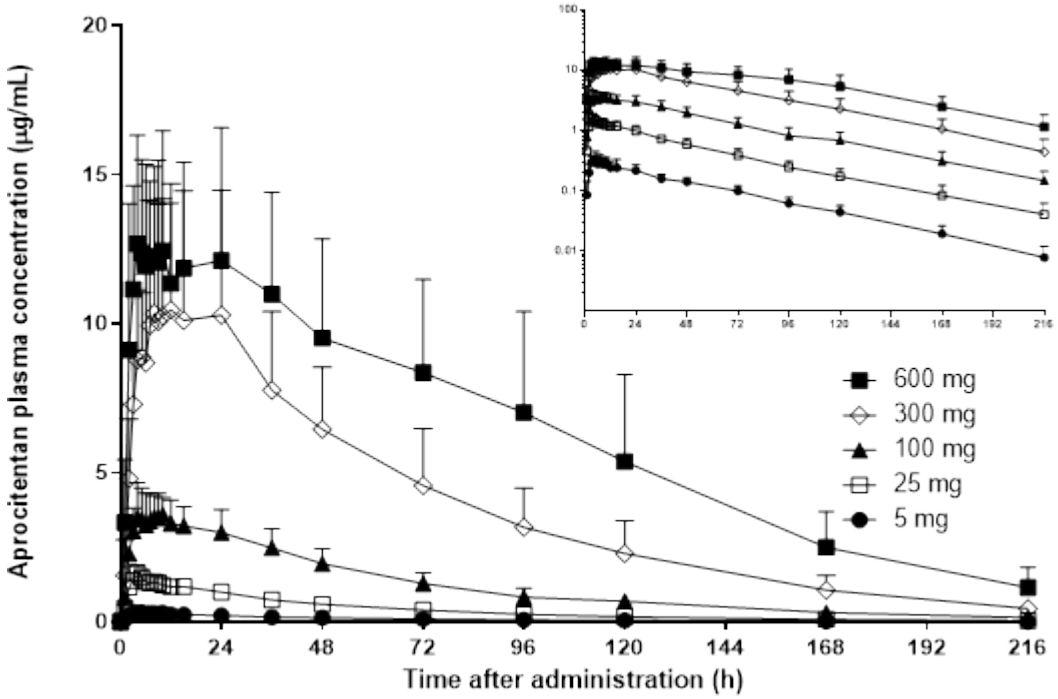
In vitro evaluation of aprocitentan permeability on MDCKII cells using common reference compounds, suggested that aprocitentan could be a moderate to high permeability compound.

An absolute bioavailability study has not been performed. Based on the mass balance study, at least 52% of the administered dose is absorbed.

The PK characteristics of aprocitentan in healthy adult subjects after single-dose administration were evaluated in 5 clinical pharmacology studies.

At fasted conditions, in healthy adult subjects, aprocitentan at doses up to and including 50 mg, had a median t_{max} between 3 and 5 h. After reaching C_{max}, aprocitentan plasma concentrations decreased slowly with a geometric mean $t_{½}$ of approximately 46 h across all studies.

Arithmetic mean plasma concentration (+SD) vs. time profiles of aprocitentan after a single dose of aprocitentan 5–600 mg in fasted healthy subjects on a linear and semilogarithmic scale (n = 6/dose; study AC-080-101).



Two oral formulations were developed and evaluated during the clinical development programme: an HPMC capsule (used in Phase 1 and Phase 2 studies) and a film-coated tablet, intended for commercial use (used in Phase 1 and Phase 3 studies).

The effect of food on the PK of aprocitentan was investigated using the capsule formulation after administration of a dose of 100 mg aprocitentan in fed and fasted states in study AC-080-101.

Investigation of the effect of food

Study #	Aprocitentan dose	Population	n	C_{max} [µg/mL]	t_{max} [h]	AUC_{0-t} [µg*h/mL]	$AUC_{0-\infty}$ [µg*h/mL]	$t_{½}$ [h]
AC-080-101	100 mg	HS, adult	6	3.76	9.0	244.14	254.26	46.8
				2.96, 4.77	4.0, 10.0	191.04, 312.00	198.20, 326.18	40.2, 54.6
	100 mg + food	HS, adult	5	5.98	5.0	292.63	304.10	50.5
				5.10, 7.01	5.0, 12.0	195.99, 436.92	206.83, 447.14	39.0, 65.4

Though some effect of food on the single dose PK of 100 mg aprocitentan is observed, this difference is considered of limited clinical relevance for a daily intake of therapeutic doses. In the pivotal clinical trial 301 aprocitentan was administered irrespectively of food intake. Hence, the suggestion, that a 12.5 or 25 mg once daily dose aprocitentan can be taken with or without food is considered acceptable.

Distribution

Volume of distribution

The geometric mean Vz/F in healthy subjects in the different studies was approximately 20 L.

Plasma protein binding and cell partitioning

Plasma protein binding was approximately 99% across studies. This is in line with the PPB determined in vitro of 99.5% in human plasma.

The estimated blood/plasma ratio based on C_{max} following oral administration of ^{14}C-radiolabeled aprocitentan (study AC-080-104) was 0.59; for $AUC_{0-\infty}$ the ratio was 0.63, indicating limited partitioning of aprocitentan into red blood cells, which was in the range of 0.54–0.69 observed in vitro in different species.

Elimination

Clearance

Healthy subjects had a CL/F of approximately 0.30 L/h.

Half-life

After reaching C_{max}, aprocitentan plasma concentrations decreased slowly with a geometric mean $t_{½}$ of approximately 46 h across all studies.

Metabolism

In plasma, nearly exclusively unchanged aprocitentan was detected (94.3% of the total radioactivity of the sample; study AC-080-104). The only metabolite detected with a relative abundance of more than 1% of the total radioactivity was metabolite M29 with 4.5% of total radioactivity.

A summary of the metabolic pathways and the structural dependency of metabolites of aprocitentan is given in the preclinical section.

Excretion

The majority of aprocitentan and its metabolites was excreted in urine, with a geometric mean recovery of approximately 52% of the administered radioactive dose, while approximately 25% of the dose was excreted in faeces.

Aprocitentan was mostly excreted as metabolites, with 0.2 and 6.8% of the administered dose excreted as unchanged aprocitentan in urine and faeces, respectively.

Two metabolic pathways contributing to ≥ 25% of ^{14}C-radioactive aprocitentan elimination were detected:

N-glucosidation of the sulfamide moiety of aprocitentan to M3 (24.3% urine, 0.8% faeces). This accounted for 25.2% of the administered dose.

Hydrolysis of the sulfamide moiety to the corresponding aminopyrimidine of aprocitentan to form M1 (10.3% faeces, 1.7% urine). M1 in turn undergoes several reactions with most notably: a) cleavage to M13 (0.8% urine) with further oxidation to A1 (5.1% urine, 1.3% faeces); b) cleavage to M5 (0.7% urine) followed by N-oxidation to M6 (4.5% urine) and O-oxidation to M16 (4.3% urine, 0.4% faeces). Other metabolites formed from M1 include A4 (0.2% faeces), A5 (0.8% faeces), M4 (0.9% urine), and M11 (0.4% faeces). Overall, elimination through M1 and its metabolites accounted for 31.5% of the administered dose.

Dose proportionality and time dependencies

After multiple-dose administration, results from the statistical analysis indicated that C_{max} and AUC_{τ} increased dose proportionally for doses up to 100 mg, with the slope estimate and 90% CI for both C_{max} and AUC_{τ} within the critical interval of 0.77–1.23.

After o.d. study treatment administration in fasted conditions, steady-state conditions were reached in healthy adult subjects by Day 8 of treatment.

Over the different studies, at a dose of 25 mg aprocitentan in healthy subjects at steady-state conditions, median t_{max} and geometric mean C_{max} and AUC_{τ} were approximately 4 h, 4 µg/mL, and 77 µg·h/mL, respectively. C_{trough} between studies in healthy adult subjects on Day 8 was 2.50–2.85 µg/mL for the 25 mg dose. The accumulation index (AI) of aprocitentan was approximately 3. The $t_{½}$ was similar to that observed after single-dose administration, with a geometric mean $t_{½}$ of about 46 h.

Intra- and inter-individual variability

When comparing the exposure expressed as Cmax and AUC0-∞ for single-dose or Cmax and AUC τ for multiple-dose Phase 1 studies, the inter-subject variability was low. For the therapeutic dose of 25 mg, the CV% ranged from 8 to 28%.

Pharmacokinetics in target population

The pharmacokinetics of aprocitentan are considered similar in healthy subjects and in patients.

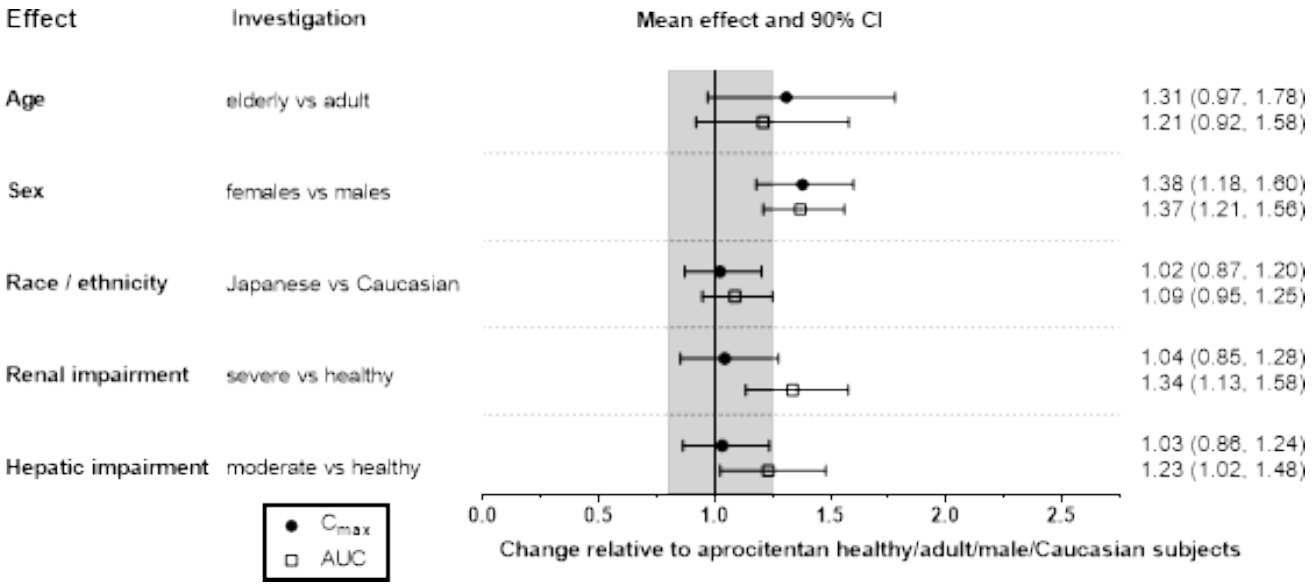
Special populations

There were no intrinsic factors identified for which dose adjustment would be needed:

Age, sex, body size, and race/ethnicity did not influence exposure to aprocitentan to a clinically relevant extent. Therefore, dose adjustment for these factors is not needed.

There is no need for dose adjustments in subjects with any degree of renal impairment with eGFR >15 mL/min/1.73 m2 or subjects with mild or moderate HI.

Effect of intrinsic factors on aprocitentan PK (data are presented as change relative to aprocitentan administered to healthy/adult/male/Caucasian subjects [test/reference] with 90% CI)



The PK of aprocitentan was not studied in patients with severe Hepatic Impairment.

However, there were only very few elderly healthy subjects included in the PK studies. In addition no patients older than 71 are evaluated in phase 1 studies.

Number of subjects with PK samples in clinical studies (including phase 2 and phase 3 studies) with aprocitentan by age category

	Age 65–74 (Older subjects number/ total number)	Age 75–84 (Older subjects number / total number)	Age 85+ (Older subjects number / total number)
Total	219/1032	40/1032	0/1032

Pharmacokinetic interaction studies

There are two main, independent, elimination pathways of aprocitentan (formation of M3) through glucosidation and formation of M1 through a combination of chemical and enzyme-mediated hydrolysis.

Given that aprocitentan is eliminated via other pathways independent of UGT, it is unlikely that inhibition of these transporters would lead to clinically relevant changes in aprocitentan concentrations. The majority of M1 is considered to result from chemical rather than enzyme-mediated metabolism. Therefore, metabolism of aprocitentan is not impacted by drugs that are inhibitors or inducers of metabolizing enzymes or drug transporters.

Aprocitentan is a substrate of P-gp and BCRP transporters in vitro. However, as aprocitentan has a high permeability across cell membranes, the cellular uptake is mainly driven by passive diffusion. Moreover,

given that the clinical studies showed dose-proportional PK in the range of 5–100 mg aprocitentan o.d., the role of both efflux transporters in the oral absorption of aprocitentan is considered to be limited.

In vitro studies indicated that hepatic uptake of aprocitentan was mostly driven by passive diffusion and was not dependent on OATP transport.

As only small amounts of aprocitentan (i.e., 0.2%) were excreted unchanged in urine, inhibition or induction of renal transporters would not result in a clinically relevant change.

Aprocitentan as perpetrator

In vitro data of aprocitentan with CYP enzymes and drug transporters and the results of midazolam (CYP3A4) DDI studies indicate that aprocitentan does not influence the PK of drugs that are substrates of CYP enzymes or most of the drug transporters investigated.

In vitro studies are inconclusive regarding the potential of aprocitentan to induce CYP1A2 or CYP2B6. In vivo induction cannot be excluded. Caution is recommended when aprocitentan is co-administered with CYP1A2 substrates with a narrow therapeutic index.

Aprocitentan inhibited OATP1B1 (IC50=19 µM), OATP1B3 (IC50=27 µM), BSEP (IC50=50 µM), NTCP (IC50=14 µM), OAT1 (IC50=4.7 µM), OAT3 (IC50=1.5 µM), BCRP (IC50=5.7 µM), P-gp (IC50 > 70 µM). The potential for OAT1 and OAT3 inhibition was not investigated in vivo.

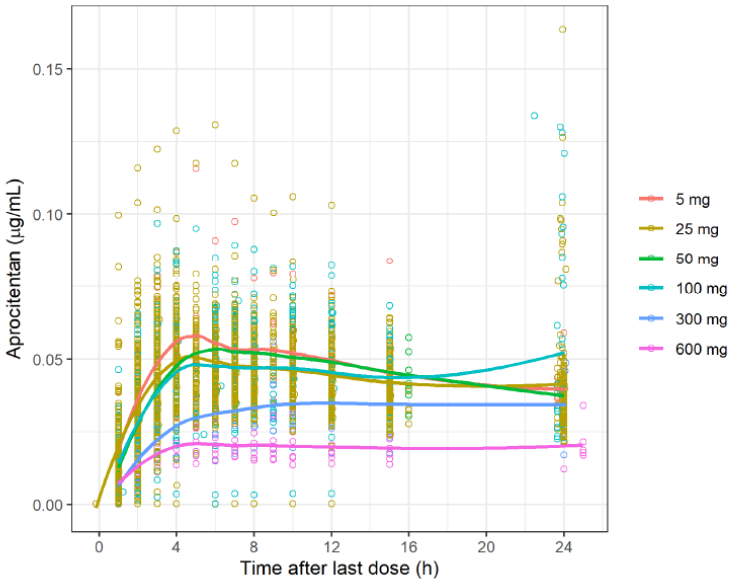
For rosuvastatin, a BCRP substrate, AUC remained unchanged but C_{max} increased (RR 1.40 (1.19; 1.65). The observed moderate effect of aprocitentan on the PK of rosuvastatin did not indicate a certain risk for the combination of aprocitentan with other drugs. The SmPC has been adapted to include the description of the impact on C_{max}.

Pharmacokinetics using human biomaterials

N/A

Population Pharmacokinetic Modelling

Aprocitentan PK was described by a two-compartment population PK model with relative bioavailability reduced at doses of 300 mg and higher, linear absorption with lag time, and linear elimination. The model included the covariates food status on absorption parameters, body weight on volume and clearance parameters, and eGFR, HI, and sex on clearance. F was fixed at 1 for doses up to 100 mg, and estimated to be 22.8% and 43.6% lower for 300 and 600 mg, respectively (Figure 1).



A subset of the modeling data set is visualized: data from subjects with a dense sampling scheme, in fasted state, without RI, HI, and not on an HSD following a single dose or the first day of multiple doses in a study period. Open bullets indicate individual measurements, lines indicate a LOESS regression line per dose group (indicated by colors).

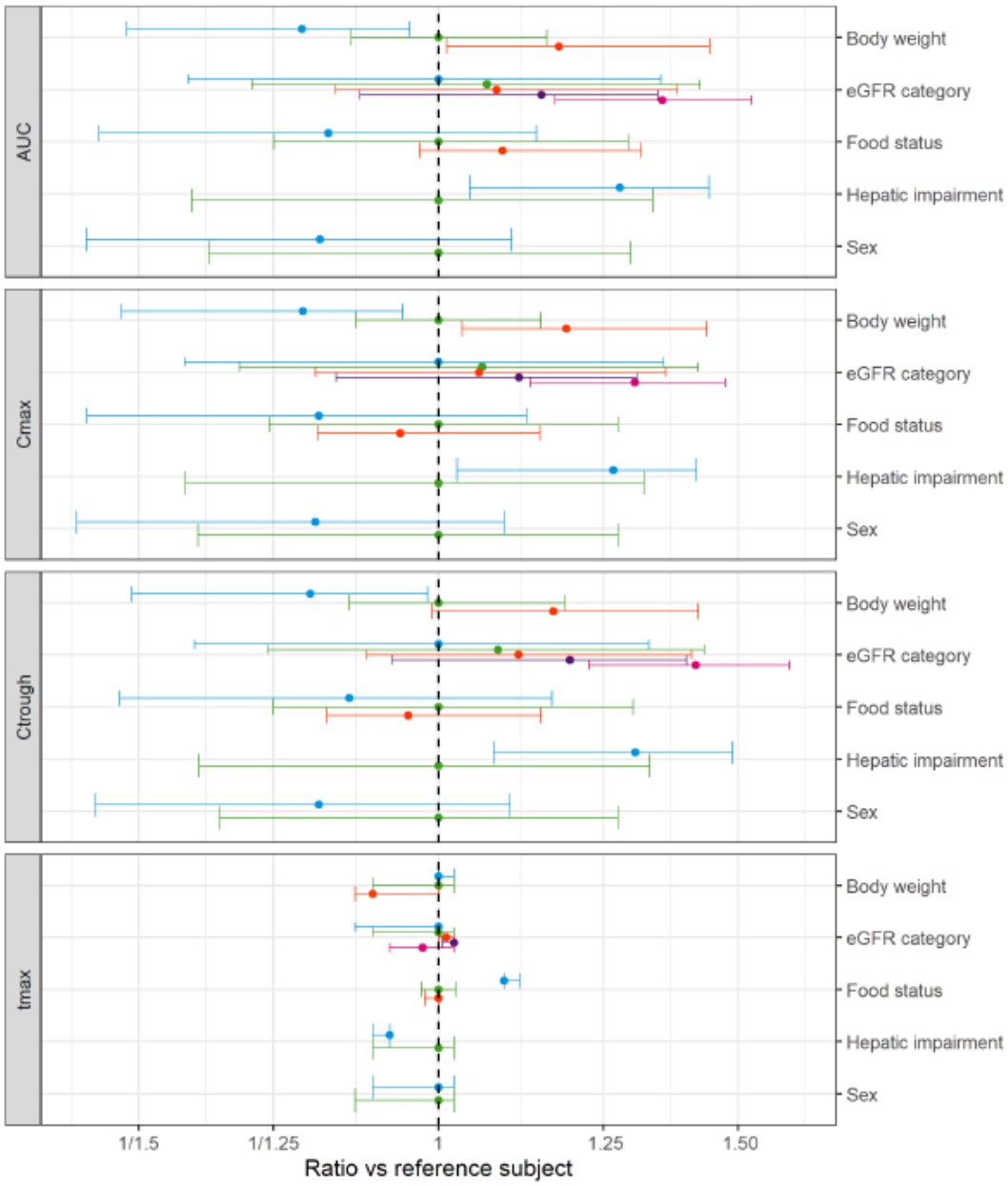
Figure 2: Dose-normalized concentration vs time by dose group for subjects with a dense sampling scheme on first day of dosing per study period

The parameter tlag was estimated as 0.593 h, and ka as 0.657 /h. Absorption parameters were fixed to HV values. Subjects in fed state had a delayed absorption, reflected by a higher tlag of 1.61 h and lower ka of 0.484 /h, while subjects in an uncontrolled food status had estimated tlag and ka in between these categories (0.700 h and 0.586 /h, respectively). Allometric scaling of parameters to a typical subject of 70 kg with body weight and fixed exponents of 0.75 and 1 were considered the best descriptors of the relationship between body size measurements and clearance and volume parameters. The parameter estimates of the final PK model including covariate effects are summarised in Table 1. Figure 2 shows the relative change in PK parameters for each covariate based on a simulation including IIV.

Table 2: Final PK model: parameter estimates

		Population parameters		IIV	
Parameter (unit)	**Description**	**Estimate**	**%RSE**	**Estimate**	**%RSE**
t_{lag} (h)	Absorption lag time	0.593	3.3	0.171	39.4
IOV on t_{lag} (-)	Inter-occasion variability	0.446	6.9	-	-
Food status on t_{lag} (-)	Covariate effect (fed)	1.00	21.9	-	-
	Covariate effect (uncontrolled)	0.166	136		
k_a (1/h)	Absorption rate constant	0.657	4.8	0.445	13.0
IOV on k_a (-)	Inter-occasion variability	0.530	7.3	-	-
Food status on k_a (-)	Covariate effect (fed)	–0.305	96	-	-
	Covariate effect (uncontrolled)	–0.114	164	-	-
F (-)	Relative bioavailability	1*	-	0.168	4.5
Dose 300 mg on F (-)	Covariate effect	–0.245*	-	-	-
Dose 600 mg on F (-)	Covariate effect	–0.572 *	-	-	-
V_c/F (L)	Apparent volume of distribution, central compartment	16.2	0.4	0.024	15.3
Body weight on V_c/F (-)	Covariate effect	1*	-	-	-
CL/F (L/h)	Apparent clearance	0.291	1.9	0.290	3.7
Body weight on CL/F (-)	Covariate effect	0.75*	-	-	-
eGFR on CL/F (-)	Covariate effect	0.222	15.3	-	-
Moderate HI on CL/F (-)	Covariate effect	–0.232	45.2	-	-
Sex on CL/F (-)	Covariate effect (male)	0.0343	68.6	-	-
Q/F (L/h)	Apparent intercompartmental drug transfer	0.512	16.6	1.77	8.8
Body weight on Q/F (-)	Covariate effect	0.75*	-	-	-
V_p/F (L)	Apparent volume of distribution, peripheral compartment	3.1	2.4	0.175	12.9
Body weight on V_p/F (-)	Covariate effect	1*	-	-	-
Residual error terms					
a_1	Constant error	0.1*	-		
b_1	Proportional error	0.146	0.9		

*Parameter was fixed in the final model estimation.
Covariates were normalized to 70 kg (standard allometric scaling), 90 mL/min/1.73 m^2 (median in modeling data set), and a reference subject was fasted, had no HI, and was female.
eGFR = estimated glomerular filtration rate; HI = hepatic impairment; IIV = interindividual variability; PK = pharmacokinetics; RSE = relative standard error.

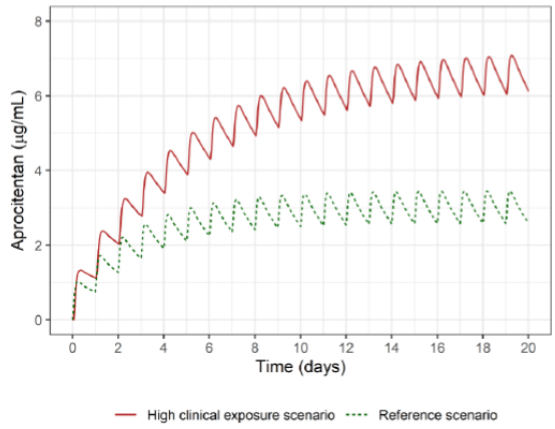


Exposure ranges at steady state (Day 10) after administration of 25 mg o.d. relative to the reference subject show medians and 90% PI of the respective covariates. For each covariate, comparisons are done to a reference category, with the following reference categories: body weight of 80.0–96.3 kg, eGFR >90 mL/min/1.73 m^2, HI: none, food status: fasted, sex: female. Colors indicate for body weight (kg): orange 43.6–80, green 80–96.3, blue 96.3–196; eGFR (mL/min/1.73 m^2): pink 15–30, purple 30–45, orange 45–60, green 60–90, blue >90; Food status: orange fed, green fasted, blue uncontrolled; HI: green none, blue moderate HI; Sex: green female, blue male.

AUC = area under the curve (exposure of one dosing interval of 24 h on Day 10); C_{max} = maximum concentration; C_{trough} = trough concentration; eGFR = estimated glomerular filtration rate; HI = hepatic impairment; o.d. = once daily; PK = pharmacokinetic; PI = prediction interval; t_{max} = time to reach maximum plasma concentration.

Figure 3: Visualization of the impact of covariates on PK parameters following administration of 25 mg aprocitentan o.d. for 10 days

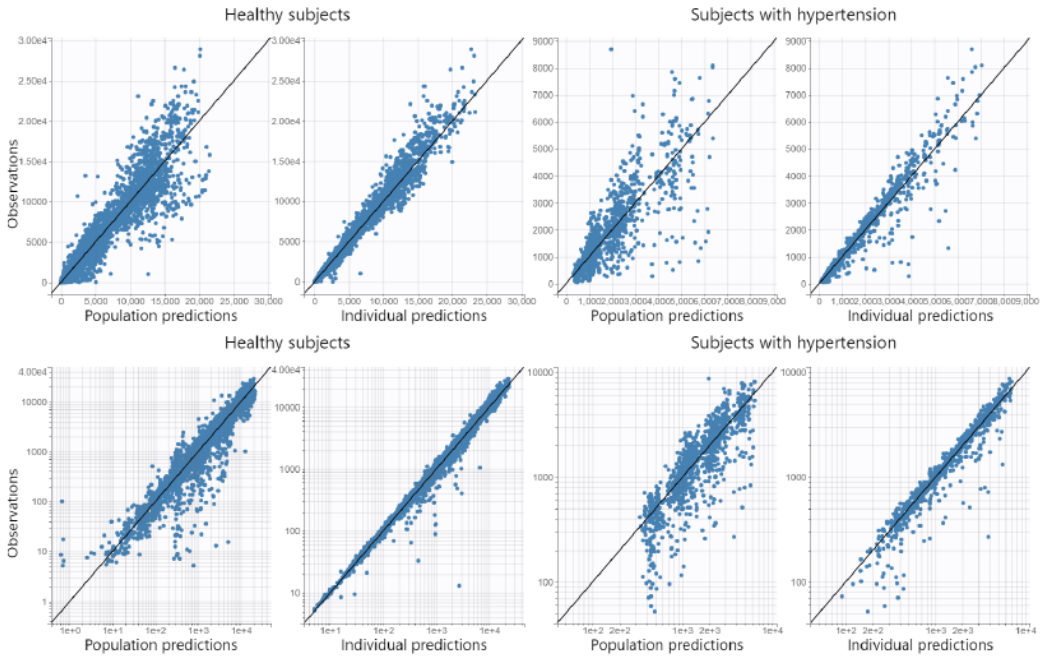
Simulations were conducted for a high exposure scenario of a female subject weighing 67 kg in fed state with moderate hepatic impairment and an eGFR of 17 mL/min/1.73 m². The resulting AUC was 2.18-fold higher compared to a standard female subject (87 kg, fasted, no HI, eGFR 90ml/min/1.73 m²) resulting in a cmax of 7.08 µg/mL (Figure 1). The description of the food effect is regarded as limited due to the high number of subjects with uncontrolled food status.



Green dashed line: prediction of aprocitentan concentration over time for a reference female subject of 87 kg, in fasted state, without HI, and an eGFR of 90 mL/min/1.73 m². Red solid line: prediction of aprocitentan concentration over time for the anticipated high clinical exposure scenario in a female subject of 67 kg, in fed state, with moderate HI, and an eGFR of 17 mL/min/1.73 m².
eGFR = estimated glomerular filtration rate; HI = hepatic impairment; o.d. = once daily.

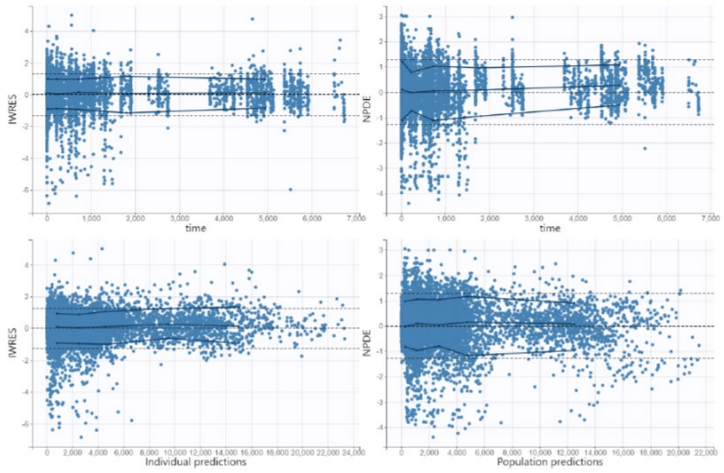
Figure 4: Visualization of reference and anticipated high clinical exposure scenarios for aprocitentan concentration-time profiles following administration of 25 mg aprocitentan o.d. for 20 days

The model was evaluated graphically with observations vs predictions depicted in Figure 9. Scatterplots and distribution of individual weighted residuals are shown in Figure 10, VPCs in Figure 11. Goodness-of-fit plots did not indicate major model misspecifications in patients and healthy subjects and VPCs showed an appropriate data description for different dose groups except for the 600 mg dose group which was overpredicted in the terminal phase.



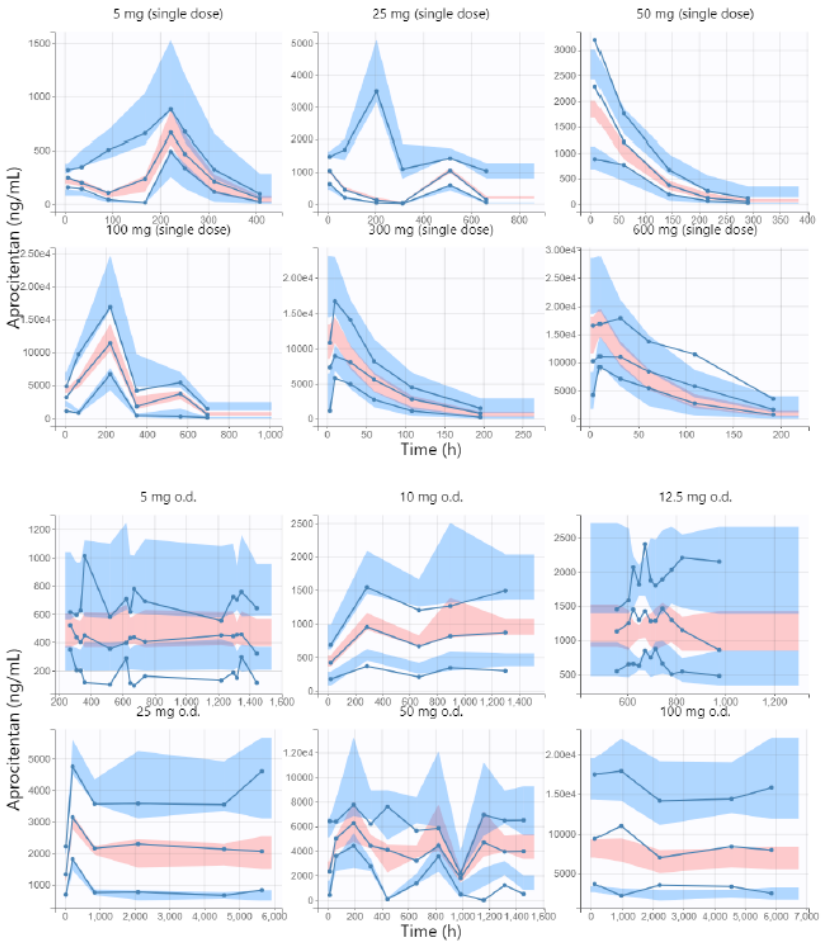
Population predictions (left) and individual predictions (right) vs observations (all in ng/mL) on linear (top row) and logarithmic scales (bottom row) for subjects without (left two columns) and with (right two columns) hypertension.
Black line: line of identity. Blue bullets depict data.
PK = pharmacokinetic(s).

Figure 5: Final PK model: observed vs predicted concentrations, population predictions and individual predictions, linear and log-log scales, stratified by healthy and subjects with hypertension



Bullets: residuals (left) and NPDE (right) vs time (top) and predicted concentration (bottom). Dark blue line: empirical median and 90% percentiles. Black dashed lines = NPDE and IWRES equals 0 and the predicted percentiles.
IWRES = individual weighted residuals; NPDE = normalized prediction distribution error.

Figure 6: Scatterplot of IWRES and normalized prediction distribution errors vs time and predicted concentrations



Aprocitentan concentration (ng/mL) vs time after first dose (h), stratified by dose (single dose vs o.d. per study period).
Blue lines indicate empirical 10th, 50th, and 90th percentiles, shaded areas indicate 90% CIs of the predicted 10th (blue), 50th (red), and 90th (blue) percentiles, respectively.
CI = confidence interval; o.d. = once daily; VPC = visual predictive check.

Figure 7: VPC by dose group

2.6.2.2. Pharmacodynamics

Aprocitentan (ACT-132577) is an orally active, dual endothelin (ET) receptor antagonist (ERA) of both the ET_A and ET_B receptors. Aprocitentan has the same chemical structure as the main pharmacologically active metabolite of macitentan with a similar pharmacological mode of action. Macitentan is approved for the treatment of pulmonary arterial hypertension.

Mechanism of action

ET-1, via its receptors (ET_A and ET_B), contributes to the regulation of vascular tone and BP. It is one of the most potent vasoconstrictors known.

Aprocitentan is being developed for use in adult patients with hypertension. The ET system is involved in the control of vascular tone, and its dysregulation plays a role in hypertension and especially in salt-sensitive/volume-dependent forms of hypertension, which are common features in patients with difficult-to-control hypertension. Based on this observation and given that current antihypertensive drugs (e.g., RAS blockers, calcium blockers, diuretics) do not target the ET pathway, ET receptor antagonism is a promising

pharmacological approach to the treatment of hypertension, in particular difficult-to control hypertension. Therefore, by blocking both ET_A and ET_B receptors, aprocitentan could be combined with background antihypertensive drugs to provide additional blood pressure (BP) reduction in these patients.

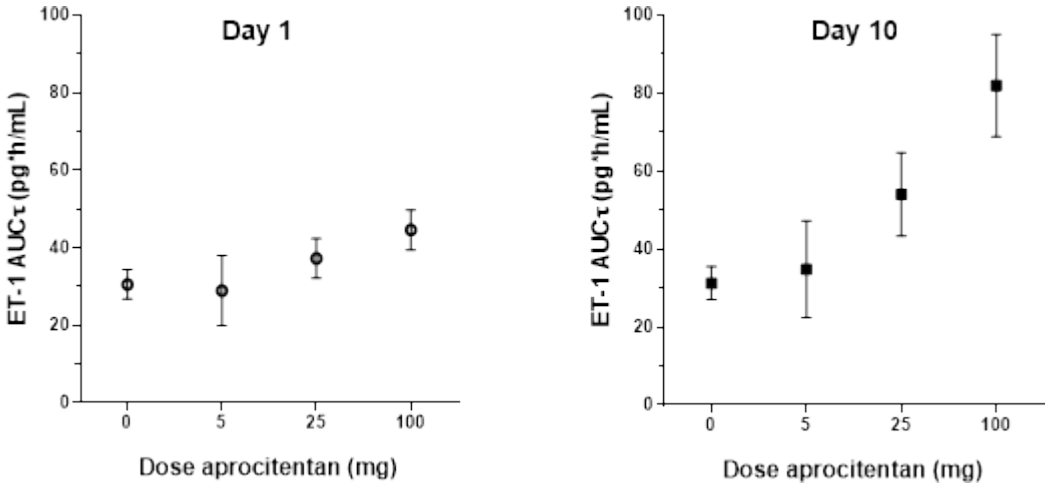
Primary and Secondary pharmacology

ET-1 plasma concentrations of healthy subjects and subjects with essential hypertension

During conduct of studies AC-080-101 (healthy subjects) and AC-080A201 (subjects with essential hypertension), ET-1 plasma concentrations were measured after multiple-dose administration.

In healthy subjects, ET-1 concentrations increased dose-dependently with doses of 25 and 100 mg aprocitentan.

Arithmetic mean AUCτ (± SD) of ET-1 on Days 1 and 10 after administration of 5, 25, or 100 mg aprocitentan or placebo o.d. for 10 days (n = 6 for 5 and 25 mg dose groups; n = 5 for 100 mg dose and placebo groups).



Similar results were found in study AC-080A201 in subjects with essential hypertension.

The studies with healthy subjects and subjects with essential hypertension indicate a dose dependent increase of endothelin-1 at least up to 100 mg aprocitentan.

Aprocitentan and its potential to retain fluid

In the mechanistic Phase 1 study AC-080-102, the potential of aprocitentan to induce fluid retention was investigated by measuring the change in body weight of healthy subjects on a high-sodium diet after treatment with placebo and 10, 25, or 50 mg aprocitentan o.d. for 9 days. Other variables of fluid retention (e.g., plasma and urine electrolytes, Hb, Hct, fluid-regulating hormones, and urinary excretion variables) were evaluated on an exploratory basis.

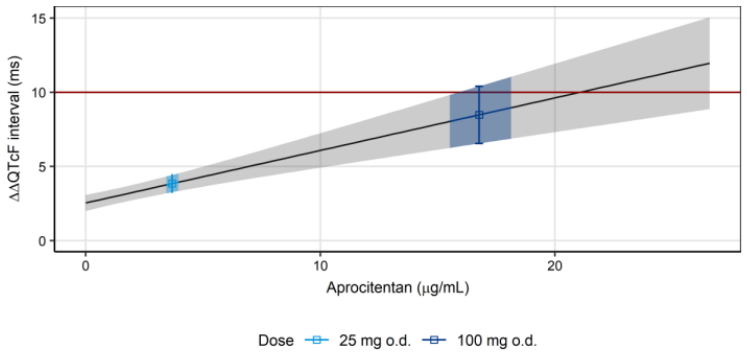
The results indicate that aprocitentan induces a moderate weight gain in healthy subjects (+0.77 kg [90% CI: 0.03, 1.51] for 25 mg aprocitentan; n = 7) associated with signs of haemodilution, and a decrease in uric acid.

Effect of aprocitentan on the QT interval

The relationship between plasma concentrations of aprocitentan and QT interval prolongation was evaluated in the TQT study ID-080-108. It was a double blind 4 fold cross over study in healthy male and female volunteers including 48 subjects in total comparing A aprocitentan 25 mg qd, B Aprocitentan 100 mg qd, C Placebo qd, all p.o. over 10 days as well as comparing D Moxiflocacin 400 mg, given as a single oral dose on Day 10. The analysis of 2329 time-matched aprocitentan concentrations and ΔΔQTcF indicated that ΔΔQTcF increased with increasing aprocitentan concentration. There was no evidence of a time-delayed effect, i.e., hysteresis.

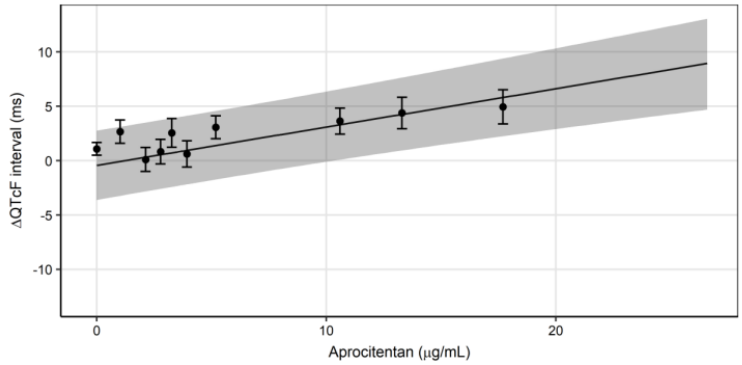
Concentration-QT modeling: The slope of the linear mixed-effects model was 0.354 ms·mL/µg (90% CI 0.233 – 0.475 ms·mL/µg) and was found to be significantly different from 0 ($P < 0.001$), indicating an increase in QTcF interval prolongation with increasing plasma concentrations of aprocitentan (Figure 11-3 and 15-8).

Figure 11-3 Mean $\Delta\Delta QTcF_{PRED}$ vs concentration, PK/ECGS



Red horizontal line, 10 ms threshold of regulatory concern; black line and height of shaded area, mean model-predicted $\Delta\Delta QTcF_{PRED}$ with two-sided 90% confidence interval; width of blue highlighted shaded areas, two-sided 95% confidence interval of geometric mean maximum concentration per group.
o.d. = once daily; $\Delta\Delta QTcF_{PRED}$ = model-predicted placebo-corrected change from baseline QT interval corrected for heart rate with Fridericia's formula.

Figure 15-8 Mean model-predicted and observed ΔQTcF vs concentration, PK/ECGS



Black line with grey shaded area, mean $\Delta QTcF_{PRED}$ with two-sided 90% confidence interval; points with error bars, mean observed $\Delta QTcF_{OBS}$ with two-sided 90% confidence interval for decentiles of observed concentrations.
$\Delta QTcF_{PRED}$ = model-predicted change from baseline QT interval corrected for heart rate with Fridericia's formula; $\Delta QTcF_{OBS}$ = observed change from baseline QT interval corrected for heart rate with Fridericia's formula.

At the observed aprocitentan geometric mean Cmax on Day 10, mean (90% CI) ΔΔQTcF was 3.846 (3.267 – 4.426) and 8.482 (6.554 – 10.411) ms for 25 mg o.d. and 100 mg o.d., respectively. The predicted two-sided 90% CI for ΔΔQTcF exceeded the 10 ms threshold of regulatory concern at an aprocitentan concentration of 16.1 µg/mL. This concentration was reached in subjects receiving 100 mg o.d. aprocitentan

who had an observed geometric mean Cmax of 16.77 µg/mL. In contrast, aprocitentan plasma concentrations in subjects receiving the therapeutic dose of 25 mg o.d. were lower (i.e., 3.68 µg/mL).

The placebo corrected heart rate increased with aprocitentan 25 mg qd by about 3 – 4 bpm over the entire day, at day 10 in study ID-080-108. In the phase 3 study however, only minor changes of the HR were observed, with an inconsistent direction, if the 12.5 mg and 25 mg aprocitentan groups and placebo are compared. Hence the apparent dose dependent increase of HR caused by aprocitentan in the phase 1 study with healthy subjects after 10 days is not reflected in patients after 4 weeks. It is therefore acknowledged, that aprocitentan did not induce an increase in heart rate in the RHT population.

2.6.3. Discussion on clinical pharmacology

Aprocitentan (ACT-132577) is a potent, orally active, dual ET receptor antagonist that inhibits the binding of ET to ETA and ETB receptors. Structurally, aprocitentan is identical to active metabolite of macitentan. Macitentan is approved in the EU from 2013 for the treatment of pulmonary arterial hypertension (PAH).The recommended dose for macitentan is 10 mg once daily, which lead to a steady state trough plasma concentrations of ~ 0.8 µg/mL aprocitentan. In the treatment of resistant hypertension, the recommended dose of aprocitentan of 25 mg QD produced steady state trough plasma concentrations of ~ 2.7 µg/mL aprocitentan.

Two oral formulations were developed and evaluated during the clinical development programme: an HPMC capsule (used in Phase 1 and Phase 2 studies) and a film-coated tablet, intended for commercial use (used in Phase 1 and Phase 3 studies). The film-coated tablets intended for commercialization differ from pivotal Phase 3 tablets only in debossing and colour of the film-coating.

No scientific advice was previously requested with regards to clinical pharmacology programme.

In vitro studies using human biomaterial were conducted to investigate plasma protein binding, blood to plasma partitioning, enzymes and transporters involved in aprocitentan disposition and aprocitentan interaction. The clinical pharmacology programme includes 10 Phase 1 studies in healthy subjects and in special populations, as well as PK and PD data from one Phase 2 and one Phase 3 study. In addition to above mentioned studies, Population PK analysis was used to characterise PK of aprocitentan in patients with RHT.

The conclusions can be summarized as follows:

Bioanalytical methods

Concentrations of aprocitentan were determined in human plasma using validated LC-MS/MS method (BA-14.026) at Actelion Pharmaceuticals Ltd, Switzerland. Bioanalytical method at Actelion site was satisfactorily validated with respect to precision, accuracy, sensitivity and selectivity, recovery, matrix effect, carryover and stability in accordance with the relevant regulatory guidelines. Performed ISR analysis meet the acceptance criteria according to ICH M10 bioanalytical method guideline.

In-study validation for clinical studies 101, 102, and 103 were performed at the same Actelion site. It was noted that in-study validation of other clinical studies was performed at different site Idorsia Pharmaceuticals Ltd, Switzerland. The applicant confirmed that only the name of the facility changed due to spin-off from Actelion Pharmaceuticals Ltd. Meaning that the test facility is the same laboratory and using the same SOPs and equipment, and working under the same test facility management and quality assurance team.

In phase 3 study, fixed combination of amlodipine, valsartan and hydrochlorothiazide were administered to patients. Within that study plasma concentrations of drugs amlodipine, valsartan and hydrochlorothiazide were not measured, thus those analytical methods were not provided. Only valsartan concentration in urine samples were measured, to test patient adherence. Data on analytical method were provided and found acceptable.

In clinical DDI studies (101 and 106) rosuvastatin, midazolam and 1-hydroxymidazolam were additionally administered. Their concentrations were measured using validated LC-MS/MS method and in-study validation methods were provided. Performed ISR analysis meet the acceptance criteria according to ICH M10 bioanalytical method guideline.

Plasma concentrations of moxiflocain in study 108 were not measured as the protocol allowed that plasma concentration could be optionally determined. Assay sensitivity for moxifloxacin was demonstrated using the Holter ECG data.

Population PK model

Data from 12 studies were pooled (AC-080-101,-102,-103,-104,-105,-106, ID-080-107,-108,-109,-110, AC-080A201, ID-080A301) to create the popPK modeling data set. Handling of missing data and excluded samples were well characterized and found acceptable.

Selection of the structural model that best described aprocitentan plasma concentration over time was based on data from Phase 1 studies in healthy subjects with dense PK sampling. Selection of base model was sufficiently described in the report. Various structural models, including transit compartment, time lag and one-, two- and three-compartment model were tested. Structural model that best described data was two-compartment model with tlag and linear clearance. Parameters estimates in the base model were estimated with good precision. A parameter for relative bioavailability (i.e., F) was introduced, fixed at 1. Dose proportionality was observed up to 100 mg. F was estimated to be lower following administration of 300 and 600 mg and included as a covariate for these two dose levels only.

Covariate selection was performed utilizing a sequential approach based on the full modeling data set, including sparse Phase 1, Phase 2, and Phase 3 data that were not used during structural model selection. In the final model, the identified covariates were visualized vs the parameters with dose on F, food status on ka and tlag, body weight on Vc, Q, and Vp, and body weight, eGFR, HI, and sex on CL. However, relevance of some covariates retained in the final model is questionable given the observed high RSE(%) (e.g. above 100% for covariate food status on absorption parameters).

All GOF plots showed that the model adequately described the observed aprocitentan concentrations. However, within plots spline interpolation is missing.

The VPCs showed that the model captured the global trend and the variability of the concentration vs time data reasonably well. Therefore, the final population PK model is deemed adequate for simulations.

Absorption

Aprocitentan is practically insoluble in aqueous media over the physiological pH.

In vitro evaluation of aprocitentan permeability on MDCKII cells using common reference compounds, suggests that aprocitentan could be a moderate to high permeability compound.

In vitro, aprocitentan was a substrate of P-gp and BCRP transporters. Further in vivo studies to evaluate impact of P-gp and BCRP inhibitors or inducers on aprocitentan exposure were not performed as no clinically relevant effect would be expected since aprocitentan showed high permeability, PK was dose-proportional and was mostly metabolized prior to excretion.

Absolute bioavailability study has not been performed. Based on the mass balance study, at least 52% of the administered dose is absorbed. High permeability of aprocitentan could not be confirmed by this study.

Following oral administration in the fasted state, median time to reach the maximum concentration (Tmax) was around 4 h at the 25 mg dose (both in SAD and MAD part of the study). Absorption was slower at higher doses administered.

When dosed once daily (QD), aprocitentan steady-state was reached after 8 days with approximately 3-fold accumulation (AC-080-101, Part C).

At a dose of 25 mg aprocitentan in healthy subjects at steady-state conditions, median t_{max} and geometric mean C_{max} and AUC_{τ} were approximately 4 h, 4 µg/mL, and 77 µg·h/mL, respectively. C_{trough} in healthy adult subjects were on Day 8 2.50–2.85 µg/mL. The AI of aprocitentan was approximately 3 with a $t_{½}$ of approximately 46 h.

As a worst-case exposure scenario, it is estimated that a combination of the effects observed on PK in one subject (e.g., elderly Japanese female with SRFI or moderate HI taking aprocitentan in the fed state) would not lead to an exposure more than 3-times that of a healthy adult Caucasian male subject taking aprocitentan in the fasted state.

Absorption related to different formulations

During the clinical development, two immediate release formulations were used. HPMC capsules were used in earlier studies 101, 102, 103, 104, 105, 106 and 201. Film-coated tablets, the same formulation as intended for the market, were used in studies 107, 108, 109, 110 and pivotal study 301.

Instead of performing a relative bioavailability study between HPMC capsule and film-coated tablet formulations, the applicant provided a descriptive comparison of PK parameters obtained in healthy subject studies after administration of 25 mg HPMC capsule and 25 mg film-coated tablet. This comparison included plasma-concentration profiles and PK parameters following administration of single 25 mg dose in study 101 (HPMC capsule) vs studies 109 and 110 (tablet), as well as comparison following multiple 25 mg doses in study 101 (HPMC capsule) vs studies 107 and 108 (tablet). Although the provided cross-study comparison suggests similar shape of the plasma-concentration curve, and also similar PK parameters (Cmax, Tmax, AUC) following both single and multiple 25 mg doses of the two different formulations, such approach is not considered sufficiently sensitive to distinguish formulation effect from other effects. Nevertheless, since pivotal Phase 3 study was performed with the formulation intended for the commercialization and the therapeutic window of aprocitentan does not appear to be narrow, a dedicated relative BA study between two formulations will not be asked for.

General biowaiver criteria for lower 12.5 mg film-coated tablet strength are not met, since the composition of the strengths is not quantitatively proportional. 12.5 mg film-coated tablet was used only in the pivotal Phase 3 study, therefore no rich PK sampling is available following administration of this strength. Ctrough at steady-state Wk 4 in study 301 was dose-proportional between 12.5 mg and 25 mg.

Changing the particle size distribution of aprocitentan API in 25 mg film-coated tablet did not have an impact on aprocitentan exposure since both formulations were found bioequivalent (study AC-080-110).

Distribution

In vitro studies (B-07.077) supported with radioactivity partitioning results from the mass balance study (AC-080-104) showed that distribution of aprocitentan to red blood cells is limited. The range of concentrations used in the in vitro assay covered well the expected in vivo concentrations. Based on total radioactivity AUC0-∞ ratios from the ADME study, the blood/plasma ratio was 0.63.

Aprocitentan was 99.5% bound to plasma proteins, as determined by equilibrium dialysis in vitro. Protein binding did not show any concentration-dependance in the range between 0.1 and 300 µg/mL (B-07.077). It was not investigated to what plasma protein aprocitentan is binding. Very high binding of aprocitentan to human plasma proteins (>99%) was confirmed in renal impairment and hepatic impairment studies.

Apparent volume of distribution (Vz/F) of aprocitentan was around 20 L indicating limited distribution to extracellular fluid.

Elimination

Most of the drug-related material was excreted in urine. Across clinical studies in healthy volunteers, aprocitentan apparent clearance (CL/F) was approximately 0.30 L/h, value which is in line with the estimate obtained from the pop PK model. The value indicates low hepatic extraction ratio of aprocitentan.

Across clinical studies in healthy volunteers, mean elimination half-life was approximately 46 hours.

The mass balance study (AC-080-104) was a single dose study using 25 mg dose of radioactively labelled aprocitentan. Due to linear and no-time-dependant PK, single dose design is acceptable. The label was placed at a metabolically stable position.

Even though plasma, urine and feces sampling was quite long, i.e. 14 days (336 h), at Day 14 none of the subjects had a cumulative recovery of 14C-radioactivity > 85%. Further sampling in the extended observation period at Day 18 (408–432 h) and Day 21 (480–504 h) was performed for 3 subjects whose total daily radioactive excretion in both urine and feces in two consecutive samples was >0.5% of the administered dose. Total cumulative recovery in study subjects ranged from 65.8 to 82.9%.

Overall mean total recovery of administered radioactivity in urine and feces was around 77% (sum of 52.4% in urine and 24.9% in feces gives 77.3%), which is well below the criteria (>90%) set in the Appendix V of *the EMA Guideline on drug interactions*, (CPMP/EWP/560/95/Rev. 1 Corr. 2**). However, it has been reported that there is a relationship between a lower recovery of radiolabeled material and a longer half-life of total radioactivity in the circulation. Similar low recovery of radioactivity was observed with macitentan. Although mass balance study provided suboptimal results in recovery of total radioactivity, it can be considered sufficient for characterization of elimination pathways of aprocitentan.

Urinary excretion (52.12% of the dose recovered) was the major route of elimination for [14C]-aprocitentan. 0.2% of dose recovered in urine was unchanged aprocitentan, indicating substantial formation of metabolites. Fecal excretion with 24.79% of the dose recovered was a minor elimination pathway. 6.8% of the dose recovered in feces was excreted as unchanged aprocitentan.

SmPC section 5.2 adequately describes results of the mass balance study.

Metabolism

In vitro studies on human liver microsomes and human hepatocytes characterized metabolic profile of ACT-132577 by the formation of six metabolites. Two primary pathways included hydrolysis to M1 and

glucosidation to M3. Formation of M1 is likely the result of a chemical hydrolysis, since it was also observed in the control experiments without liver microsomes or hepatocytes. (B-14.033)

In the incubations with recombinant human UGT enzymes, UGT1A1 and UGT2B7 metabolized aprocitentan into its glucoside metabolite M3. (B-18.023)

Based on metabolic profiling from mass balance study AC-080-104, unchanged aprocitentan was a predominant moiety in plasma (94.3%). The only other metabolite of higher abundance in human plasma was M29 (4.5%). Metabolite M29 was not detected in in vitro studies on human liver preparations.

The most abundant metabolite in urine was M3 (46.4%), followed by A1 (9.7%), M6 (8.5%) and M16 (8.2%). Unchanged aprocitentan contributed with only 0.2%.

In feces, the most predominant species was M1 (41.5%), followed by unchanged aprocitentan (27.4%).

Based on these data, the applicant proposed two main metabolic pathways contributing to >25% of aprocitentan elimination: glucosidation of aprocitentan to M3 (25.2% of administered dose) and hydrolysis of aprocitentan to M1 (31.5% of administered dose) which undergoes further metabolism.

SmPC section 5.2 adequately describes Biotransformation of aprocitentan.

Inter-conversion:

The molecule has no chiral centers.

Pharmacokinetics of metabolites

PK of aprocitentan metabolites was not investigated. According to the metabolic profiling of plasma samples from study 104, aprocitentan was a predominant compound in plasma contributing to 94.3% of total plasma radioactivity. The second most abundant compound was metabolite M29 contributing to 4.5% of total plasma radioactivity. Based on these results, there were no major circulating metabolites in human plasma.

Dose-proportionality and time-dependency

Dose proportionality was evaluated in healthy subjects over a dose range of 5 mg to 600 mg in single dose part of the study 101 and over a dose range of 5 mg to 100 mg once daily in multiple dose part of study 101. Overall, less than dose-proportional exposure was observed following single doses and dose-proportional exposure was observed following multiple doses in healthy subjects.

The SmPC adequately reflects the observed results following multiple dosing.

Apparent elimination half-lives were similar following single and multiple doses of aprocitentan. When dosed once daily (QD), aprocitentan steady-state was reached after 8 days with approximately 3-fold accumulation. This degree of accumulation is consistent with elimination half-life of 46 hours. Taken together, it does not appear that aprocitentan exhibits a time-dependent PK.

Pharmacokinetic in target population

Trough concentrations from patient population having essential hypertension and resistant hypertension were collected at steady state from one Phase 2 study (essential) and one Phase 3 study (resistant hypertension), respectively.

Trough concentrations at steady state, at day 10 in healthy subjects for clinical dose of 25 mg were comparable to trough concentration at week 4 in patients with resistant hypertension. Similar was observed in popPK model which didn’t find disease status relevant for the final model.

Intra- and inter-individual variability

Inter-subject variability (%CV) following single and multiple doses in healthy subjects was low.

Special populations

Pharmacokinetics in special populations has been sufficiently evaluated by the Applicant.

Covariates age, gender, race and weight were investigated using population PK modelling. Results indicate that no dose adjustment is needed with regards above mentioned covariates.

Pharmacokinetic of aprocitentan was separately investigated in renal impairment study (105) and in hepatic impairment study (109).

Section 4.2 of the SmPC (Posology) include a note on the limited clinical experience in patients over the age of 75 years.

Renal impairment study

A reduced study design was used to investigate the impact of severe renal impairment (eGFR < 30 mL/min/1.73 m2, not requiring dialysis) on PK of aprocitentan compared to subjects with normal renal function matched for age, gender and body weight. Since 0.2% of unchanged aprocitentan is excreted unchanged in urine, the reduced study design is considered acceptable.

Single dose of 50 mg aprocitenan was investigated, which is higher than the proposed dose of 12.5 mg and 25 mg. Aprocitentan exhibits linear PK up to 100 mg dose, therefore single dose study is acceptable. Blood samples were obtained up to 14 days post-dose, given the half-life of drugs it seems sufficient to adequately describe PK profile.

The PK of aprocitentan after administration of a single oral dose of 50 mg aprocitentan were similar in healthy subjects and subjects with severe renal function impairment. Cmax was unchanged, while AUC was observed to be around 30% higher in patients with severe renal impairment. Moreover, slightly longer half-life and lower clearance was observed in patients with severe renal impairment.

Simulations from the final population PK model were employed to enable judgment about clinical relevance of renal impairment impact on PK of aprocitentan. Simulation using dose of 25 mg and eGFR categories of interest, i.e., 17, 30, and 45 mL/min/1.73 m2 showed similar results as in renal impairment study 105.

Given that drug is highly bound to plasma proteins, geometric mean plasma protein binding was measured at 8 hours and 168 hours after study treatment. No difference in plasma protein binding at both times and between groups were observed.

The proposed wording in the SmPC with regards to renal impairment is considered acceptable from the pharmacokinetic point of view, however for the safety issues identified in this special population, please see Safety discussion. From the PK perspective there is no need for dose adjustments in subjects with any degree of renal impairment with eGFR >15 mL/min/1.73 m2.

Hepatic impairment study

The effect of hepatic impairment on the PK of aprocitentan was studied in a reduced design study including moderate hepatic impairment group according to the Child-Pugh classification (score 7-9). No study was perfomed in patients with severe hepatic impairment.

Subjects with normal hepatic function and moderate hepatic impairment were comparable with regards to age, gender and weight.

Blood PK samples were obtained up to 312 hours post-dose, given the half-life of drug it seems sufficient to adequately describe PK profile. The PK of aprocitentan after administration of a single oral dose of 25 mg aprocitentan were similar between subjects with moderate hepatic impairment and healthy subjects. With regards of PK parameter, Cmax it is comparable between groups indicated by the GMR of 1, while AUC was around 20% higher in patients with moderate hepatic impairment compared to healthy subjects. Also somewhat lower clearance (around 20%) and slightly longer half-life of drug were observed in patients with moderate hepatic impairment. Similar was observed in popPK model and employed simulations. This increase of exposure in moderate hepatic impairment is not considered clinically relevant. Thus wording in the SmPC that no dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh class A or B, respectively) is acceptable.

There were no differences in plasma protein binding between the two groups with arithmetic mean values ranging from 98.7% to 99.0%.

Children

Aprocitentan has not been studied in children. A product-specific waiver was granted for the paediatric population from birth to less than 18 years of age.

Interactions

In vitro

Enzymes

Aprocitentan inhibited CYP2C8 (IC50=23 µM), CYP2C9 (IC50=31 µM, Ki=11 µM), CYP2C19 (IC50=15 µM) and CYP3A4 (IC50(midazolam)=7.3 µM, IC50(testosterone)=11 µM, Ki=6.3 µM). Given the Ki values being higher than 50x$C_{max,u}$ (3.37 µM), potential for in vivo systemic CYP450 inhibition is low.

Ki value for CYP3A4 inhibition (6.3 µM) < 0.1×dose/250 ml (18.3 µM) suggested potential for intestinal CYP3A4 inhibition which was further investigated in a clinical study AC-080-103.

In vitro, aprocitentan was not a time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4.

Aprocitentan was found to be a CYP3A4 inducer in vitro, this was further investigated in clinical study AC-080-103.

In vitro, aprocitentan was not a CYP2C9 inducer.

Given >2-fold increase in mRNA vs control observed for both CYP1A2 and CYP2B6, as well as concentration-dependent increase in mRNA, potential of aprocitentan to induce CYP1A2 or CYP2B6 cannot be currently excluded. An adequate wording has been implemented in the SmPC.

Aprocitentan inhibited UGT1A1 and UGT2B7 with IC50 values of 23 µM and 43 µM, therefore potential for in vivo inhibition is considered low.

Transporters

Aprocitentan was a P-gp and BCRP substrate and was not an OATP1B1 or OATP1B3 substrate in vitro.

Aprocitentan inhibited OATP1B1 (IC50=19 µM), OATP1B3 (IC50=27 µM), BSEP (IC50=50 µM), NTCP (IC50=14 µM), OAT1 (IC50=4.7 µM), OAT3 (IC50=1.5 µM), BCRP (IC50=5.7 µM), P-gp (IC50 > 70 µM). Potential for in vivo inhibition of BCRP was further investigated in clinical study AC-080-106.

Aprocitentan did not inhibit OCT1, OCT2, MATE1 and MATE2K in vitro.

In vivo

Two clinical studies were performed to evaluate potential for interactions with aprocitentan as a perpetrator and none to evaluate aprocitentan as a victim.

Study AC-080-103 evaluated effect of steady-state aprocitentan concentrations on the PK of a sensitive CYP3A4 substrate, midazolam. There was no significant effect observed on the exposure of midazolam and its 1-hydroxy metabolite, therefore, there is no need for adjusting the dose when aprocitentan is co-administered with CYP3A4 substrates.

Study AC-080-106 evaluated effect of aprocitentan on the PK of a sensitive BCRP substrate, rosuvastatin. At steady-state, aprocitentan increased C_{max} of rosuvastatin by 40% (90%CI: 1.19-1.65) and decreased $t_{1/2}$ by 21% (90%CI: 0.60-1.03). AUC of rosuvastatin was not affected by aprocitentan, as 90%CI of the GMR were completely within the reference interval 0.80-1.25.

In pivotal Phase 3 study, aprocitentan was co-administered with other antihypertensive medication, i.e. amlodipine, valsartan and hydrochlorothiazide. No PK interaction studies were performed, and concentrations of co-administered medication were not measured. This is considered acceptable given the seemingly low potential of aprocitentan to act both as a perpetrator and a victim of DDIs. Aprocitentan C_{trough} concentrations in pivotal Phase 3 study were very similar to C_{trough} concentrations following administration of aprocitentan 25 mg QD alone in healthy volunteers, not suggesting any effect of other co-administered medication on aprocitentan exposure.

According to the EMA Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**), for potential human teratogens, such as aprocitentan, an in vivo study should be conducted to study effects on oral contraceptives. The Applicant has agreed to perform a dedicated DDI study between aprocitentan and oral contraceptives post-authorisation.

Pharmacodynamics

Aprocitentan (ACT-132577) is a potent, orally active, dual ETA/ETB endothelin receptor antagonist.

Binding of an endothelin receptor antagonists (ERB) to ETA and ETB receptors causes an increase in plasma endothelin (ET-1) levels, which can be used as a marker of pharmacological effect and potency on the ETA and ETB receptor.

Endothelin plasma levels were evaluated in two studies, Phase II study AC-080A 201 in subjects with essential hypertension and Phase I study AC-080-101 in heathy subjects.

In both studies plasma concentrations of ET-1 were measured at steady state of aprocitentan. Range of doses administrated were from 5 mg to 100 mg, while recommended dosage regimen is 12.5 mg and 25 mg. Similar results were shown in both studies. Both demonstrated increase of ET-1 with dose increase. In study AC-080-101, at dose of 100 mg, trend of ET-1 plasma concentration increase is still evident after 10 days, while for dose of 50 mg stable ET-1 plasma concentrations are observed between 3 days and 10 days. Similar stable ET-1 concentrations were observed in study 201 up to 8 weeks.

Furthermore, two pharmacodynamics mechanistic studies have been performed; study AC – 080- 102 to evaluate the effect of aprocitentan on body weight in heathy subjects on high sodium diet and study ID-080-108 to investigate the effect of aprocitentan in QTc interval.

Study AC-080-102 was to evaluate potential body weight increase induced by fluid retention in healthy male subjects on a high-sodium diet. Investigational drugs in recommended dosage regimen were administered to subjects for 10 consecutive days to ensure steady state had been reached. Giving study was designed, as cross over, wash out period of 7 days doesn't seem to be sufficiently long given that mean elimination half-life is approximately 46 hours. However, results indicate an increase in body weight of >1 kg for therapeutic dose of 25 mg (LSM difference [90% CI] 25 mg: 0.7708 [0.0292, 1.5125).

An increase in body weight of >2 kg from baseline was observed in study 301 for 34.7% subjects with edema/fluid retention. Weight gain was associated with signs of haemodilution, and a decrease in uric acid. For further discussion on body weight increase, please refer to safety part of clinical report.

Study ID-080-108 aimed to investigate the potentially relevant QT effects of the non-antiarrhythmic compound aprocitentan at therapeutic (25 mg) and supratherapeutic (100 mg) doses in healthy male and female subjects using a concentration-QT analysis approach in compliance with the ICH E14 guideline. A crossover study design with 4 periods separated by adequate in-between periods was allowed for intra-subject comparison of the 4 study treatments. The treatments (10 days dosing and 18 days observation, limits included) were separated by in-between periods of a minimum of 2 days to ensure that exposure levels of aprocitentan pre-dose were <5% of Cmax.

QTc increased dose dependently at the observed aprocitentan geometric mean Cmax on Day 10, mean (90% CI) ΔΔQTcF was 3.846 (3.267 – 4.426) and 8.482 (6.554 – 10.411) ms for 25 mg o.d. and 100 mg o.d., respectively. The predicted two-sided 90% CI for ΔΔQTcF exceeded the 10 ms threshold of regulatory concern at an aprocitentan concentration of 16.1 µg/mL corresponding roughly to a supratherapeutic dose of 100 mg, more than twice the model calculated concentration at high clinical exposure (7 µg/mL).

Effects of aprocitentan on blood pressure are discussed in the clinical section.

2.6.4. Conclusions on clinical pharmacology

Aprocitentan (ACT-132577) is an endothelin (ET) receptor antagonist (ERA) of both the ETA and ETB receptors. PK and PD properties are overall well characterized. There are no objections to the approval of aprocitentan from the clinical pharmacology point of view and the SmPC adequately updated reflects the clinical pharmacology findings.

2.6.5. Clinical efficacy

Study reports of two clinical studies were provided, a phase 2 dose finding study in patients with stage 1 and 2 mild to moderate arterial hypertension, not on antihypertensive background treatment at the time of administration of aprocitentan (Study 201) and a pivotal phase 3 study in patients with resistant arterial hypertension uncontrolled at stage 1 and 2 despite of treatment with 3 antihypertensive drugs of different classes (target group of the indication).

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Route of Administration; Regimen	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
					single dose				
Phase 2 and Phase 3 studies in subjects with HTN									
Dose-finding Phase 2 study	AC-080A201	5.3.4.2	To investigate the BP dose-response of aprocitentan monotherapy on SBP/DBP and 24 h ABPM in subjects with HTN treatment naive or antihypertensives washed out. To evaluate the safety and tolerability of a o.d. oral regimen of 4 doses of aprocitentan.	Multi-center Double-blind Double-dummy Randomized Placebo-controlled Active-controlled Parallel group	HPMC capsules; 5, 10, 25, 50 mg or placebo or over-encapsulated lisinopril 20 mg Oral, o.d. Monotherapy[#]	490 (409 aprocitentan, 82 placebo)	Adult subjects (≤ 18 to ≥ 75 years) with HTN (grade 1 and grade 2) with or without ongoing anti-HTN treatment(s) with SiDBP ≥ 90 mmHg as recorded by uAOBP	4–6-week SB placebo run-in period 8-week DB randomized treatment period 2-week SB placebo WD period	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Route of Administration; Regimen	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Confirmatory Phase 3 study	ID-080A301	5.3.5.1	To investigate BP lowering effect of aprocitentan add-on therapy, its durability and its long-term safety and tolerability in subjects with difficult-to-control HTN despite 3 antihypertensives.	Multi-center Randomized Parallel-group study in 3 parts: **Part 1:** DB, placebo-controlled **Part 2**: SB, single arm **Part 3:** DB, placebo-controlled	Film-coated tablets; 12.5 mg, 25 mg or placebo Oral, o.d. In combination with 3 anti-HTN of different pharmacological classes: valsartan 160 mg / amlodipine 10 or 5 mg / hydrochlorothiazide 25 mg.	730 (486 aprocitentan, 244 placebo)	Adult subjects (≥ 18 years) with HTN (grade 1 and 2) uncontrolled despite the use of 3 anti-HTN medications of different pharmacological classes (SiSBP ≥ 140 mmHg as recorded by uAOBP)	4-week SB placebo run-in period 48-week randomized treatment period in 3 parts: **DB Part 1**: aprocitentan 12.5 mg or 25 mg or placebo (4 weeks) **SB Part 2**: aprocitentan 25 mg (32 weeks) **DB-WD Part 3:** aprocitentan 25 mg or placebo (12 weeks)	Complete; Full

[#] Background anti-hypertensive treatment-naïve or treatment washed out during the study's run-in period.

ABPM = ambulatory blood pressure monitoring; BCRP = breast cancer resistance protein; BE = bioequivalence; CYP = cytochrome P450; DB = double-blind; DBP = diastolic blood pressure; DDI = drug-drug interaction; HI = hepatic impairment; HPMC = hydroxypropyl methylcellulose; HTN = hypertension; MAD = multiple-ascending dose; o.d. = once daily; PD = pharmacodynamic; PK = pharmacokinetic; QTc = QT interval corrected for heart rate; SAD = single-ascending dose; SB = single-blind; SBP = systolic blood pressure; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure; SRFI = severe renal function impairment; TQT= thorough QT; uAOBP = unattended automatic office blood pressure; WD = withdrawal.

2.6.5.1. Dose response studies

The dose selection for Phase 3 was based on the totality of data from phase 1 and phase 2 studies, but was mainly driven by dose-finding study 201 in patients with mild to moderate HTN. A Phase 1 study (study AC-080-101, see above) in healthy subjects investigated multiple doses ranging from 5 to 100 mg. After 10 days of treatment with 100 mg in healthy subjects, there were frequent headaches and a signal of body weight

increase, in particular in elderly subjects; therefore, the 100 mg dose was not carried forward to Phase 2. 50 mg was selected as the highest aprocitentan dose to be evaluated in study 201.

The Phase 2 study AC-080A201 (study 201, for a detailed assessment see below) was a dose-finding study designed to estimate the minimum effective dose and maximum tolerated dose of aprocitentan as monotherapy vs. placebo in subjects with HTN. A dose-dependent reduction in BP (measured as SiDBP/SiSBP at Week 8) was observed over a dose range of 5 to 50 mg, 25 mg giving the largest decrease in BP.

The hemodilution effect (decrease in hemoglobin concentration and increase in ePV), which may signal a potential for fluid retention, was numerically larger at 50 mg than at 25 mg. This was consistent with the results of the clinical pharmacology mechanistic study to evaluate the effect of aprocitentan on body weight and fluid retention in healthy subjects on a high sodium diet (study AC-080-102, see above) which showed lower weight increase (vs placebo) with 10 mg (+0.4 kg) than with 25 or 50 mg (+0.8 kg).

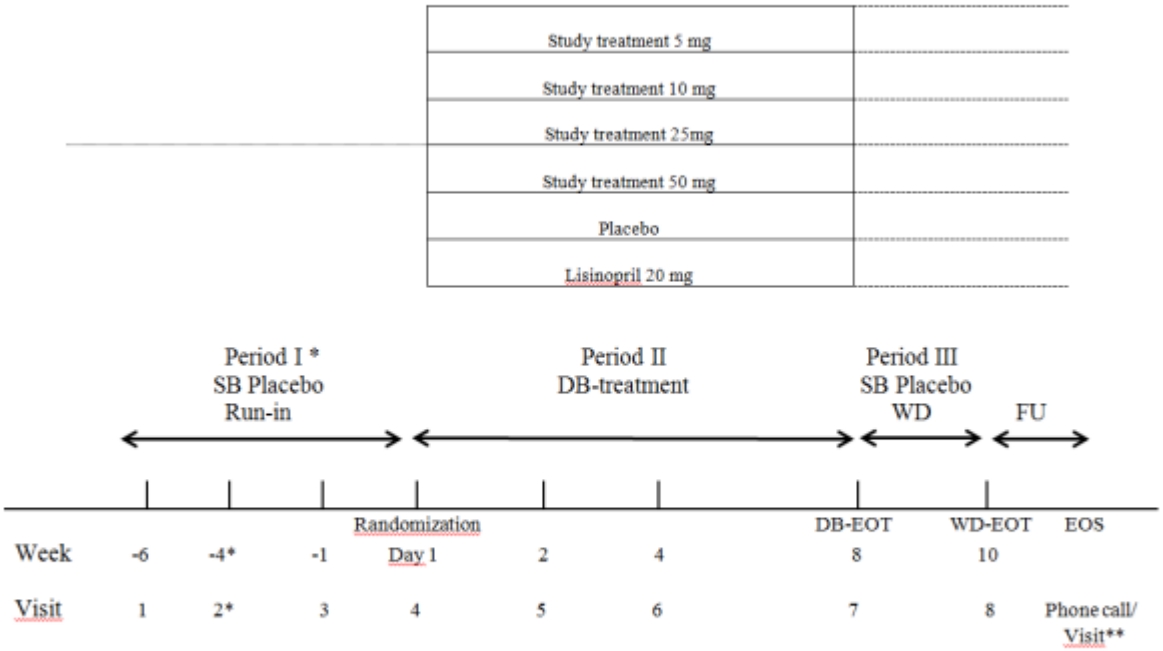
Based on these efficacy and safety arguments, the dose range of 10 to 25 mg was selected for further evaluation. This led to selection of the doses of 12.5 and 25 mg o.d. for the Phase 3 program in subjects with difficult-to-control HTN. The dose of 12.5 mg was selected instead of 10 mg as it represented half of the expected maximum therapeutic dose. Regarding data coming from the pivotal trial 301 on dose selection see below.

Study AC-080A201 (Study 201)

A multi-center, double-blind, double-dummy, randomized, placebo- and active-reference, parallel group, Phase 2, dose-finding study with ACT-132577 in subjects with essential hypertension (Grade 1 and 2) The study design is shown in Figure 9-1

Subject participation in the study lasted up to 18 weeks. The study design is summarized in Figure 9-1. It included a pre-screening and a screening period, a Run-in period (I) (single-blind (SB) placebo period of 4 weeks for anti-hypertensive treatment-naïve subjects or of 6 weeks for subjects on anti-hypertensive treatments including a 2-week wash-out period for anti-hypertensive treatment); a DB treatment period of 8 weeks (II); a withdrawal (WD) period of 2 weeks (III); follow-up period of 2 weeks.

Figure 9-1 Study design



* SB placebo run-in period is 4 weeks for anti-hypertensive treatment-naïve subjects; Visit 1 is combined with Visit 2 for these subjects.
** Only for women of childbearing potential.
DB = double-blind; EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up; SB = single-blind; WD = withdrawal.

Key inclusion criteria were:

Male and female subjects aged 18–75 years (inclusive) diagnosed with mild-to-moderate essential hypertension (i.e., grade 1 and grade 2) with or without ongoing anti-hypertensive treatment(s).

At visit 1 – DBP ≥ 90 mmHg, as a mean of 5 measurements with OBPM (office blood pressure measurement, modified to ≥ 90 mmHg from ≥ 95 mmHg following protocol amendment 2 leading to global protocol version 3) with additional BP criterial up to randomization (visit 4).

Study treatment: ACT-132577: 5 mg, 10 mg (2 × 5 mg), 25 mg, and 50 mg, lisinopril 20 mg and placebo. No baseline antihypertensive therapy was allowed at the time of randomization.

Primary efficacy endpoint: Change from baseline to Week 8 of DB treatment period (Period II) in mean trough (i.e., 24 h post-dose) SiDBP, measured by OBPM.

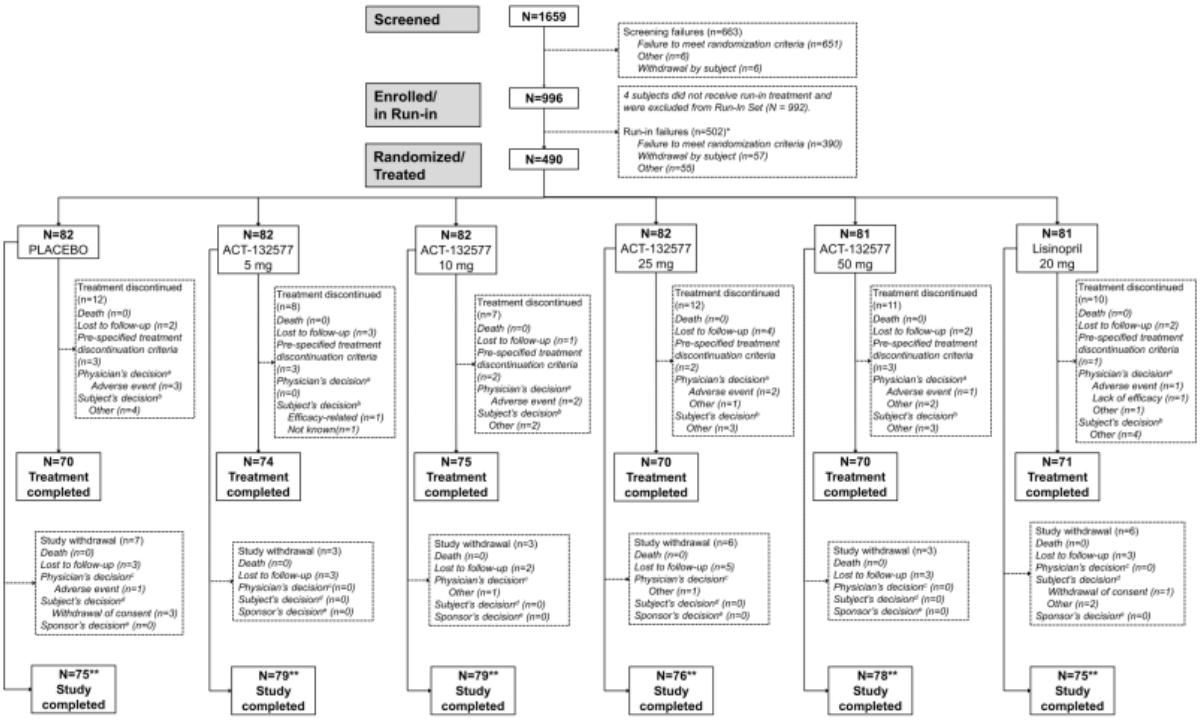
Secondary hypertension related endpoints including ABPM measurements were predefined.

Results

Participant flow

Disposition of patients is summarized in Fig 10-1.

Figure 10-1 Disposition of subjects



* The run-in failures include subjects who prematurely discontinued run-in treatment and also the study.
** A subject was considered to have completed the study when they had completed their 30-day safety follow-up telephone call / visit (i.e., End-of-Study [EOS]). For a subject who withdrew consent from further participation from the study, the date of consent withdrawal was the EOS for this subject. If a subject was

A total of 1659 subjects were screened, of whom 996 were enrolled into the SB placebo run-in period (Period I). Of the 996 subjects enrolled into the run-in period, 992 received at least one dose of the SB placebo and comprised the RIS. Of these 992 subjects, 50.6% (n = 502) of subjects were considered run-in failures with 39.3% (n = 390) of subjects failing to meet randomization criteria.

There were two global amendments. The major protocol amendment related to blinded reassessment of the sample size. Changes in BP criteria for inclusion were introduced by Amendment 2. A sensitivity analysis on patients included before and after amendment 2 was provided indicating no relevant impact on the overall conclusions.

Baseline data

Demographic characteristics were overall balanced between the groups with some variability as expected for the sample size per treatment arm (Table 10-2). The demographics and baseline clinical characteristics were similar in the PPS and the PK Set. There were no notable between-group differences in blood pressure measurement at baseline, with mean (SD) SiDBP and mean (SD) SiSBP measured by BpTRU® ranging from 96.8 (4.6) mmHg to 98.2 (5.3) mmHg, and from 148.6 (12.8) mmHg to 151.2 (13.7) mmHg, respectively, in the PPS.

Table 10-2 Demographic characteristics, Full Analysis Set

ACT-132577
Protocol: AC-080A201
Demographic characteristics
Analysis Set: Full Analysis Set

	Placebo N = 82	ACT-132577 5 mg N = 82	ACT-132577 10 mg N = 82	ACT-132577 25 mg N = 82	ACT-132577 50 mg N = 81	Lisinopril 20 mg N = 81	Total N = 490
Sex [n (%)]							
Male	55 (67.1)	48 (58.5)	51 (62.2)	45 (54.9)	53 (65.4)	45 (55.6)	297 (60.6)
Female	27 (32.9)	34 (41.5)	31 (37.8)	37 (45.1)	28 (34.6)	36 (44.4)	193 (39.4)
Age (years)							
n	82	82	82	82	81	81	490
Mean	53.5	54.1	55.3	55.1	54.2	56.0	54.7
SD	9.1	8.5	9.8	10.0	9.3	9.0	9.3
Median	54	54	54	57	55	56	55
Q1, Q3	49, 60	48, 59	48, 63	50, 62	50, 59	52, 63	49, 61
Min, Max	31, 72	33, 74	30, 74	21, 73	30, 71	33, 74	21, 74
Age [n (%)]							
<65	74 (90.2)	74 (90.2)	64 (78.0)	67 (81.7)	69 (85.2)	68 (84.0)	416 (84.9)
>=65	8 (9.8)	8 (9.8)	18 (22.0)	15 (18.3)	12 (14.8)	13 (16.0)	74 (15.1)
Race [n (%)]							
Black or African American	31 (37.8)	28 (34.1)	26 (31.7)	35 (42.7)	26 (32.1)	32 (39.5)	178 (36.3)
American Indian or Alaska Native	1 (1.2)	0	2 (2.4)	1 (1.2)	0	0	4 (0.8)
Asian	2 (2.4)	0	1 (1.2)	0	0	2 (2.5)	5 (1.0)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	1 (1.2)	1 (0.2)
White	48 (58.5)	54 (65.9)	53 (64.6)	46 (56.1)	55 (67.9)	46 (56.8)	302 (61.6)

SD=Standard Deviation
Output: T_DEMOG_FAS, Produced by biarnal1 on 16MAY2017 17:44 (CET), SDTM production date: 12MAY2017
Program: val_csr/program_output/dem01.sas
Page 1 of 2

Ethnicity [n (%)]							
Hispanic or latino	23 (28.0)	26 (31.7)	31 (37.8)	27 (32.9)	28 (34.6)	26 (32.1)	161 (32.9)
Not hispanic or latino	59 (72.0)	56 (68.3)	51 (62.2)	55 (67.1)	53 (65.4)	55 (67.9)	329 (67.1)
Country [n (%)]							
United States	75 (91.5)	75 (91.5)	74 (90.2)	73 (89.0)	75 (92.6)	71 (87.7)	443 (90.4)
Canada	3 (3.7)	1 (1.2)	6 (7.3)	4 (4.9)	2 (2.5)	5 (6.2)	21 (4.3)
Israel	4 (4.9)	6 (7.3)	2 (2.4)	5 (6.1)	4 (4.9)	5 (6.2)	26 (5.3)

SD=Standard Deviation
Output: T_DEMOG_FAS, Produced by biarnal1 on 16MAY2017 17:44 (CET), SDTM production date: 12MAY2017
Program: val_csr/program_output/dem01.sas
Page 2 of 2

Table 15-5 summarizes patient representatin in the different analysis sets.

Table 15-5 Overview of FAS, PPS, SAF, and PK analysis sets, All Randomized Set

ACT-132577
Protocol: AC-080A201
Overview of FAS, PPS, SAF and PK analysis sets
Analysis Set: All Randomized Set

Analysis Set	Placebo n	ACT-132577 5 mg n	ACT-132577 10 mg n	ACT-132577 25 mg n	ACT-132577 50 mg n	Lisinopril 20 mg n	Total n
All randomized Set	82	82	82	82	81	81	490
Full Analysis Set	82	82	82	82	81	81	490
Per-Protocol Set	67	68	71	67	68	69	410
Pharmacokinetic Set*	67	68	71	65	67	69	407
Safety Set*	82	82	82	82	81	81	490

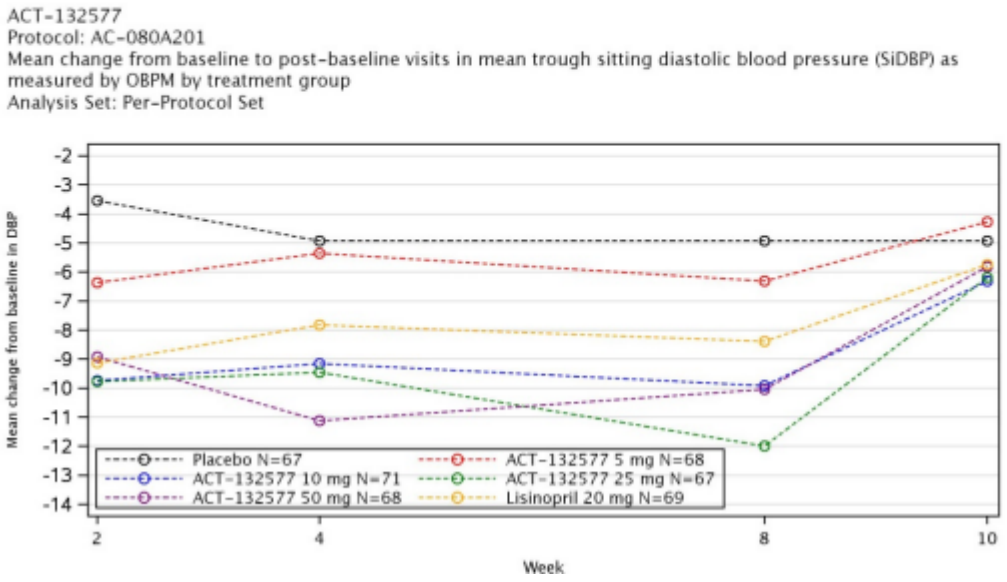
*Based on actual treatment
Output: T_ANSETOV_RND, Produced by biarnal1 on 16MAY2017 17:43 (CET), SDTM production date: 12MAY2017
Program: val_csr/program_output/anset.sas
Page 1 of 1

Outcomes and estimation

Primary analyses and key secondary analysis

Overall reductions from baseline in SiDBP were achieved by Week 2 for all four ACT-132577 doses, with the reductions relative to baseline being sustained for the 10, 25, and 50 mg dose groups up to Week 8 [Figure 11-2 and 11-3]. For the 50 mg dose group, there was a slight increase in the mean SiDBP going from Week 4 to Week 8, although the overall reduction from baseline was maintained. The changes in SiDBP from baseline to Week 8 for the 20 mg lisinopril group were greater than the changes observed with the placebo and 5 mg ACT-132577 groups but less than the 10, 25, and 50 mg ACT-132577 dose groups. Similar dose related results were observed for SiSBP.

Figure 11-2 Mean change from baseline to post-baseline visits in mean trough sitting diastolic blood pressure (SiDBP) as measured by OBPM by treatment group, Per-Protocol Set



The primary efficacy objective for this study was met, in that a dose-response relationship on the change from baseline to Week 8 (i.e., end of the DB treatment period) in mean trough SiDBP was observed for the ACT-132577 doses ($P < 0.001$ for all six pre-specified dose-response models: linear, linear in log, quadratic, Emax, sigmoidal Emax and logistic) [Figure 15-3.] The placebo group was plotted as ACT-132577 = 0 mg. A quadratic model fit these data best.

Table 11-2 Change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) as measured by OBPM by treatment group, Per-Protocol Set

ACT-132577
Protocol: AC-080A201
Change from baseline to post-baseline visits in mean trough sitting diastolic blood pressure (SiDBP) as measured by OBPM by treatment group
Analysis Set: Per-Protocol Set

Diastolic Blood Pressure (mmHg), Week 8

	Placebo N = 67*	ACT-132577 5 mg N = 68	ACT-132577 10 mg N = 71	ACT-132577 25 mg N = 67	ACT-132577 50 mg N = 68	Lisinopril 20 mg N = 69
Observed Values At Baseline						
n	66	68	71	67	68	69
Missing	1	0	0	0	0	0
Mean (SD)	97.5 (5.4)	97.8 (5.5)	97.7 (4.3)	97.8 (4.8)	98.2 (5.3)	96.8 (4.6)
Median (Min, Max)	97 (79, 109)	98 (73, 107)	97 (90, 108)	97 (90, 109)	99 (81, 108)	96 (90, 107)
Observed Values At Week 8						
n	66	68	71	67	68	69
Missing	1	0	0	0	0	0
Mean (SD)	92.6 (11.0)	91.5 (9.2)	87.8 (10.4)	85.8 (8.4)	88.1 (9.3)	88.4 (9.7)
Median (Min, Max)	94 (66, 122)	92 (70, 108)	89 (61, 108)	86 (67, 104)	89 (59, 112)	88 (63, 114)
Absolute Change from Baseline to Week 8						
n	66	68	71	67	68	69
Missing	1	0	0	0	0	0
Mean (SD)	-4.9 (11.1)	-6.3 (8.9)	-9.9 (8.7)	-12.0 (8.2)	-10.0 (7.9)	-8.4 (9.6)
Median (Min, Max)	-3 (-34, 17)	-5 (-27, 10)	-9 (-34, 7)	-11 (-30, 7)	-11 (-32, 10)	-9 (-30, 7)

SD=Standard Deviation, Number Missing corresponds to change from baseline

*In the placebo group, one subject had out of analysis window blood pressure measurement.. This subject was part of the PPS [see Section 9.9.3]
Source: Modified from Table 15-31 (T_DBP_CHG_PPS).

Table 11-4 Change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP) as measured by OBPM by treatment group, Per-Protocol Set

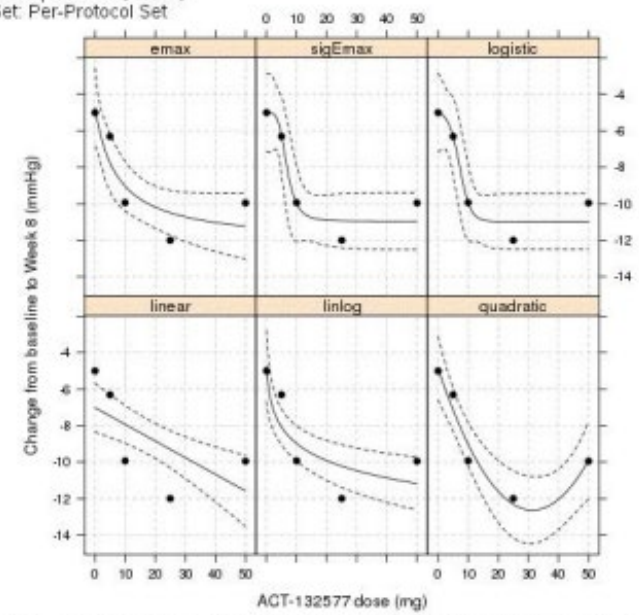
ACT-132577
Protocol: AC-080A201
Change from baseline to post-baseline visits in mean trough sitting systolic blood pressure (SiSBP) as measured by OBPM by treatment group
Analysis Set: Per-Protocol Set

	Placebo N = 67*	ACT-132577 5 mg N = 68	ACT-132577 10 mg N = 71	ACT-132577 25 mg N = 67	ACT-132577 50 mg N = 68	Lisinopril 20 mg N = 69
Observed Values At Baseline						
n	66	68	71	67	68	69
Missing	1	0	0	0	0	0
Mean (SD)	149.2 (13.1)	149.4 (13.9)	149.8 (12.7)	151.2 (13.7)	148.6 (12.8)	149.8 (14.2)
Median (Min, Max)	148 (126, 187)	149 (99, 178)	148 (127, 196)	152 (121, 179)	148 (119, 177)	149 (118, 179)
Observed Values At Week 8						
n	66	68	71	67	68	69
Missing	1	0	0	0	0	0
Mean (SD)	141.5 (18.6)	139.1 (16.8)	134.8 (15.6)	132.7 (15.6)	133.6 (13.3)	137.0 (18.5)
Median (Min, Max)	138 (128, 156)	139 (129, 151)	136 (122, 146)	131 (121, 144)	134 (125, 144)	137 (122, 149)
Absolute Change from Baseline to Week 8						
n	66	68	71	67	68	69
Missing	1	0	0	0	0	0
Mean (SD)	-7.7 (18.8)	-10.3 (15.3)	-15.0 (14.5)	-18.5 (15.0)	-15.1 (11.8)	-12.8 (16.0)
Median (Min, Max)	-8 (-19, 3)	-8 (-19, 1)	-13 (-23,-5)	-18 (-27,-9)	-14 (-22,-9)	-11 (-21, 3)

SD=Standard Deviation, Number Missing corresponds to change from baseline

* In the placebo group, one subject had out of analysis window blood pressure measurement. This subject was part of the PPS [see Section 9.9.3], and a missing value assigned.
Source: Modified from Table 15-63 (T_SBP_CHG_PPS).

ACT-132577
Protocol: AC-080A201
MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP)
Analysis Set: Per-Protocol Set



Output: F_DBP_MCPMOD_PPS, Produced by petratd on 16MAY2017 19:05 (CET), SDTM production date: 12MAY2017
Program: val_csr/program_output/anc02_il3.sas

Source: Figure 15-3

The primary endpoint was also analysed in the PPS and in the FAS using an ANCOVA model with a factor for treatment group and a covariate for baseline mean trough SiDBP. Each of the four doses of ACT-132577 was compared with placebo, applying Dunnett's test. Of the four ACT-132577 dose groups, three (10, 25 and 50 mg) showed statistically significant reductions in mean trough SiDBP and mean trough SiSBP at the end of the DB treatment period (i.e., Week 8). The differences vs placebo were for SiDBP −4.93 mmHg (95% CI: −8.68, −1.17; P = 0.0053), −6.99 mmHg (95% CI: −10.80, −3.19; P < .0001) and −4.95 mmHg (95% CI: −8.75, −1.15; P = 0.0057) for the 10, 25 and 50 mg groups, respectively in the PPS, and were similar in the FAS. For the secondary endpoint SiSBP the changes were: −7.05 mmHg (−12.98, −1.12; P = 0.0138), −9.90 mmHg (−15.92 −3.88; P = 0.0003), and −7.58 mmHg (−13.58, −1.59; P = 0.0077) for the 10, 25 and 50 mg groups, respectively in the PPS (similar in the FAS).

Differences vs placebo across all aprocitentan dose groups for the change from baseline to Week 10 (i.e., end of the SB withdrawal period) in BP were small (ranged from −1.3 to 0.6 for the SiDBP and from −2.5 to 1.4 for SiSBP) indicating reversibility of pharmacological effect of aprocitentan without a rebound phenomenon at Week 10.

Subgroup analyses by age, sex, and race on the change from baseline to Week 8 in SiDBP and SiSBP did not reveal remarkable differences in the dose-response relationship between subgroups.

24 h and daytime/night-time SBP and DBP recorded via ABPM

Week 8 24 h ambulatory and daytime and night-time BP values are summarized in Table 4-2. 24 h Mean DBP decreased significantly at the 10, 25 and 50 mg aprocitentan dose levels, for mean SBP the decrease was significant for 25 mg. When analysed separately by daytime and night-time, there was a numerically larger decrease for these dose levels as compared to placebo that reached statistical significance for daytime DBP at

the 10 and 25 mg dose and for DBP and SBP at night-time for the 25 mg dose.

Table 4-2 Between-treatment analysis for changes from baseline to Week 8 of DB treatment in 24 h and daytime/night-time SBP and DBP: PPS

Treatment group	Baseline # Mean (SD)	LS Mean (95% CL)	Difference to placebo LS Mean (95% CL)	Difference to placebo p-value
24 h mean SBP				
50 mg (N= 33)	141.28 (14.73)	−6.11 (−9.08, −3.13)	−2.20 (−6.64, 2.23)	0.3282
25 mg (N= 30)	140.83 (11.23)	−9.41 (−12.54, −6.29)	−5.51 (−10.05, −0.97)	0.0176
10 mg (N=36)	144.30 (15.68)	−6.76 (−9.63, −3.90)	−2.86 (−7.23, 1.51)	0.1975
5 mg (N= 37)	139.90 (15.87)	−3.65 (−6.51, −0.80)	0.25 (−4.11, 4.60)	0.9103
Placebo (N= 27)	140.28 (14.20)	−3.90 (−7.19, −0.61)	-	-
24 h mean DBP				
50 mg (N= 33)	91.53 (10.54)	−5.82 (−7.86, −3.77)	−3.18 (−6.23, −0.13)	0.0410
25 mg (N= 30)	89.28 (9.53)	−9.34 (−11.49, −7.19)	−6.71 (−9.82, −3.59)	<.0001
10 mg (N=36)	92.60 (10.92)	−6.08 (−8.04, −4.12)	−3.45 (−6.44, −0.45)	0.0244
5 mg (N= 37)	90.60 (10.19)	−3.86 (−5.82, −1.90)	−1.23 (−4.22, 1.76)	0.4188
Placebo (N= 27)	90.46 (10.66)	−2.64 (−4.90, −0.37)	-	-
Daytime mean SBP				
50 mg (N= 33)	146.39 (16.22)	−5.08 (−8.61, −1.54)	−1.01 (−6.28, 4.26)	0.7057
25 mg (N= 30)	144.08 (13.15)	−7.06 (−10.76, −3.35)	−2.99 (−8.37, 2.39)	0.2740
10 mg (N=36)	148.83 (17.52)	−6.52 (−9.92, −3.12)	−2.45 (−7.64, 2.74)	0.3521
5 mg (N= 37)	142.67 (18.29)	−1.46 (−4.85, 1.94)	2.61 (−2.55, 7.78)	0.3193
Placebo (N= 27)	143.92 (14.82)	−4.07 (−7.97, −0.16)	-	-
Daytime mean DBP				
50 mg (N= 33)	95.76 (11.95)	−5.23 (−7.65, −2.81)	−3.00 (−6.61, 0.62)	0.1037
25 mg (N= 30)	92.56 (10.98)	−7.56 (−10.10, −5.02)	−5.32 (−9.01, −1.64)	0.0049
10 mg (N=36)	96.34 (12.53)	−6.31 (−8.63, −3.98)	−4.07 (−7.62, −0.52)	0.0250
5 mg (N= 37)	93.41 (12.34)	−2.48 (−4.79, −0.16)	−0.24 (−3.78, 3.30)	0.8923
Placebo (N= 27)	92.94 (11.12)	−2.23 (−4.91, 0.44)	-	-

Night-time mean SBP				
50 mg (N= 33)	129.93 (15.36)	−7.06 (−11.07, −3.06)	−3.13 (−9.09, 2.83)	0.3010
25 mg (N= 30)	132.09 (12.61)	−12.08 (−16.27, −7.88)	−8.14 (−14.24, −2.05)	0.0092
10 mg (N=36)	134.25 (19.35)	−6.66 (−10.50, −2.82)	−2.73 (−8.59, 3.14)	0.3597
5 mg (N= 37)	133.49 (15.50)	−6.13 (−9.96, −2.30)	−2.20 (−8.05, 3.66)	0.4596
Placebo (N= 27)	130.58 (16.46)	−3.93 (−8.36, 0.49)	-	-
Night-time mean DBP				
50 mg (N= 33)	83.61 (11.23)	−6.01 (−8.80, −3.23)	−2.54 (−6.69, 1.61)	0.2278
25 mg (N= 30)	80.91 (10.08)	−11.46 (−14.39, −8.53)	−7.99 (−12.24, −3.74)	0.0003
10 mg (N=36)	84.58 (13.40)	−5.27 (−7.94, −2.60)	−1.80 (−5.87, 2.27)	0.3837
5 mg (N= 37)	83.98 (9.22)	−5.35 (−8.02, −2.68)	−1.88 (−5.95, 2.19)	0.3631
Placebo (N= 27)	83.68 (13.16)	−3.47 (−6.55, −0.39)	-	-

ANCOVA model with a factor for treatment and a covariate for baseline mean 24−h/daytime/night−time SBP/DBP.
ANCOVA= analysis of covariance; CL = confidence limit; DB= double−blind; DBP = diastolic blood pressure; LS mean = least squares mean; PPS = Per-protocol set; SBP = systolic blood pressure; SD = standard deviation.
Source: Compiled from D-17.023, table 15-100, table 15-101, table 15-103, table 15-104, table 15-109, table 15-110, table 15-111, table 15-112, table 15-113, table 15-114, table 15-115 and table 15-116.

- The Applicant stated that a quadratic model was most appropriate for the BP data and that the maximum effect was reached at a dose of approximately 30 mg, and half of the effect at approximately 10 mg. The underlying assumption of a lower efficacy of the 50 mg vs. the 25 mg dose is not quite understood and it may well be a chance finding. Data indicating a lack of an association between efficacy and plasma ET-1 concentrations indicated that increases of plasma ET-1 at higher doses were not a likely explanation for a potentially lower efficacy of the 50 vs. the 25 mg dose. Overall, the U-shaped dose-response curve is not entirely understood.

2.6.5.2. Main study

The pivotal study for this application was study ID-080A301 ("Study 301", PRECISION) conducted in the target group of patients with RHT.

Title of study

Study number: ID-080A301 (PRECISION)

Multi-center, blinded, randomized, PaRallEl-group, Phase 3 study with aproCItentan in Subjects with ResIstant HypertensiON (RHT)

Study Dates: First subject, first visit: 18 June 2018 Last subject, last visit: 25 April 2022

Coordinating Investigator: Markus Schlaich, MD Royal Perth Hospital Level 3, MRF Building, Rear 50 Murray St., Perth WA 6000, Australia

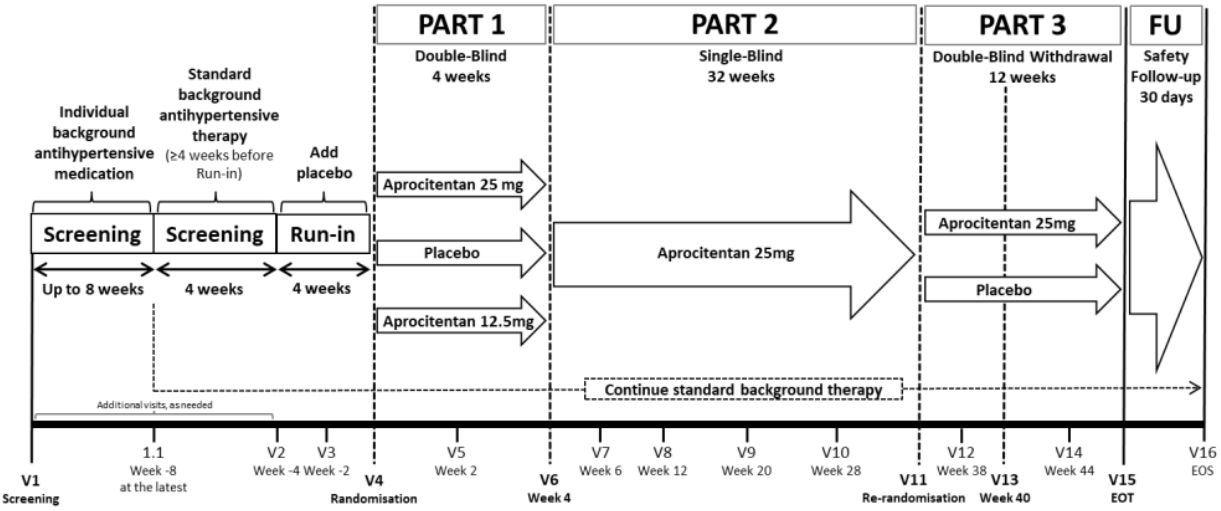
Methods

It was a prospective, multi-center, randomized, parallel-group, blinded Phase 3 study with aprocitentan in subjects with RHT.

The study was conducted (i.e., subjects were screened) at 193 sites in 22 countries countries, subjects were randomized at 138 sites in 20 countries in Australia, Western and Eastern Europe, Canada, US, , and Asia.

The study consisted of a screening period, placebo run-in period, randomized treatment period, and safety follow-up (FU) period [Figure 2-1]

Figure 2-1 Study design for ID-080A301/PRECISION



EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up; SBAT = standardized background antihypertensive therapy; V = study visit.

Screening period (4–12 weeks):

The purpose of the screening period was among others to select subjects with a confirmed diagnosis of RHT, i.e., exclusion of pseudo RHT and secondary causes of hypertension according to local medical practice.

At least 4 weeks before the start of the placebo run-in period, individual background antihypertensive medications (except beta-blockers) were switched to a standardized background antihypertensive therapy (SBAT): a fixed dose combination of a calcium channel blocker (amlodipine, 5 or 10 mg), an angiotensin receptor blocker (valsartan, 160 mg), and a diuretic (hydrochlorothiazide, 25 mg).

Placebo run-in period (4 weeks):

During this single-blind (SB) period, placebo was added to SBAT. The purpose of this period was to confirm that mean trough sitting systolic BP (SiSBP) remained ≥ 140 mmHg, despite administration of placebo for 4 weeks in addition to SBAT, and thus to exclude potential placebo responders.

Randomized treatment period (48 weeks; 3 sequential parts):

• Double-blind (DB) part 1 (4 weeks): subjects were randomized 1:1:1 to receive aprocitentan 25 mg, aprocitentan 12.5 mg, or placebo.

• SB part 2 (32 weeks): all subjects received aprocitentan 25 mg.

• DB withdrawal (DB-WD) part 3 (12 weeks): subjects were re-randomized 1:1 to receive aprocitentan 25 mg or placebo. The End-of-Treatment (EOT) visit was to take place at Week 48 (end of DB-WD part 3), or earlier if a subject prematurely discontinued study treatment. The EOT visit was to take place as soon as possible and no later than 7 days after the last dose of study treatment.

Safety FU period (30–33 days).

- **Study Participants**

Key inclusion criteria:

• Male and female subjects; 18 years (or year of country-specific majority) or older.

• Historical documentation of uncontrolled BP, despite at least 3 background antihypertensive medications within 1 year before the screening visit.

• Treatment with at least 3 antihypertensive therapies of different pharmacological classes for at least 4 weeks before the screening visit (Visit 1).

Requirement to include a diuretic as 1 of 3 antihypertensives was removed and clarification regarding the use of beta-blockers were provided in Global Protocol Amendment 2.

• Mean SiSBP ≥ 140 mmHg recorded via uAOBPM at the screening visit and at the switch from individual background antihypertensive medications

RI entry criteria (among others)

• Mean trough SiSBP ≥ 140 mmHg (uAOBPM).

Randomization criteria (end of RI, among others)

• Mean trough SiSBP ≥ 140 mmHg (uAOBPM).

Main exclusion criteria (among others):

• Confirmed severe hypertension (grade 3), defined as mean SiSBP ≥ 180 mmHg and/or sitting diastolic blood pressure (SiDBP) ≥ 110 mmHg recorded via uAOBPM at two different time points.

• Transient ischemic attack, stroke, unstable angina, or myocardial infarction within 6 months prior to screening.

• Clinically significant unstable cardiac disease at screening or in the past, in the opinion of the investigator, e.g., uncontrolled symptomatic arrhythmia, atrial fibrillation, congestive heart failure NYHA stage II with relevant mitral valve insufficiency and/or aortic stenosis, congestive heart failure NYHA stage III or IV.

• Severe renal insufficiency (defined as an estimated glomerular filtration rate [eGFR] per the chronic kidney disease-epidemiology collaboration creatinine equation < 15 mL/min/1.73 m2) or type 1 diabetes.

• Presence of marked laboratory abnormalities: – Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of the normal range (ULN) (or severe hepatic impairment). – Hemoglobin < 100 g/L. – N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥ 500 pg/mL.

- **Treatments**

Assessment of compliance was calculated based on study treatment accountability.

INVESTIGATIONAL TREATMENT BATCH No. / DOSE / ROUTE / REGIMEN / DURATION

Aprocitentan 12.5 and 25 mg film-coated tablets. Batch numbers 12.5 mg: 1711985, 1815788, 2010225, Batch numbers 25 mg: 1711993, 1815781, 2010217

1 tablet was taken orally each morning, irrespective of food intake. On study visit days, study treatment was administered after completion of the visit assessments.

DB part 1: 12.5 or 25 mg once daily (o.d.) for 4 weeks

SB part 2: 25 mg o.d. for 32 weeks DB-WD part 3: 25 mg o.d. for 12 week

REFERENCE TREATMENT BATCH No. / DOSE / ROUTE / REGIMEN / DURATION

Placebo film-coated tablets matching aprocitentan 12.5 and 25 mg film-coated tablets. Batch numbers: 1712798, 1814797, 2010536

1 tablet was taken orally each morning, irrespective of food intake. On study visit days, study treatment was administered after completion of the visit assessments.

Placebo RI period: o.d. for 4 weeks

DB part 1: o.d. for 4 weeks DB-WD part 3: o.d. for 12 weeks

MANDATORY STANDARDIZED BACKGROUND ANTIHYPERTENSIVE THERAPY (SBAT) BATCH No. / DOSE / ROUTE / REGIMEN / DURATION

Single-pill, triple fixed dose combination: amlodipine (5 or 10 mg) + valsartan (160 mg) + hydrochlorothiazide (25 mg), Batch numbers: APCA073, APCA214, APCA359, APCA475, APCC006, APCC092, APCC547, APCC549, APCC959, APCD024, BAL12, BAL98, BAM03, BAX96, BCJ53, BDJ34, BDJ35, BEH52, BEP65, BHP71, BHW18, BJH05, BJR32, BPH90, BPU86, BTY06, BTY17.

- **Objectives**

Primary objective: To demonstrate the blood pressure (BP) lowering effect of aprocitentan when added to standard-of-care in subjects with "true RHT" (i.e., diagnosed following exclusion of pseudo RHT and secondary causes of hypertension, according to local medical practice).

Secondary objective

s: To demonstrate that the effect of aprocitentan on BP is durable when added to standard-of-care in subjects with RHT, and to evaluate the long-term safety and tolerability of aprocitentan in subjects with RHT during 48 weeks of treatment.

- **Outcomes/endpoints**

Primary efficacy endpoint:

• Change from baseline to Week 4 of double-blind treatment in mean trough SiSBP (Unattended automated office blood pressure measurement (uAOBPM)).

Secondary efficacy endpoints:

Key secondary efficacy endpoint:

• Change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP (uAOBPM).

Other secondary efficacy endpoints:

• Change from baseline to Week 4 of double-blind treatment in mean trough SiDBP (uAOBPM).

• Change from DB-WD baseline (Week 36) to Week 40 in mean trough SiDBP (uAOBPM).

• Changes from baseline to Week 4 of double-blind treatment in 24 h mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) recorded via ambulatory blood pressure monitoring (ABPM)).

• Changes from DB-WD baseline (Week 36) to Week 40 in 24 h mean SBP and DBP (ABPM).

And other BP related endpoints, PD endpoints, and safety endpoints.

- **Sample size**

Approximately 4000 subjects were expected to be screened, in order to include approximately 1500 subjects with a diagnosis of RHT in the placebo run-in period. At least 600 subjects were planned to be randomized 1:1:1 to receive aprocitentan 12.5 mg, aprocitentan 25 mg, or placebo in DB part 1; and at least 380 subjects were expected to be re-randomized 1:1 to receive aprocitentan 25 mg or placebo in DB-WD part 3.

- **Randomisation and Blinding (masking)**

Patients were assigned to treatments via an IRT system handled by an independent vendor which generated two randomization lists, one for DB part 1 and one for DB-WD part 3

Two parts of the study were performed in a single-blind fashion: the placebo RI period prior to randomization, and SB part 2. Two parts were performed in a double-blind fashion: DB part 1 and DB-WD part 3.

- **Statistical methods**

<u>Estimand (Target of Estimation)</u>

This section describes the strategy for addressing intercurrent events for the primary and key secondary efficacy endpoints.

The target population is described in Section 9.3 of the CSR and the endpoints measured are described in Section 8.2 of the CSR. Treatment was aprocitentan compared to placebo, each added to standard-of-care.

There were 3 types of intercurrent events during DB part 1 that could interfere with the analysis of the primary efficacy endpoint: premature discontinuation of double-blind treatment, addition / dose increase of a diuretic, and use of antihypertensive rescue medication (although rescue medication was not allowed during DB part 1). Two strategies for handling intercurrent events were considered:

Treatment policy strategy estimand (primary) [ICH 2019]: all uAOBPM recordings, irrespective of any intercurrent event(s), were included in the main analysis.

Hypothetical strategy estimand (supplementary) [ICH 2019]: uAOBPM recordings obtained more than 1 day after premature discontinuation of double-blind treatment were excluded from the main analysis (i.e., considered missing). This approach reflected that it was anticipated that the effect of treatment on BP would be lost after discontinuation of treatment. In this setting, it is not usual practice to assess effectiveness after (premature) treatment discontinuation [O'Neill 2012]. uAOBPM recordings obtained after the addition of a diuretic, or use of rescue medication, were also excluded from the analysis.

The key secondary estimand was specified accordingly.

Following comments received from regulatory agencies on SAP Version 2, the treatment policy strategy was used in the main analysis.

Statistical methods

The statistical analyses of study data were described in the protocol and elaborated in the SAP, which was updated during the conduct of the study and finalized on 6 April 2022, prior to database lock (12 May 2022).

Analysis populations:

Full analysis set (FAS): All subjects who were randomized and had a baseline SiSBP recorded via uAOBPM at trough. Subjects were evaluated according to their assigned study treatment in DB part 1: aprocitentan 25 mg, aprocitentan 12.5 mg, or placebo.
Modified Full analysis set (mFAS): All subjects from the FAS who were re-randomized in DB-WD part 3 and had a DB-WD baseline SiSBP recorded via uAOBPM at trough. Subjects were evaluated according to their assigned study treatment in DB-WD part 3: aprocitentan 25 mg or placebo.

The main analysis of the primary endpoint change from baseline to Week 4 in mean trough SiSBP recorded via uAOBPM was conducted on the FAS for the 3 treatment groups (aprocitentan 25 mg, aprocitentan 12.5 mg, and placebo). All uAOBPM recordings, irrespective of any intercurrent event(s), were included in the main analysis, leading to a treatment policy strategy estimand.

The main analysis for the change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP recorded via uAOBPM was conducted on the mFAS for the 2 treatment groups (aprocitentan 25 mg and placebo).

The first H_{10} and second H_{20} null hypotheses were that, in the DB part, no difference existed between aprocitentan 25 mg and placebo, or aprocitentan 12.5 mg and placebo, respectively, in the mean change from baseline to Week 4 in mean trough SiSBP. These hypotheses were tested at a two-sided significance level of 0.025 using the Bonferroni correction.
The third null hypothesis H_{30} was that there was no difference between aprocitentan 25 mg and placebo in the mean change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP in the DB-WD part. It was only planned to be tested if H_{10} or H_{20} were rejected: at a two-sided significance level of 0.05 if both H_{10} and H_{20} were rejected and at a two-sided significance level of 0.025 if only one was rejected. In that way, the overall type I error was protected at 0.05.

All other secondary efficacy variables were tested at the two-sided significance level of 0.05. No correction for multiplicity was applied.

Changes from baseline to post-baseline visits up to Week 4 were analyzed using a mixed model with factors for treatment group, visit, and treatment by visit interaction, and covariates for baseline SiSBP and the interaction between baseline SiSBP and visit. An unstructured covariance matrix was used to account for the correlation between repeated BP measurements from the same subject. LS mean differences vs placebo at Week 4 and their 97.5% CIs were obtained from the model. The associated p-values were used to test the first and second null hypotheses.

The main analysis for the key secondary endpoint, change from DB-WD (Week 36) to visits up to Week 40 in mean trough SiSBP, was conducted on the mFAS using a mixed model as described above but using the DB-WD baseline and an additional factor for stratum (i.e., randomized treatment in the DB part).

The following sensitivity analyses were conducted for the primary endpoint and key secondary efficacy endpoint:

(1) The impact of deviations from the MAR assumption underlying the mixed model was investigated assuming that, in the aprocitentan groups, the data were MNAR. Two control-based multiple imputation procedures were performed under MNAR: a copy-reference and a jump-to-reference approach [Carpenter 2013].
(2) A tipping point approach was used to assess how severe departures from the MAR assumption had to be to overturn the conclusions of the main analysis.
(3) All uAOBP recordings obtained more than 1 day after premature discontinuation of DB and DB-WD treatments or obtained after the addition of a diuretic were excluded from the main analysis (i.e., considered missing), leading to a hypothetical strategy estimand in ICH terminology [ICH 2019]. In addition, uAOBP recordings obtained after initiation of antihypertensive rescue medication were also excluded from these analyses.
(4) Site 4204, from which the data were considered not trustworthy (as per internal audit report), was excluded
(5) ANCOVAs were performed on the FAS for the change from baseline to Week 4 imputing missing data using LOCF, and BOCF,

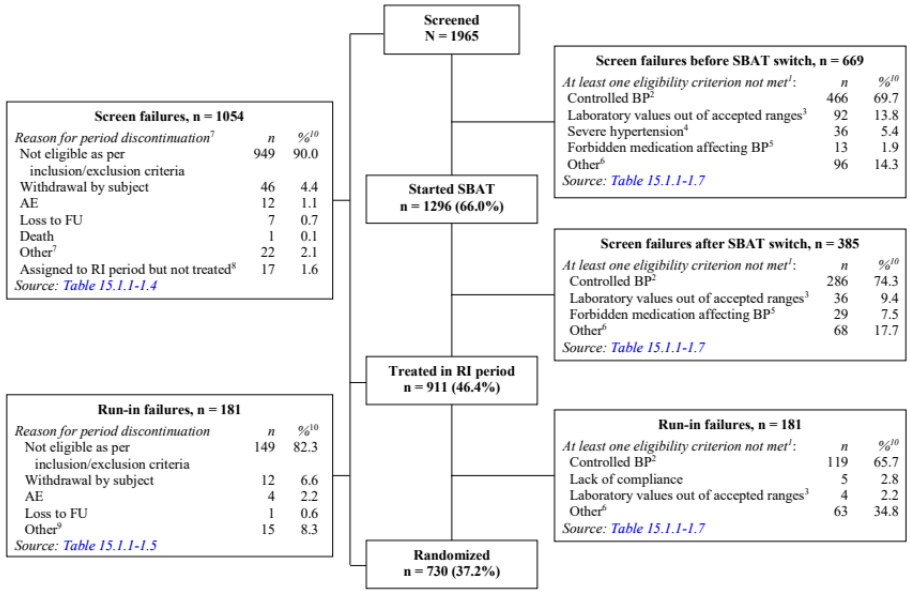
Subgroup analyses were conducted to explore the consistency of treatment effect in relevant subgroups, and results were displayed in a forest plot.

Results

- **Participant flow**

Disposition of patients is summarized in Figures 10-1 and updated figure 4 including reasons for discontinuing (including "withdrawal by subject due to AE" and the single case of SSDC fluid retention)

Figure 10-1 Disposition of subjects in the screening and RI periods



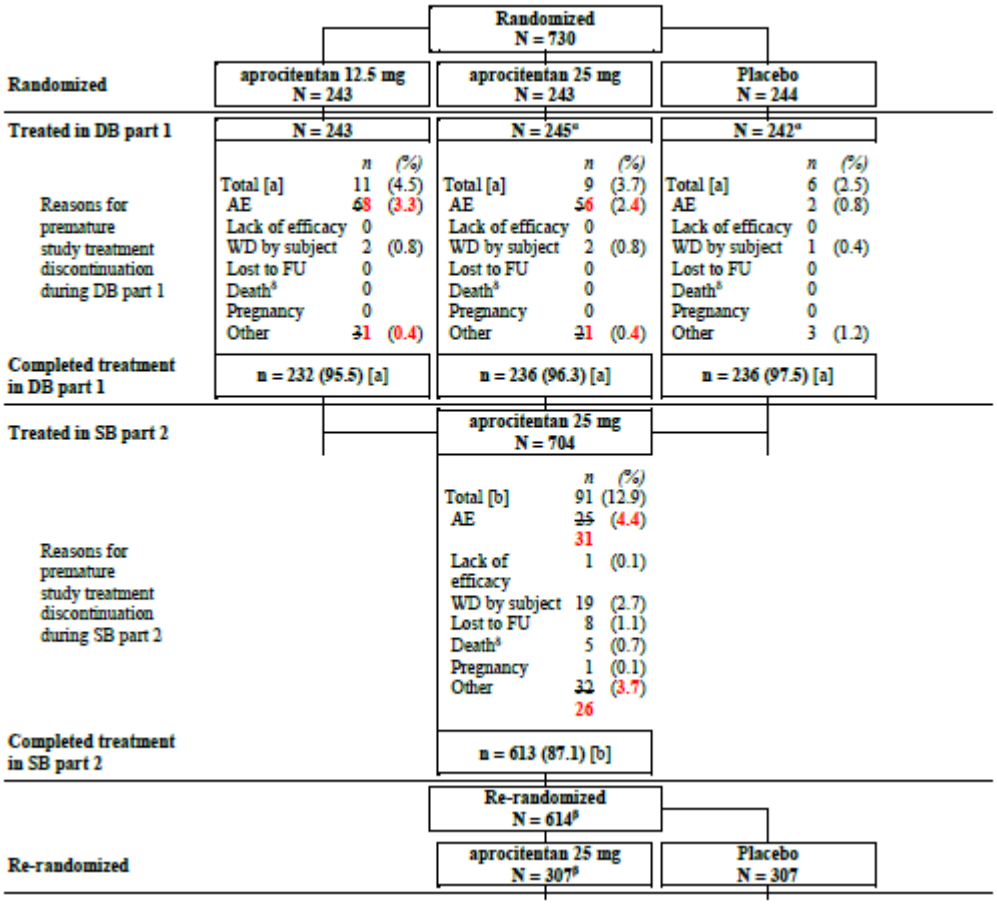
Unless otherwise stated, percentages are calculated based on total number of subjects screened.

[1] Refers to subjects with at least one IC not met / EC met, irrespective of their reason for period discontinuation. Subjects may be counted in multiple rows if multiple eligibility criteria were not met.

[2] Refers to mean SiSBP < 140 mmHg; as per IC 5, 8, 10, and 12 [Section 9.3.3], subjects were required to have a mean SiSBP ≥ 140 mmHg at the screening visit, at the switch to SBAT, at entry to the RI period, and at randomization.

[3] Screen failures: laboratory values out of accepted ranges based on EC 16 [Section 9.3.4]: alanine aminotransferase or aspartate aminotransferase > 3 times the upper limit of normal, hemoglobin < 100 g/L, and N-terminal pro-brain natriuretic peptide ≥ 500 pg/mL.

Figure 4 Updated disposition of randomized subjects



Treated in DB-WD part 3	**N = 310[x]**			**N = 303[x]**		
		n	*(%)*		*n*	*(%)*
Reasons for premature study treatment discontinuation during DB-WD part 3	Total [c]	19	(6.1)	Total [c]	17	(5.6)
	AE	~~9~~12	(3.9)	AE	~~6~~8	(2.6)
	Lack of efficacy	0		Lack of efficacy	0	
	WD by subject	1	(0.3)	WD by subject	4	(1.3)
	Lost to FU	0		Lost to FU	1	(0.3)
	Death[δ]	0		Death[δ]	0	
	Pregnancy	0		Pregnancy	0	
	Other	~~6~~6	(1.9)	Other	~~4~~4	(1.3)
Completed treatment in DB-WD part 3	**n = 291 (93.9) [c]**			**n = 286 (94.4) [c]**		

Completed End-of-Study visit	**N = 662**				
Prematurely discontinued study (during any study part)	**Discontinued study n = 68 (9.3) [d]**				
	WD by subject	AE	Lost to FU	Death[δ]	Other
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
	24 (3.3)	7 (1.0)	9 (1.2)	12 (1.6)	16 (2.2)

N = number of subjects treated per study part.

n (%) = number (%) of subjects who prematurely discontinued each study part, and those who completed each study part.

Percentages are based on number of subjects: [a] treated in DB part 1; [b] treated in SB part 2; [c] treated in DB-WD part 3; [d] randomized.

[α] Two subjects (1069002 and 1113001) randomized to placebo received at least one dose of aprocitentan 25 mg during DB part 1 and were attributed to the aprocitentan 25 mg group in the SAF.

[β] One subject (1092013) who had discontinued study treatment in SB part 2 was re-randomized in error to the aprocitentan 25 mg group in DB-WD part 3 but did not receive DB-WD study treatment.

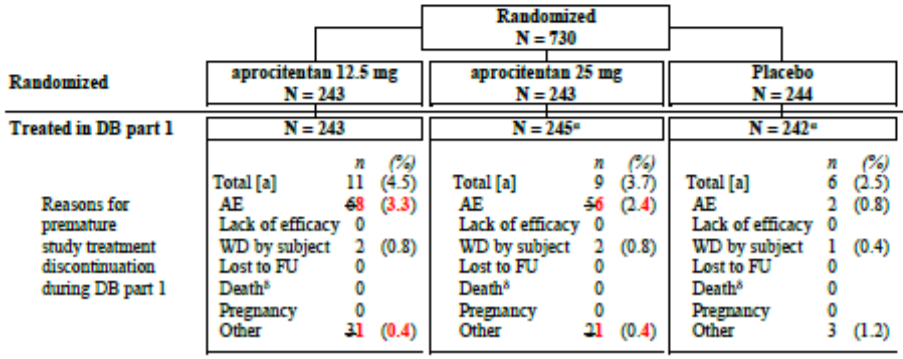
[χ] Four subjects (1026013, 3800002, 3800006 and 4308006) randomized to placebo received at least one dose of aprocitentan 25 mg during DB-WD part 3 and were attributed to the aprocitentan 25 mg group in the SAF.

[δ] 12 randomized subjects died during the study: 1 during DB part 1, 9 during SB part 2, 1 during DB-WD part 3, and 1 subject who died > 30 days after study treatment discontinuation. For 5 of the subjects who died during SB part 2, death was reported as the reason for premature study treatment discontinuation.

AE = adverse event; DB = double-blind; DB-WD = double-blind withdrawal; FU = follow-up; RI = run-in; SAF = Safety set; SB = single-blind; WD = withdrawal.

Source: Compiled from table 15-1.1-1.1, table 15.1.1-1.10, table 15.1.1-1.11, table 15.1.1-1.12, table 15.1.1-1.13

Figure 5 Updated disposition of randomized subjects (extended)



Treated in DB-WD part 3	**N = 310[χ]**			**N = 303[χ]**		
		n	*(%)*		*n*	*(%)*
Reasons for premature study treatment discontinuation during DB-WD part 3	Total [c]	19	(6.1)	Total [c]	17	(5.6)
	AE	~~9~~12	(3.9)	AE	~~6~~8	(2.6)
	Lack of efficacy	0		Lack of efficacy	0	
	WD by subject	1	(0.3)	WD by subject	4	(1.3)
	Lost to FU	0		Lost to FU	1	(0.3)
	Death[δ]	0		Death[δ]	0	
	Pregnancy	0		Pregnancy	0	
	Other	~~9~~6	(1.9)	Other	~~6~~4	(1.3)
Completed treatment in DB-WD part 3	**n = 291 (93.9)** [c]			**n = 286 (94.4)** [c]		
Completed End-of-Study visit	**N = 662**					
Prematurely discontinued study (during any study part)	**Discontinued study n = 68 (9.3)** [d]					
	WD by subject	AE	Lost to FU	Death[δ]	Other	
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
	24 (3.3)	7 (1.0)	9 (1.2)	12 (1.6)	16 (2.2)	

N = number of subjects treated per study part.

n (%) = number (%) of subjects who prematurely discontinued each study part, and those who completed each study part.

Percentages are based on number of subjects: [a] treated in DB part 1; [b] treated in SB part 2; [c] treated in DB-WD part 3; [d] randomized.

[α] Two subjects ([redacted] and [redacted]) randomized to placebo received at least one dose of aprocitentan 25 mg during DB part 1 and were attributed to the aprocitentan 25 mg group in the SAF.

[β] One subject ([redacted]) who had discontinued study treatment in SB part 2 was re-randomized in error to the aprocitentan 25 mg group in DB-WD part 3 but did not receive DB-WD study treatment.

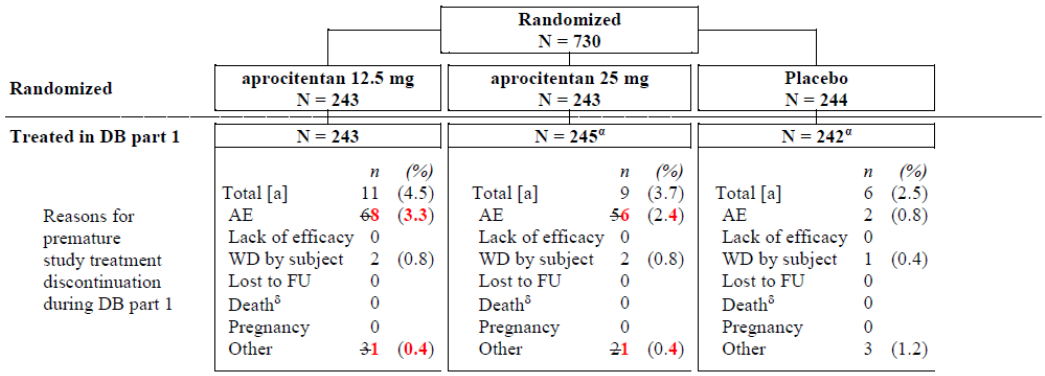
[χ] Four subjects ([redacted]) randomized to placebo received at least one dose of aprocitentan 25 mg during DB-WD part 3 and were attributed to the aprocitentan 25 mg group in the SAF.

[δ] 12 randomized subjects died during the study: 1 during DB part 1, 9 during SB part 2, 1 during DB-WD part 3, and 1 subject who died > 30 days after study treatment discontinuation. For 5 of the subjects who died during SB part 2, death was reported as the reason for premature study treatment discontinuation.

AE = adverse event; DB = double-blind; DB-WD = double-blind withdrawal; FU = follow-up; RI = run-in; SAF = Safety set; SB = single-blind; WD = withdrawal.

Source: Compiled from table 15-1.1-1.1, table 15.1.1-1.10, table 15.1.1-1.11, table 15.1.1-1.12, table 15.1.1-1.13

Figure 5 Updated disposition of randomized subjects (extended)



- **Recruitment and numbers analysed**

Out of 1965 screened subjects, 911 were included in the placebo RI period and 730 were randomized [Table 3-1].

Actual number of screened, randomized, and re-randomized subjects were as follows:

Screened set	(SCR)	1965 subjects were screened, of whom 1296 started SBAT.
Run-in set	(RIS)	911 subjects received placebo during the placebo RI period.
Full analysis set	(FAS)	730 subjects were randomized 1:1:1 and had a mean trough baseline SiSBP value recorded. Assigned treatment: 243 (aprocitentan 12.5 mg), 243 (aprocitentan 25 mg), and 244 (placebo).
Safety analysis set	(SAF)	730 subjects received at least 1 dose of study treatment during DB part 1. Actual treatment: 243 (aprocitentan 12.5 mg), 245 (aprocitentan 25 mg), and 242 (placebo).
Pharmacokinetic set	(PK)	399 subjects received at least 1 dose of aprocitentan and had evaluable plasma concentrations: 199 (12.5 mg) and 200 (25 mg).
Restricted Safety analysis set	(rSAF)	704 subjects received at least 1 dose of aprocitentan 25 mg during SB part 2.
Modified Full analysis set	(mFAS)	614 subjects were re-randomized and had a mean trough DB-WD baseline SiSBP value recorded. Assigned treatment: 307 (aprocitentan 25 mg) and 307 (placebo).
Modified Safety analysis set	(mSAF)	613 subjects received at least one dose of study treatment during DB-WD part 3. Actual treatment: 310 (aprocitentan 25 mg) and 303 (placebo)

A high proportion of the FAS (approximately 87%) was also included in the ambulatory blood pressure monitoring Full analysis set (i.e., had an evaluable baseline ABPM assessment),(Table 3-2)).

Table 3-2 Overview of the analysis sets

Study part / Analysis set		Aprocitentan 12.5 mg N (n%)	Aprocitentan 25 mg N (n%)	Placebo N (n%)	TOTAL N (n%)
DB part 1					
FAS	randomized subjects who had a mean trough baseline SiSBP (uAOBP)	243 (100)	243 (100)	244 (100)	730 (100)
aFAS	subjects from the FAS with a baseline 24 h mean SBP value (ABPM)	206 (84.8)	207 (85.2)	220 (90.2)	633 (86.7)
DB-WD part 3					
mFAS	re-randomized subjects in DB-WD part 3 who had a mean trough DB-WD baseline SiSBP (uAOBP)		307 (100)	307 (100)	614 (100)
maFAS	subjects from the mFAS with a DB-WD baseline 24 h mean SBP value (ABPM)		237 (77.2)	241 (78.5)	478 (77.9)

N refers to the total number of subjects in a given treatment group within a specific analysis set (FAS, mFAS); n (%) refers to the number (%) of subjects in a subset of the main analysis sets.
ABPM = ambulatory blood pressure monitoring; aFAS = ambulatory blood pressure monitoring Full analysis set; DB = double-blind; DB-WD = double-blind withdrawal; FAS = Full analysis set; maFAS = modified ambulatory blood pressure monitoring Full analysis set; mFAS = modified Full analysis set; (Si)SBP = (sitting) systolic blood pressure; uAOBP = unattended automated office blood pressure.
Source: Compiled from D-22.269 table 15.1.2-1.1 and table 15.1.2-1.3.

- **Conduct of the study**

According to the clinical study report (CSR) the study was performed in compliance with Good Clinical Practice.

GCP issues

Scientific misconduct, which led to subject participation in 2 clinical trials concurrently and serious violation of ALCOA+ requirements for trial site study documentation was identified at Site 4204, leading to premature closure of the site. Consequently, 9 randomized subjects prematurely discontinued study treatment and completed the 30-day safety FU period thereafter. In addition, a sensitivity analysis was conducted excluding all 27 randomized subjects from Site 4204 (Russian federation), i.e., 11 subjects (aprocitentan 12.5 mg), 7 subjects (aprocitentan 25 mg), and 9 subjects (placebo).

Other serious and/or persistent GCP non-compliance issues (e.g., consenting process, handling of source data, non-compliance with protocol, and non-compliance with ALCOA+ principles) were identified at 3 additional sites (1009, 1133, (both US based), 3700 (Italy)). Sponsor/oversight activities were implemented, in addition to those originally planned, in order to secure compliance, all issues were considered resolved by the Applicant.

Some additional issues were reported.

- Protocol deviations

Of the 490 subjects in the FAS, 33 (6.7%) subjects had at least one important deviation during DB treatment period, with the proportions across the 5, 10, 25, and 50 mg ACT-132577 dose groups being 9.8% (n = 8), 8.5% (n = 7), 6.1% (n = 5), and 4.9% (n = 4), respectively, compared with 6.1% (n = 5) in the placebo group and 4.9% (n = 4) in the 20 mg lisinopril group.

The impact of COVID-19 and of the Ukrainian war on the conduct of the study were assessed. Protocol deviations, COVID.19, and the Ukrainina war were not considered to have had a relevant impact on the robustness of the data and the conclusion on benefit and risk.

There were 2 Amendments concerning among others inclusion criteria, concomitant medication, exclusion of patients at high doses of loop diuretics at screening.

Mean compliance with study treatment and SBAT was above 97% through all parts of the study.

- **Baseline data**

The baseline characteristics of the randomized population were well balanced across treatment groups. The randomized population was predominantly male (59.5%) and White (82.9%), and the mean age was 61.7 years [Table 3-3]. 44% of subjects were aged ≥ 65 years, including 9.9% aged ≥ 75 years. 11.2% of subjects were Black or African American, representing 33.6% of the randomized subjects in North America. Most subjects were enrolled in Europe (61.4%) or in North America (31.8%). Subject retention rate in the study was high overall and in subpopulations, resulting in similar characteristics of the randomized (part 1) and re-randomized populations (part 3). The baseline characteristics of the re-randomized population were sufficiently balanced across treatment groups.

Table 3-3 Demographic characteristics of randomized and re-randomized subjects

	Randomized subjects (FAS)				Re-randomized subjects (mFAS)		
Variable	12.5 mg N=243	25 mg N=243	Placebo N=244	Total N=730	25 mg N=307	Placebo N=307	Total N=614
Age at screening [years] Mean (SD)	61.2 (10.3)	61.7 (10.4)	62.2 (11.2)	61.7 (10.6)	62.2 (10.5)	60.8 (10.7)	61.5 (10.6)
Age at screening (years) [n (%)]							
18 – < 65	143 (58.8)	136 (56.0)	130 (53.3)	409 (56.0)	160 (52.1)	189 (61.6)	349 (56.8)
65 – < 75	78 (32.1)	85 (35.0)	86 (35.2)	249 (34.1)	114 (37.1)	90 (29.3)	204 (33.2)
≥ 75	22 (9.1)	22 (9.1)	28 (11.5)	72 (9.9)	33 (10.7)	28 (9.1)	61 (9.9)
Sex [n (%)]							
Male	144 (59.3)	145 (59.7)	145 (59.4)	434 (59.5)	183 (59.6)	185 (60.3)	368 (59.9)
Race [n (%)]							
Black or African American	28 (11.5)	28 (11.5)	26 (10.7)	82 (11.2)	30 (9.8)	36 (11.7)	66 (10.7)
Asian	11 (4.5)	14 (5.8)	13 (5.3)	38 (5.2)	16 (5.2)	14 (4.6)	30 (4.9)
White	203 (83.5)	200 (82.3)	202 (82.8)	605 (82.9)	259 (84.4)	256 (83.4)	515 (83.9)
Ethnicity [n (%)]							
Not Hispanic or Latino	213 (87.7)	219 (90.1)	218 (89.3)	650 (89.0)	276 (89.9)	279 (90.9)	555 (90.4)
Hispanic or Latino	28 (11.5)	22 (9.1)	23 (9.4)	73 (10.0)	28 (9.1)	26 (8.5)	54 (8.8)
Region [n (%)]							
Europe	153 (63.0)	143 (58.8)	152 (62.3)	448 (61.4)	205 (66.8)	190 (61.9)	395 (64.3)
North America	76 (31.3)	81 (33.3)	75 (30.7)	232 (31.8)	81 (26.4)	96 (31.3)	177 (28.8)

Variable	Randomized subjects (FAS) 12.5 mg N=243	25 mg N=243	Placebo N=244	Total N=730	Re-randomized subjects (mFAS) 25 mg N=307	Placebo N=307	Total N=614
BMI at screening [kg/m^2] Mean (SD)	33.6 (6.2)	34.3 (6.8)	33.3 (5.6)	33.7 (6.2)	33.4 (6.5)	33.9 (5.9)	33.6 (6.2)
BMI at screening [kg/m^2] [n (%)]							
≤ 30	75 (30.9)	70 (28.8)	79 (32.4)	224 (30.7)	106 (34.5)	87 (28.3)	193 (31.4)
30 – 40	135 (55.6)	132 (54.3)	132 (54.1)	399 (54.7)	152 (49.5)	180 (58.6)	332 (54.1)
≥ 40	33 (13.6)	41 (16.9)	33 (13.5)	107 (14.7)	49 (16.0)	40 (13.0)	89 (14.5)

BMI = body mass index; FAS = Full analysis set; mFAS = modified Full analysis set; SD = standard deviation.
Source: Compiled from D-22.269 table 15.1.4-1.1 and table 15.1.4-1.2.

Baseline disease (hypertension) characteristics

Patients had multiple comorbidities characteristics for patients with RHT [Table 3-5]. 22.2% of subjects had CKD stage 3 or 4 (eGFR 15 – < 60 mL/min/1.73 m2 at screening and 14% had sleep apnea. Subjects with diabetes mellitus (Type II; 54.1%), ischemic heart disease (30.8%), stroke (7.8%), congestive heart failure (19.6%), and obesity (69.3%) were highly represented [Table 3-3, Table 3-5]. 63.0% of randomized subjects were receiving ≥ 4 antihypertensive therapies at screening, with RAS blockers, diuretics, and CCBs being the most common treatments. 62.5% of patients received a beta-blocker. Treatment with beta-blockers was maintained during the study. A few subjects (4.0%) had previously undergone renal denervation. Background antihypertensive therapies ongoing at screening were balanced across treatment groups in randomized subjects, with renin-angiotensin system blockers (716 subjects, 98.1%), diuretics (635 subjects, 87.0% including 10.4% of subjects treated with a mineralocorticoid receptor antagonist), and CCBs (613 subjects, 84.0%) being the most common treatments; 62.5% of subjects received beta-blockers (Figure 10-3).

Table 3-5 Medical history / concomitant diseases by category

Medical History Category	Randomized subjects (FAS) 12.5 mg N = 243	25 mg N = 245	Placebo N = 242	Total N = 730	Re-randomized subjects (mFAS) 25 mg N=307	Placebo N=307	Total N=614
Diabetes	131 (53.9)	136 (56.0)	128 (52.5)	395 (54.1)	189 (54.5)	154 (50.8)	323 (52.6)
Ischaemic heart disease	73 (30.0)	79 (32.5)	73 (29.9)	225 (30.8)	90 (29.0)	96 (31.7)	186 (30.3)
Congestive heart failure	48 (19.8)	50 (20.6)	45 (18.4)	143 (19.6)	63 (20.3)	59 (19.5)	122 (19.9)
Sleep apnoea syndrome	33 (13.6)	38 (15.6)	32 (13.1)	103 (14.1)	36 (11.6)	42 (13.9)	78 (12.7)
Stroke	20 (8.2)	21 (8.6)	16 (6.6)	57 (7.8)	22 (7.1)	28 (9.2)	50 (8.1)

FAS = Full analysis set; mFAS = modified Full analysis set.
Medical history / concomitant disease categories are defined in D-22.269 table 10-7.
Source: table ISS-1.2.3, table ISS-1.2.4.

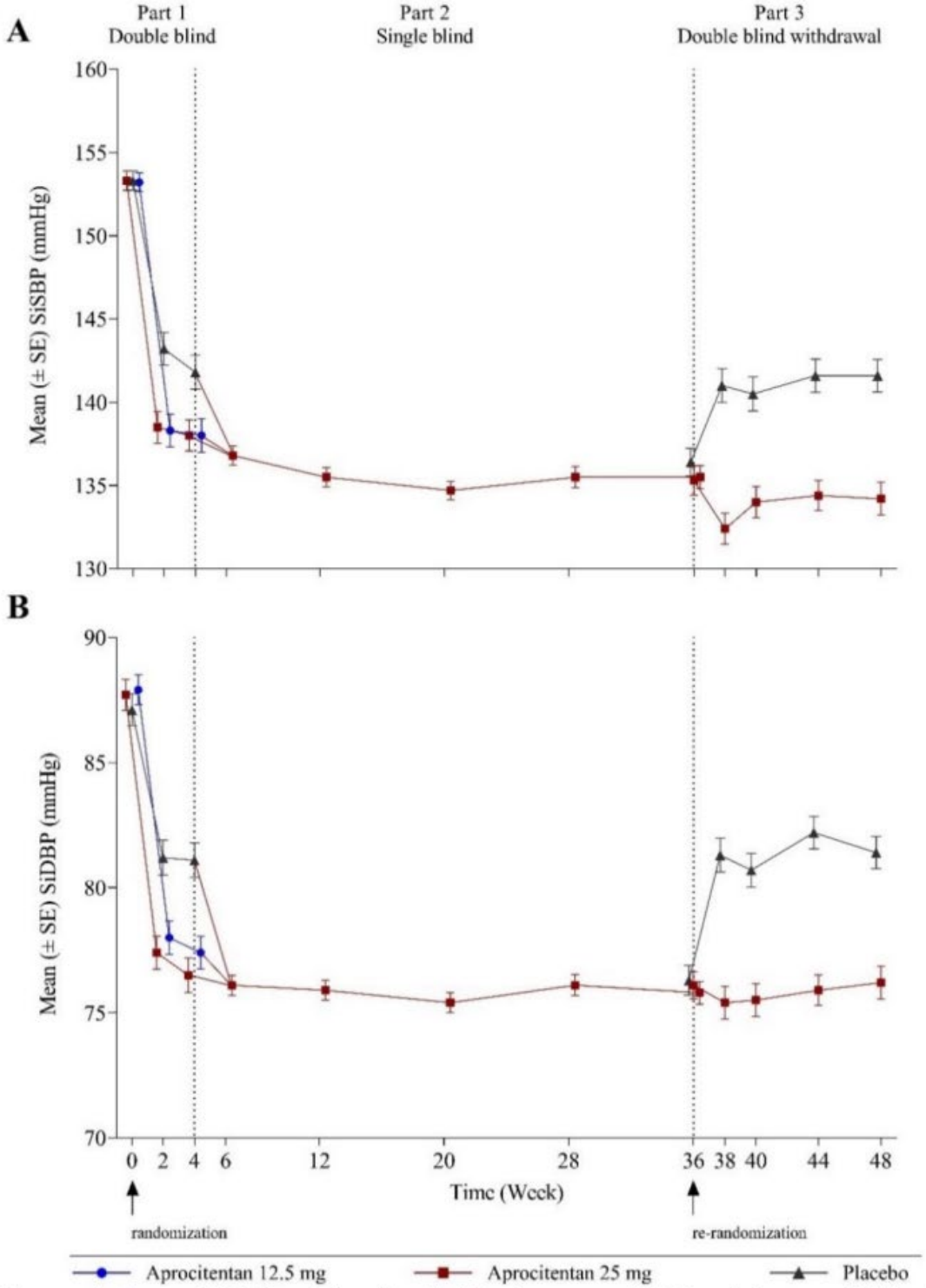
- **Outcomes and estimation**

Primary and key secondary efficacy endpoints

The primary and key secondary efficacy analyses were restricted to SiSBP values with analyses for SiDBP being only secondary. However, results for SiSBP and SiDBP are presented together for clarity.

The course of office BP (mmHg) from baseline up to Week 48 is shown in Figure 4-3

Figure 4-3 Course of office BP (mmHg) from baseline up to Week 48



SE = standard error; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.
Source: [D-22.269 table 15.2.2-1.1, table 15.2.2-2.1, table 15.2.2-3.1, table 15.2.2-3.12].

There was a statistically significant difference between aprocitentan 25 mg and placebo, and between aprocitentan 12.5 mg and placebo, in the mean change from baseline to Week 4 in **SiSBP** (primary efficacy endpoint) and between 25 mg and placebo after rerandomization in the DB withdrawal period (Table 11-4).

Table 11-4 Overview of hypothesis testing results related to the primary and key secondary efficacy endpoints

Hypothesis	Contrast (aprocitentan vs placebo)	Two-sided p-value	Threshold for significance	Statistically significant
H_{10}	Aprocitentan 25 mg for SiSBP at Week 4 of DB part 1	0.0046	0.025	Yes
H_{20}	Aprocitentan 12.5 mg for SiSBP at Week 4 of DB part 1	0.0042	0.025	Yes
H_{30}	Aprocitentan 25 mg for SiSBP at Week 40 of DB-WD part 3	< 0.0001	0.05	Yes

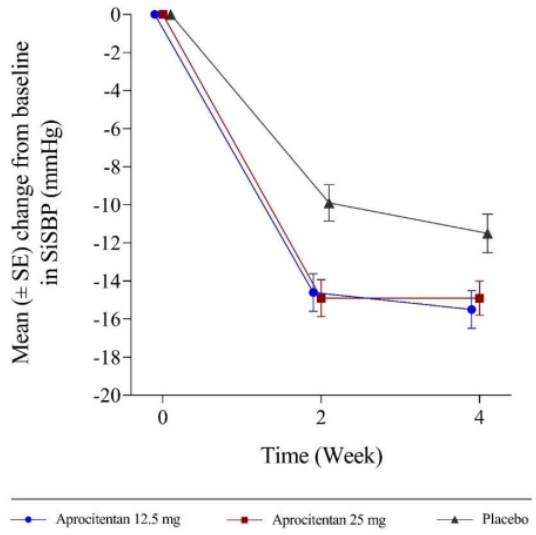
DB = double-blind; DB-WD = double-blind withdrawal; SiSBP = sitting systolic blood pressure.

The primary efficacy endpoint was change from baseline to Week 4 of double-blind treatment in mean trough SiSBP recorded via uAOBPM (Figure 11-1, Table 11-5), the respective values for SiDBP are shown in Figure 11-3 and Table 11-14.

The results from mixed models for changes from baseline in **SiSBP** are presented in Table 11-6 for the primary efficacy endpoint. For the respective SiDBP values the results are shown in Table 11-15.

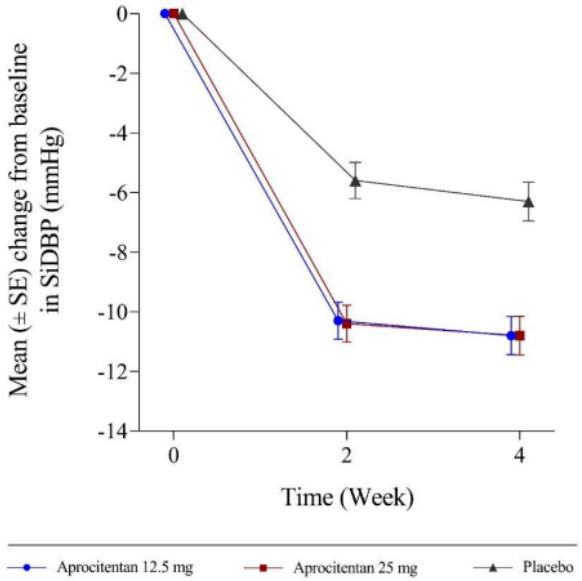
Overall, changes in **SiDBP** were consistent with the changes observed in **SiSBP**. Mean baseline **SiDBP** was similar across treatment groups. The mean **SiDBP** reduction after 2 and 4 weeks of treatment is displayed in Table 11-14 and Figure 11-3. In both aprocitentan groups, a numerically greater reduction compared to the placebo group was observed at Week 2 and Week 4.

Figure 11-1 Mean (± SE) change in SiSBP (mmHg) from baseline to Week 4 (uAOBPM): FAS



FAS = Full analysis set; SE = standard error; SiSBP = sitting systolic blood pressure; uAOBPM = unattended automated office blood pressure measurement.
Source: Table 15.2.2-1.1

Figure 11-3 Mean (± SE) change in SiDBP (mmHg) from baseline to Week 4 (uAOBPM): FAS



Source: Table 15.2.2-3.1
FAS = Full analysis set; SE = standard error; SiDBP = sitting diastolic blood pressure; uAOBPM = unattended automated office blood pressure measurement

Table 11-5 Change in SiSBP (mmHg) from baseline to Week 4 (uAOBPM): FAS

Time point Statistic	Aprocitentan 12.5 mg	Aprocitentan 25 mg	Placebo
Baseline			
n	243	243	244
Mean (SD)	153.2 (8.8)	153.3 (9.0)	153.3 (9.0)
Week 2			
n	215	223	220
Mean (SD)	138.3 (14.4)	138.5 (14.2)	143.2 (14.6)
Change from baseline to Week 2 (other efficacy endpoint)			
Mean (SD)	-14.6 (14.5)	-14.9 (14.5)	-9.9 (14.1)
Week 4			
n	223	231	224
Mean (SD)	138.0 (14.9)	138.0 (14.2)	141.8 (15.2)
Change from baseline to Week 4 (primary efficacy endpoint)			
Mean (SD)	-15.5 (14.8)	-14.9 (13.6)	-11.5 (15.3)

Based on unattended automated office blood pressure measurement at trough.
FAS = Full analysis set; SD = standard deviation; SiSBP = sitting systolic blood pressure; uAOBPM = unattended automated office blood pressure measurement.
Source: Abridged from Table 15.2.2-1.1

Table 11-14 Change in SiDBP (mmHg) from baseline to Weeks 2 and 4 (uAOBPM): FAS

Time point Statistic	Aprocitentan 12.5 mg	Aprocitentan 25 mg	Placebo
Baseline			
n	243	243	244
Mean (SD)	87.9 (9.4)	87.7 (9.7)	87.1 (9.9)
Week 2			
n	215	223	220
Mean (SD)	78.0 (9.9)	77.4 (10.0)	81.2 (10.3)
Change from baseline to Week 2			
Mean (SD)	-10.3 (9.1)	-10.4 (9.3)	-5.6 (9.0)
Week 4			
n	223	231	224
Mean (SD)	77.4 (9.9)	76.5 (10.5)	81.1 (10.3)
Change from baseline to Week 4			
Mean (SD)	-10.8 (9.6)	-10.8 (9.8)	-6.3 (9.8)

Based on unattended automated office blood pressure measurement at trough.
FAS = Full analysis set; SD = standard deviation; SiDBP = sitting diastolic blood pressure; uAOBPM = unattended automated office blood pressure measurement.
Source: Abridged from Table 15.2.2-3.1

Between-treatment analysis for change in SiSBP at Week 4

In the linear mixed effects model, the difference to placebo for change in **SiSBP** from baseline to Week 4 in both aprocitentan treatment groups was statistically significant (Table 11-6). Significant differences to placebo for change in SiSBP from baseline were already observed at Week 2 ('other efficacy endpoint').

In the linear mixed model, differences to placebo for change in **SiDBP** from baseline to Weeks 2 and 4 were observed in both aprocitentan treatment groups ($p < 0.0001$) (Table 11-15).

Table 11-6 Between-treatment analyses for change in SiSBP (mmHg) from baseline to Week 4 (uAOBPM): FAS

Timepoint / Treatment group	n	LS Mean (SE)	97.5% CL	Difference to placebo LS Mean (SE)	97.5% CL	p-value
Change from baseline to Week 2 (other efficacy endpoint)						
Aprocitentan 12.5 mg (N = 243)	215	–14.52 (0.93)	–16.61, –12.43	–4.79 (1.31)	–7.73, –1.84	0.0003
Aprocitentan 25 mg (N = 243)	223	–14.68 (0.92)	–16.74, –12.62	–4.94 (1.30)	–7.87, –2.02	0.0002
Placebo (N = 244)	220	–9.74 (0.92)	–11.81, –7.66			
Change from baseline to Week 4 (primary efficacy endpoint)						
Aprocitentan 12.5 mg (N = 243)	223	–15.26 (0.93)	–17.36, –13.17	–3.79 (1.32)	–6.76, –0.82	0.0042*
Aprocitentan 25 mg (N = 243)	231	–15.20 (0.92)	–17.27, –13.13	–3.73 (1.31)	–6.67, –0.78	0.0046*
Placebo (N = 244)	224	–11.47 (0.93)	–13.57, –9.38			

* Statistically significant at the 2.5% level (as per testing strategy, Section 9.8.4.1).
Mixed effects model for repeated measures: change from baseline in SiSBP = baseline SiSBP + treatment + visit + treatment × visit + baseline × visit.
CL = confidence limit; FAS = Full analysis set; LS mean = least squares mean; SE = standard error; SiSBP = sitting systolic blood pressure; uAOBPM = unattended automated office blood pressure measurement.
Source: Abridged from Table 15.2.2-1.6

Table 11-15 Between-treatment analysis for change in SiDBP (mmHg) from baseline to Weeks 2 and 4 (uAOBPM): FAS

Timepoint / Treatment group	n	LS Mean (SE)	95% CL	Difference to placebo LS Mean (SE)	95% CL	p-value
Change from baseline to Week 2 (other efficacy endpoint)						
Aprocitentan 12.5 mg (N = 243)	215	-10.08 (0.56)	-11.18, -8.99	-4.31 (0.79)	-5.85, -2.76	< 0.0001
Aprocitentan 25 mg (N = 243)	223	-10.25 (0.55)	-11.32, -9.17	-4.47 (0.78)	-6.00, -2.94	< 0.0001
Placebo (N = 244)	220	-5.78 (0.55)	-6.86, -4.69			
Change from baseline to Week 4 (secondary efficacy endpoint)						
Aprocitentan 12.5 mg (N = 243)	223	-10.43 (0.59)	-11.58, -9.27	-3.94 (0.83)	-5.57, -2.31	< 0.0001
Aprocitentan 25 mg (N = 243)	231	-10.95 (0.58)	-12.09, -9.82	-4.47 (0.82)	-6.09, -2.85	< 0.0001
Placebo (N = 244)	224	-6.48 (0.59)	-7.63, -5.33			

Mixed effects model for repeated measures: change from baseline in SiDBP = baseline SiDBP + treatment + visit + treatment × visit + baseline × visit.
CL = confidence limit; FAS = Full analysis set; LS mean = least squares mean; SE = standard error; SiDBP = sitting diastolic blood pressure; uAOBPM = unattended automated office blood pressure measurement.
Source: Table 15.2.2-3.5

Results for the PPS were consistent with those of the main analyses on the FAS for SiSBP and SiDBP. The results of sensitivity analyses were generally consistent with the main analysis.

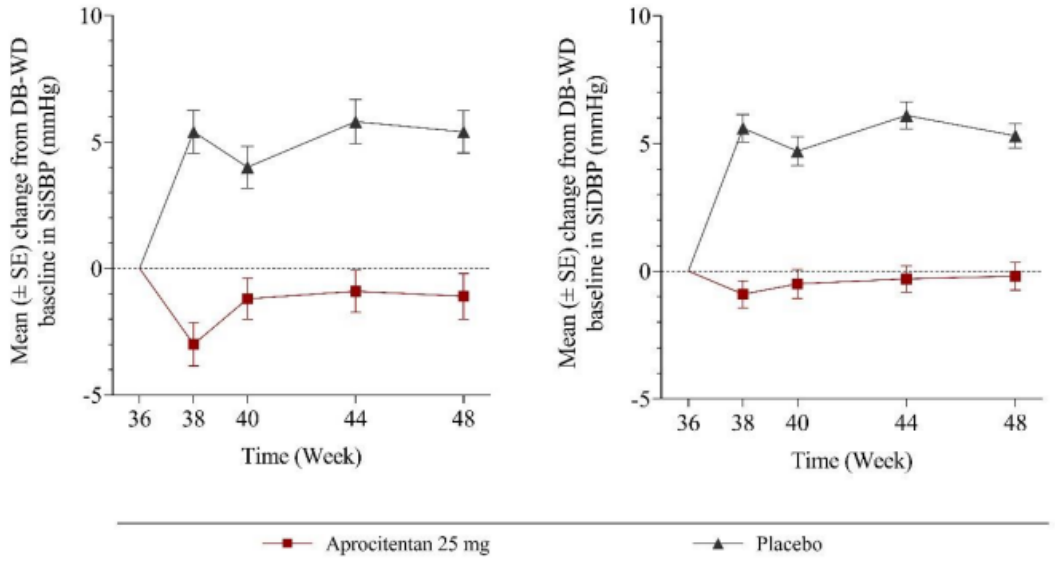
SiSBP in DB-WD part 3 – key secondary efficacy endpoint and SiDBP in DB-WD part 3

The key secondary efficacy endpoint was change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP recorded via uAOBPM (Figure 3-3 shows data up to week 48 for SiSBP and SiDBP). The mean SiSBP change 4 weeks after withdrawal of aprocitentan is displayed in Table 11-8. A marked increase in SiSBP was observed in the placebo at week 38 (other secondary endpoint) and at week 40 group, whereas

subjects who remained on aprocitentan 25 mg showed a small decrease in SiSBP at week 38 and week 40. A statistically significant difference to placebo was observed for change in SiSBP from DB-WD baseline to Week 38 and to Week 40 in the aprocitentan 25 mg group (Table 11-9) and was sustained up to week 44 and 48 (Figure 11-2).

Results of this analysis on the mPPS and of sensitivity analyses were consistent with those of the main analysis on the mFAS. Changes in SiDBP up to week 48 were consistent with the changes observed in SiSBP (Figure 3-3- and Table 11-16 and 11-17). The withdrawal effect in the placebo group was already apparent at Week 38, whereas subjects who remained on aprocitentan 25 mg kept their SiDBP stable until the end of DB-WD part 3 (Week 48).

Figure 3-3 Changes from DB-WD baseline in SiSBP (mmHg; left) and SiDBP (mmHg; right) to visits in the DB-WD part 3 up to Week 48: mFAS



DB-WD baseline: Week 36
DB-WD = double-blind-withdrawal; mFAS = modified Full analysis set; SE = standard error; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.
Source: D-22.269, table 15.2.2-2.1 and table 15.2.2-3.12

Table 11-8 Change in SiSBP (mmHg) from DB-WD baseline to Week 40 (uAOBPM): mFAS

Timepoint Statistic	Aprocitentan 25 mg	Placebo
DB-WD baseline (Week 36)		
N	307	307
Mean (SD)	135.3 (15.6)	136.4 (14.8)
Week 38		
n	225	252
Mean (SD)	132.4 (14.0)	141.0 (16.2)
Change from DB-WD baseline to Week 38 (other efficacy endpoint)		
Mean (SD)	-3.0 (12.8)	5.4 (13.6)
Week 40		
n	261	267
Mean (SD)	134.0 (15.3)	140.5 (16.7)
Change from DB-WD baseline to Week 40		
Mean (SD)	–1.2 (13.0)	4.0 (13.7)

Based on unattended automated office blood pressure measurement at trough.
DB-WD = double-blind withdrawal; mFAS = modified Full analysis set; SD = standard deviation; SiSBP = sitting systolic blood pressure; uAOBPM = unattended automated office blood pressure measurement.
Source: Abridged from Table 15.2.2-2.1

Table 11-9 Between-treatment analysis for changes in SiSBP (mmHg) from DB-WD baseline to Week 40 (uAOBPM): mFAS

Timepoint Treatment group	n	LS Mean (SE)	95% CL	Difference to placebo LS Mean (SE)	95% CL	p-value
Change from DB-WD baseline to Week 38 (other efficacy endpoint)						
Aprocitentan 25 mg (N = 307)	225	–3.01 (0.80)	–4.58, –1.44	–8.41 (1.10)	–10.58, –6.24	< 0.0001
Placebo (N = 307)	252	5.40 (0.76)	3.90, 6.89			
Change from DB-WD baseline to Week 40 (key secondary efficacy endpoint)						
Aprocitentan 25 mg (N = 307)	261	–1.47 (0.76)	–2.97, 0.04	–5.82 (1.08)	–7.94, –3.71	< 0.0001*
Placebo (N = 307)	267	4.36 (0.76)	2.87, 5.85			

*Statistically significant at the 5% level (as per testing strategy [Section 9.8.4.1]).
DB-WD baseline: Week 36
Mixed effects model for repeated measures: change from DB-WD baseline in SiSBP = DB-WD baseline SiSBP + stratum (randomized treatment in DB part 1) + treatment + visit + treatment × visit + DB-WD baseline × visit.
CL = confidence limit; DB-WD = double-blind withdrawal; LS mean = least squares mean; mFAS = modified Full analysis set; SE = standard error; SiSBP = sitting systolic blood pressure; uAOBPM = unattended automated office blood pressure measurement.
Source: Table 15.2.2-2.6

Table 11-16 Change in SiDBP (mmHg) from DB-WD baseline up to Week 48 (uAOBPM): mFAS

Timepoint Statistic	Aprocitentan 25 mg	Placebo
DB-WD baseline (Week 36)		
n	307	307
Mean (SD)	76.1 (9.5)	76.3 (10.3)
Week 38		
n	225	252
Mean (SD)	75.4 (9.8)	81.3 (10.8)
Change from DB-WD baseline to Week 38		
n	225	252
Mean (SD)	-0.9 (8.0)	5.6 (8.5)
Week 40		
n	261	267
Mean (SD)	75.5 (10.6)	80.7 (11.0)
Change from DB-WD baseline to Week 40		
n	261	267
Mean (SD)	-0.5 (9.2)	4.7 (9.2)
Week 44		
n	293	284
Mean (SD)	75.9 (10.5)	82.2 (10.9)
Change from DB-WD baseline to Week 44		
n	293	284
Mean (SD)	-0.3 (8.9)	6.1 (9.1)
Week 48		
n	273	284
Mean (SD)	76.2 (10.9)	81.4 (10.8)
Change from DB-WD baseline to Week 48		
n	273	284
Mean (SD)	-0.2 (9.0)	5.3 (8.0)

Based on unattended automated office blood pressure measurement at trough.
DB-WD = double-blind withdrawal; mFAS = modified Full analysis set; SD = standard deviation; SiDBP = sitting diastolic blood pressure; uAOBPM = unattended automated office blood pressure measurement.
Source: Abridged from Table 15.2.2-3.12

Table 11-17 Between-treatment analysis for change in SiDBP (mmHg) from DB-WD baseline up to Week 48 (uAOBPM): mFAS

Timepoint / Treatment group	n	LS Mean (SE)	95% CL	Difference to placebo LS Mean (SE)	Difference to placebo 95% CL	Difference to placebo p-value
Change from DB-WD baseline to Week 38						
Aprocitentan 25 mg (N = 307)	225	-0.75 (0.49)	-1.72, 0.22	-6.26 (0.69)	-7.61, -4.92	< 0.0001
Placebo (N = 307)	252	5.51 (0.47)	4.58, 6.45			
Change from DB-WD baseline to Week 40						
Aprocitentan 25 mg (N = 307)	261	-0.51 (0.52)	-1.53, 0.50	-5.29 (0.73)	-6.72, -3.86	< 0.0001
Placebo (N = 307)	267	4.77 (0.51)	3.76, 5.78			
Change from DB-WD baseline to Week 44						
Aprocitentan 25 mg (N = 307)	293	-0.16 (0.49)	-1.12, 0.80	-6.18 (0.70)	-7.55, -4.82	< 0.0001
Placebo (N = 307)	284	6.02 (0.49)	5.05, 6.99			
Change from DB-WD baseline to Week 48						
Aprocitentan 25 mg (N = 307)	273	0.03 (0.49)	-0.92, 0.99	-5.37 (0.68)	-6.71, -4.03	< 0.0001
Placebo (N = 307)	284	5.40 (0.48)	4.46, 6.34			

DB-WD baseline: Week 36
CL = confidence limit; DB-WD = double-blind withdrawal; LS mean = least squares mean; mFAS = modified Full analysis set; SE = standard error; SiDBP = sitting diastolic blood pressure; uAOBPM = unattended automated office blood pressure measurement.
Mixed effects model for repeated measures: change from DB-WD baseline in SiDBP = DB-WD baseline SiDBP + stratum (randomized treatment in DB part 1) + treatment + visit + treatment × visit + DB-WD baseline × visit.
Source: Table 15.2.2-4.10

Ambulatory 24h blood pressure measurements (ABPM)

SBP and DBP in DB part 1 (ABPM)

24 h

Figure 11-5 displays mean SBP and DBP over a 24 h recording period, indicating that an o.d. regimen of aprocitentan 12.5 mg and 25 mg exerts BP control during the entire 24 hours.

At baseline, 24 h mean SBP and DBP was similar in all 3 treatment groups [Figure 11-5, Table 11-18). At Week 4, a numerically greater reduction in 24 h mean SBP and DBP was observed in both aprocitentan groups than in the placebo group. The observed placebo effect with ABPM was small.

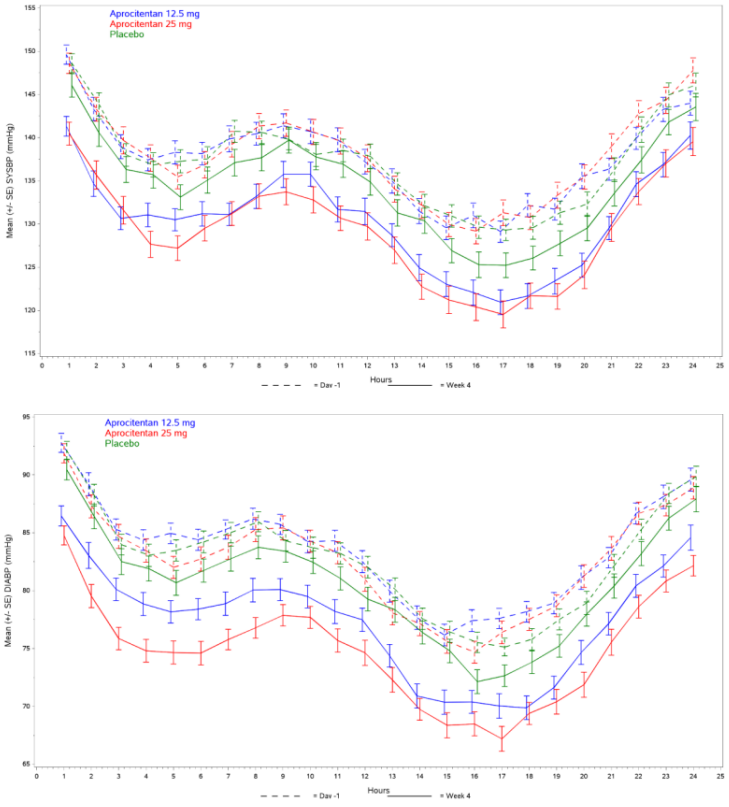
Daytime

At baseline, daytime (as the time between 09:00 and 21:00) mean SBP and DBP were similar in all 3 treatment groups, [Figure 11-5, Table 11-20,]. At Week 4, a reduction in daytime mean SBP was more pronounced in both aprocitentan groups compared to placebo. Similar changes were observed in daytime mean DBP.

Nighttime

At baseline, night-time mean SBP and DBP were similar in all 3 treatment groups [Figure 11-5, Table 11-22]. For analysis, night-time was defined as the time between 01:00 and 06:00. At Week 4, a reduction in night-time mean SBP was more pronounced in both aprocitentan groups compared to placebo. Similar changes were observed in night-time mean DBP [Table 11-22]. Of note, the reductions from baseline at Week 4 in night-time SBP and DBP in both aprocitentan treatment groups were larger than the reductions in daytime SBP and DBP.

Figure 11-5 24 h mean SBP and DBP (mmHg) at baseline and at Week 4 (ABP!



Hours indicate the time from start of ambulatory blood pressure measurement.
ABPM = ambulatory blood pressure monitoring; DBP = diastolic blood pressure; SBP = systolic blood pressure.
Source: post-hoc Figure 15.2.2-6.1 and post-hoc Figure 15.2.2-6.2.

Table 11-18 Changes in 24 h mean SBP and DBP (mmHg) from baseline to Week 4 (ABPM): aFAS

Variable Timepoint Statistic	Aprocitentan 12.5 mg N = 206	Aprocitentan 25 mg N = 207	Placebo N = 220
24 h mean SBP			
Baseline			
n	206	207	220
Mean (SD)	137.65 (13.30)	137.62 (15.24)	137.10 (13.62)
Week 4			
n	175	182	179
Mean (SD)	130.67 (12.94)	129.15 (14.33)	134.57 (14.00)
Change from baseline to Week 4			
Mean (SD)	-6.74 (10.56)	-8.54 (11.14)	-2.43 (10.62)
24 h mean DBP			
Baseline			
n	206	207	220
Mean (SD)	83.51 (8.66)	82.47 (10.00)	82.47 (9.12)
Week 4			
n	175	182	179
Mean (SD)	77.34 (9.02)	74.85 (9.37)	80.68 (9.52)
Change from baseline to Week 4			
Mean (SD)	-6.50 (6.73)	-7.61 (7.22)	-1.80 (6.76)

24 h mean SBP/DBP: recorded via ambulatory blood pressure monitoring.
ABPM = ambulatory blood pressure monitoring; aFAS = ambulatory blood pressure monitoring Full analysis set; DBP = diastolic blood pressure; SBP = systolic blood pressure; SD = standard deviation.
Source: Abridged from Table 15.2.2-3.8, Table 15.2.2-3.9

Table 11-20 Changes in daytime mean SBP and DBP (mmHg) from baseline to Week 4 (ABPM): aFAS

Variable Timepoint Statistic	Aprocitentan 12.5 mg N = 206	Aprocitentan 25 mg N = 207	Placebo N = 220
Daytime mean SBP			
Baseline			
n	206	207	220
Mean (SD)	141.29 (14.06)	141.64 (16.61)	140.87 (15.16)
Week 4			
n	175	182	179
Mean (SD)	134.85 (13.56)	133.54 (15.80)	138.59 (16.10)
Change from baseline to Week 4			
Mean (SD)	-6.20 (12.82)	-7.83 (14.21)	-2.28 (14.08)
Daytime mean DBP			
Baseline			
n	206	207	220
Mean (SD)	86.73 (9.69)	85.41 (10.54)	85.65 (10.64)
Week 4			
n	175	182	179
Mean (SD)	80.64 (9.41)	77.59 (10.06)	83.51 (11.01)
Change from baseline to Week 4			
Mean (SD)	-6.48 (8.15)	-7.83 (8.88)	-2.34 (9.25)

24 h mean SBP/DBP: recorded via ambulatory blood pressure monitoring.
ABPM = ambulatory blood pressure monitoring; aFAS = ambulatory blood pressure monitoring Full analysis set; DBP = diastolic blood pressure; SBP = systolic blood pressure; SD = standard deviation.
Source: Abridged from Table 15.2.2-4.1, Table 15.2.2-4.2

Table 11-22 Changes in night-time mean SBP and DBP (mmHg) from baseline to Week 4 (ABPM): aFAS

Variable Timepoint Statistic	Aprocitentan 12.5 mg N = 206	Aprocitentan 25 mg N = 207	Placebo N = 220
Night-time mean SBP			
Baseline			
n	206	207	219
Mean (SD)	130.94 (15.05)	131.61 (18.06)	129.99 (16.56)
Week 4			
n	174	182	178
Mean (SD)	122.58 (16.24)	121.23 (17.49)	127.07 (16.16)
Change from baseline to Week 4			
Mean (SD)	-8.07 (13.65)	-10.95 (14.91)	-2.63 (13.84)
Night-time mean DBP			
Baseline			
n	206	207	219
Mean (SD)	77.99 (10.15)	77.17 (11.60)	76.14 (10.65)
Week 4			
n	174	182	178
Mean (SD)	70.88 (11.11)	69.10 (11.38)	74.44 (10.79)
Change from baseline to Week 4			
Mean (SD)	-7.30 (9.59)	-8.28 (10.16)	-1.64 (9.97)

24 h mean SBP/DBP: recorded via ambulatory blood pressure monitoring.
ABPM = ambulatory blood pressure monitoring; aFAS = ambulatory blood pressure monitoring Full analysis set; DBP = diastolic blood pressure; SBP = systolic blood pressure; SD = standard deviation.
Source: Abridged from Table 15.2.2-4.5, Table 15.2.2-4.6

ANCOVA for changes in 24 h, daytime and nighttime mean SBP and DBP from baseline to Week 4

Significant differences to placebo were observed for changes in 24 h, daytime and night-time mean SBP and DBP from baseline to Week 4 in both aprocitentan treatment groups; the difference to placebo was consistently numerically greater in the aprocitentan 25 mg group than in the 12.5 mg group [Table 3-8].

Table 3-8 Between-treatment analyses for changes from baseline to Week 4 of DB treatment in 24 h, daytime and night-time mean SBP and DBP (mmHg): aFAS

		Change from baseline	Difference to placebo	
Treatment group	Baseline [#] Mean (SD)	LS Mean (95% CL)	LS Mean (95% CL)	p-value
24 h mean SBP				
12.5 mg (N=206)	137.7 (13.3)	−6.73 (−8.20 −5.26)	−4.18 (−6.25, −2.12)	<0.0001
25 mg (N=207)	137.6 (15.2)	−8.44 (−9.88, −7.00)	−5.90 (−7.94, −3.85)	<0.0001
Placebo (N=220)	137.1 (13.6)	−2.55 (−4.00, −1.10)	-	-
24 h mean DBP				
12.5 mg (N=206)	83.5 (8.7)	−6.25 (−7.20, −5.29)	−4.32 (−5.66, −2.98)	<0.0001
25 mg (N=207)	82.5 (10.0)	−7.74 (−8.67, −6.80)	−5.81 (−7.14, −4.49)	<0.0001
Placebo (N=220)	82.5 (9.1)	−1.92 (−2.87, −0.98)	-	-
Daytime mean SBP				
12.5 mg (N=206)	141.3 (14.1)	−6.22 (−8.04, −4.39)	−3.85 (−6.42, −1.28)	0.0033
25 mg (N=207)	141.6 (16.6)	−7.72 (−9.51, −5.93)	−5.35 (−7.89, −2.81)	<0.0001
Placebo (N=220)	140.9 (15.2)	−2.37 (−4.17, −0.57)	-	-
Daytime mean DBP				
12.5 mg (N=206)	86.7 (9.7)	−6.11 (−7.28, −4.94)	−3.66 (−5.31, −2.02)	<0.0001
25 mg (N=207)	85.4 (10.5)	−8.10 (−9.24, −6.95)	−5.65 (−7.28, −4.02)	<0.0001
Placebo (N=220)	85.7 (10.6)	−2.44 (−3.60, −1.29)	-	-
Night-time mean SBP				
12.5 mg (N=206)	130.9 (15.1)	−8.14 (−10.05, −6.24)	−5.10 (−7.78, −2.41)	0.0002
25 mg (N=207)	131.6 (18.1)	−10.47 (−12.34, −8.60)	−7.42 (−10.08, −4.77)	<0.0001
Placebo (N=220)	130.0 (16.6)	−3.05 (−4.94, −1.16)	-	-
Night-time mean DBP				
12.5 mg (N=206)	78.0 (10.2)	−6.91 (−8.24, −5.58)	−4.83 (−6.70, −2.95)	<0.0001
25 mg (N=207)	77.2 (11.6)	−8.21 (−9.51, −6.91)	−6.13 (−7.98, −4.28)	<0.0001
Placebo (N=220)	76.1 (10.7)	−2.08 (−3.40, −0.77)	-	-

aFAS = ambulatory blood pressure monitoring Full analysis set; CL = confidence limit; DB = double-blind; DBP = diastolic blood pressure; LS mean = least squares mean; SBP = systolic blood pressure; SD = standard deviation.

[#] Observed baseline value.

Source: Compiled from D-22.269, table 15.2.2-3.8, table 15.2.2-3.9, table 15.2.2-3.10, table 15.2.2-3.11, table 15.2.2-4.1, table 15.2.2-4.2, table 15.2.2-4.3, table 15.2.2-4.4, table 15.2.2-4.5, table 15.2.2-4.6, table 15.2.2-4.7, table 15.2.2-4.8.

SBP and DBP in DB-WD part 3 (ABPM)

At DB-WD baseline, 24 h, daytime, and nighttime mean SBP and DBP were similar in both treatment groups. At Week 40, 4 weeks after withdrawal of aprocitentan, a marked increase in 24 h mean SBP and DBP had occurred in the placebo group. No changes in 24 h, daytime, and nighttime mean SBP or DBP were noted in subjects who remained on aprocitentan 25 mg.

At Week 40, 4 weeks after re-randomization to aprocitentan 25 mg or placebo, a marked increase in the SBP/DBP (mmHg) occurred in the placebo group (LS mean change +6.5/+6.3 for 24 h, +5.2/+5.6 for daytime and +8.8/+7.1 for night-time). In contrast, in the aprocitentan 25 mg group, SBP/DBP remained at a similar level as at DB-WD baseline (−0.1/−0.5 for 24 h, −0.7/−0.2 for daytime and +0.3/ −0.7 for night-time). The differences to placebo ($p < 0.0001$) indicated a sustained efficacy of aprocitentan to lower BP (Table 3-10).

Table 3-10 Between-treatment analyses for changes from DB-WD baseline to Week 40 in 24 h, daytime and night-time SBP and DBP (mmHg): maFAS

		Change from DB-WD baseline	Difference to placebo	
Treatment group	DB-WD Baseline [#] Mean (SD)	LS Mean (95% CL)	LS Mean (95% CL)	p-value
24 h mean SBP				
25 mg (N=237)	129.09 (13.91)	−0.07 (−1.46, 1.32)	−6.53 (−8.50, −4.56)	<0.0001
Placebo (N=241)	128.75 (13.51)	6.46 (5.06, 7.85)	-	
24 h mean DBP				
25 mg (N=237)	75.71 (8.68)	−0.47 (−1.34, 0.40)	−6.75 (−7.98, −5.52)	<0.0001
Placebo (N=241)	75.10 (9.00)	6.28 (5.40, 7.15)	-	
Daytime mean SBP				
25 mg (N=237)	133.36 (15.48)	−0.70 (−2.31, 0.92)	−5.93 (−8.22, −3.65)	<0.0001
Placebo (N=241)	132.78 (14.33)	5.24 (3.62, 6.85)	-	
Daytime mean DBP				
25 mg (N=237)	78.55 (9.65)	−0.22 (−1.27, 0.82)	−5.84 (−7.32, −4.36)	<0.0001
Placebo (N=241)	78.62 (9.65)	5.62 (4.57, 6.66)	-	
Night-time mean SBP				
25 mg (N=237)	121.62 (15.66)	0.26 (−1.47, 1.99)	−8.51 (−10.96, −6.06)	<0.0001
Placebo (N=241)	121.47 (16.38)	8.76 (7.03, 10.50)	-	
Night-time mean DBP				
25 mg (N=237)	69.80 (9.86)	−0.73 (−1.86, 0.40)	−7.79 (−9.39, −6.19)	<0.0001
Placebo (N=241)	69.14 (10.60)	7.06 (5.93, 8.19)	-	

DB-WD baseline: Week 36

[#] Observed baseline value.

CL = confidence limit; DBP = diastolic blood pressure; DB-WD = double-blind withdrawal; LS mean = least squares mean; maFAS = modified ambulatory blood pressure monitoring Full analysis set; SBP = systolic blood pressure; SD = standard deviation.

Source: Compiled from D-22.269 table 15.2.2-3.18, table 15.2.2-3.19, table 15.2.2-4.11, table 15.2.2-4.12, table 15.2.2-4.13, table 15.2.2-4.14, table 15.2.2-3.20, table 15.2.2-3.21, table 15.2.2-4.15, table 15.2.2-4.16, table 15.2.2-4.17, table 15.2.2-4.18.

BP control and response rates

Overall, control rates for SiSBP, for SiDBP and for SiSBP/SiDBP combined during DB part 1 were numerically in favor of aprocitentan vs placebo (odds ratio > 1, indicating higher probability of BP control). Control rates were similar with aprocitentan 25 mg and 12.5 mg.

Table 11-30 Control rates at Week 4 of DB part 1 for SiSBP and SiDBP: FAS

Variable Statistic	Aprocitentan 12.5 mg N = 243 n / Nn (%)	Aprocitentan 25 mg N = 243 n / Nn (%)	Placebo N = 244 n / Nn (%)
SiSBP < 140 mmHg	125 / 223 (56.1)	132 / 231 (57.1)	98 / 224 (43.8)
Odds ratio (95% CL) vs placebo	1.64 (1.13, 2.38)	1.71 (1.18, 2.48)	-
SiSBP < 135 mmHg	90 / 223 (40.4)	97 / 231 (42.0)	77 / 224 (34.4)
Odds ratio (95% CL) vs placebo	1.29 (0.88, 1.90)	1.38 (0.95, 2.02)	-
SiDBP < 90 mmHg	194 / 223 (87.0)	204 / 231 (88.3)	172 / 224 (76.8)
Odds ratio (95% CL) vs placebo	2.02 (1.23, 3.33)	2.28 (1.38, 3.80)	-
SiDBP < 85 mmHg	173 / 223 (77.6)	186 / 231 (80.5)	139 / 224 (62.1)
Odds ratio (95% CL) vs placebo	2.12 (1.40, 3.20)	2.53 (1.66, 3.86)	-
SiSBP < 140 mmHg and SiDBP < 90 mmHg	122 / 223 (54.7)	127 / 231 (55.0)	91 / 224 (40.6)
Odds ratio (95% CL) vs placebo	1.77 (1.21, 2.57)	1.79 (1.23, 2.59)	-
SiSBP < 135 mmHg and SiDBP < 85 mmHg	83 / 223 (37.2)	91 / 231 (39.4)	64 / 224 (28.6)
Odds ratio (95% CL) vs placebo	1.48 (1.00, 2.21)	1.63 (1.10, 2.41)	-

Control: blood pressure values below defined limit.
n = number of subjects fulfilling the condition; Nn = number of subjects with a value at the visit and having a baseline value if the response was a change.
CL = confidence limit; DB = double-blind; FAS = Full analysis set; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.
Source: Compiled from Table 15.2.2-4.33, Table 15.2.2-4.36, Table 15.2.2-4.39.

Response rates

Response rates for SiSBP and SiDBP at Week 4 are summarized in Table 11-31. Response rates for SiSBP, for SiDBP and for SiSBP/SiDBP combined during DB part 1 were numerically favoring aprocitentan over placebo. Response rates were similar with aprocitentan 25 mg and 12.5 mg.

Overall, control rates for SiSBP, for SiDBP and for SiSBP/SiDBP combined during DB part 1 were numerically in favor of aprocitentan vs placebo (odds ratio > 1, indicating higher probability of BP control). Control rates were similar with aprocitentan 25 mg and 12.5 mg.

Table 11-30 Control rates at Week 4 of DB part 1 for SiSBP and SiDBP: FAS

Variable Statistic	Aprocitentan 12.5 mg N = 243 n / Nn (%)	Aprocitentan 25 mg N = 243 n / Nn (%)	Placebo N = 244 n / Nn (%)
SiSBP < 140 mmHg	125 / 223 (56.1)	132 / 231 (57.1)	98 / 224 (43.8)
Odds ratio (95% CL) vs placebo	1.64 (1.13, 2.38)	1.71 (1.18, 2.48)	-
SiSBP < 135 mmHg	90 / 223 (40.4)	97 / 231 (42.0)	77 / 224 (34.4)
Odds ratio (95% CL) vs placebo	1.29 (0.88, 1.90)	1.38 (0.95, 2.02)	-
SiDBP < 90 mmHg	194 / 223 (87.0)	204 / 231 (88.3)	172 / 224 (76.8)
Odds ratio (95% CL) vs placebo	2.02 (1.23, 3.33)	2.28 (1.38, 3.80)	-
SiDBP < 85 mmHg	173 / 223 (77.6)	186 / 231 (80.5)	139 / 224 (62.1)
Odds ratio (95% CL) vs placebo	2.12 (1.40, 3.20)	2.53 (1.66, 3.86)	-
SiSBP < 140 mmHg and SiDBP < 90 mmHg	122 / 223 (54.7)	127 / 231 (55.0)	91 / 224 (40.6)
Odds ratio (95% CL) vs placebo	1.77 (1.21, 2.57)	1.79 (1.23, 2.59)	-
SiSBP < 135 mmHg and SiDBP < 85 mmHg	83 / 223 (37.2)	91 / 231 (39.4)	64 / 224 (28.6)
Odds ratio (95% CL) vs placebo	1.48 (1.00, 2.21)	1.63 (1.10, 2.41)	-

Control: blood pressure values below defined limit.
n = number of subjects fulfilling the condition; Nn = number of subjects with a value at the visit and having a baseline value if the response was a change.
CL = confidence limit; DB = double-blind; FAS = Full analysis set; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.
Source: Compiled from Table 15.2.2-4.33, Table 15.2.2-4.36, Table 15.2.2-4.39.

Response rates

Response rates for SiSBP and SiDBP at Week 4 are summarized in Table 11-31. At Week 2, response rates for SiSBP, for SiDBP and for SiSBP/SiDBP combined were, for all defined thresholds, numerically higher in the aprocitentan groups than in the placebo group. Response rates for SiSBP, for SiDBP and for SiSBP/SiDBP combined during DB part 1 were numerically favoring aprocitentan over placebo. Response rates were similar with aprocitentan 25 mg and 12.5 mg.

Table 11-31 Response rates at Week 4 of DB part 1 for SiSBP and SiDBP: FAS

Time point Statistic	Aprocitentan 12.5 mg N = 243 n / Nn (%)	Aprocitentan 25 mg N = 243 n / Nn (%)	Placebo N = 244 n / Nn (%)
Reduction from baseline in			
SiSBP ≥ 10 mmHg	145 / 223 (65.0)	152 / 231 (65.8)	125 / 224 (55.8)
Odds ratio (95% CL) vs placebo	1.47 (1.01, 2.16)	1.52 (1.04, 2.23)	-
SiSBP ≥ 15 mmHg	117 / 223 (52.5)	113 / 231 (48.9)	91 / 224 (40.6)
Odds ratio (95% CL) vs placebo	1.61 (1.11, 2.35)	1.40 (0.97, 2.03)	-
SiDBP ≥ 5 mmHg	161 / 223 (72.2)	173 / 231 (74.9)	120 / 224 (53.6)
Odds ratio (95% CL) vs placebo	2.25 (1.52, 3.34)	2.59 (1.74, 3.84)	-
SiDBP ≥ 10 mmHg	123 / 223 (55.2)	125 / 231 (54.1)	72 / 224 (32.1)
Odds ratio (95% CL) vs placebo	2.60 (1.77, 3.82)	2.49 (1.70, 3.65)	-
SiSBP ≥ 10 and SiDBP ≥ 5 mmHg	128 / 223 (57.4)	133 / 231 (57.6)	91 / 224 (40.6)
Odds ratio (95% CL) vs placebo	1.97 (1.35, 2.87)	1.98 (1.37, 2.88)	-
SiSBP ≥ 15 and SiDBP ≥ 10 mmHg	94 / 223 (42.2)	85 / 231 (36.8)	56 / 224 (25.0)
Odds ratio (95% CL) vs placebo	2.19 (1.46, 3.27)	1.75 (1.17, 2.62)	-

Response: reduction from baseline in blood pressure values.
n = number of subjects fulfilling the condition; Nn = number of subjects with a value at the visit and having a baseline value if the response was a change.
CL = confidence limit; DB = double-blind; FAS = Full analysis set; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.
Source: Compiled from Table 15.2.2-4.33, Table 15.2.2-4.36, Table 15.2.2-4.39.

Control and response rates during DB-WD part 3

Control rates

At Week 40, control rates for SiSBP, for SiDBP, and for SiSBP/SiDBP combined, for all defined thresholds, were numerically higher in the aprocitentan 25 mg group than in the placebo group. These proportions remained stable throughout DB-WD part 3. Overall, regardless of the criteria applied, control rates during the DB-WD part 3 were numerically favoring treatment with aprocitentan 25 mg vs placebo

Loss of response rates

Of note, in DB-WD part 3, loss of BP response was defined as an increase in BP, aimed at capturing the effect of the withdrawal of aprocitentan 25 mg (in subjects re-randomized to placebo). At Week 40 and Week 48, loss of response rates for SiSBP, for SiDBP and for SiSBP/SiDBP combined, were for all defined thresholds numerically higher in the placebo group than in the aprocitentan 25 mg group.

Table 11-31 Response rates at Week 4 of DB part 1 for SiSBP and SiDBP: FAS

Time point Statistic	Aprocitentan 12.5 mg N = 243 n / Nn (%)	Aprocitentan 25 mg N = 243 n / Nn (%)	Placebo N = 244 n / Nn (%)
Reduction from baseline in			
SiSBP ≥ 10 mmHg	145 / 223 (65.0)	152 / 231 (65.8)	125 / 224 (55.8)
Odds ratio (95% CL) vs placebo	1.47 (1.01, 2.16)	1.52 (1.04, 2.23)	-
SiSBP ≥ 15 mmHg	117 / 223 (52.5)	113 / 231 (48.9)	91 / 224 (40.6)
Odds ratio (95% CL) vs placebo	1.61 (1.11, 2.35)	1.40 (0.97, 2.03)	-
SiDBP ≥ 5 mmHg	161 / 223 (72.2)	173 / 231 (74.9)	120 / 224 (53.6)
Odds ratio (95% CL) vs placebo	2.25 (1.52, 3.34)	2.59 (1.74, 3.84)	-
SiDBP ≥ 10 mmHg	123 / 223 (55.2)	125 / 231 (54.1)	72 / 224 (32.1)
Odds ratio (95% CL) vs placebo	2.60 (1.77, 3.82)	2.49 (1.70, 3.65)	-
SiSBP ≥ 10 and SiDBP ≥ 5 mmHg	128 / 223 (57.4)	133 / 231 (57.6)	91 / 224 (40.6)
Odds ratio (95% CL) vs placebo	1.97 (1.35, 2.87)	1.98 (1.37, 2.88)	-
SiSBP ≥ 15 and SiDBP ≥ 10 mmHg	94 / 223 (42.2)	85 / 231 (36.8)	56 / 224 (25.0)
Odds ratio (95% CL) vs placebo	2.19 (1.46, 3.27)	1.75 (1.17, 2.62)	-

Response: reduction from baseline in blood pressure values.
n = number of subjects fulfilling the condition; Nn = number of subjects with a value at the visit and having a baseline value if the response was a change.
CL = confidence limit; DB = double-blind; FAS = Full analysis set; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.
Source: Compiled from Table 15.2.2-4.33, Table 15.2.2-4.36, Table 15.2.2-4.39.

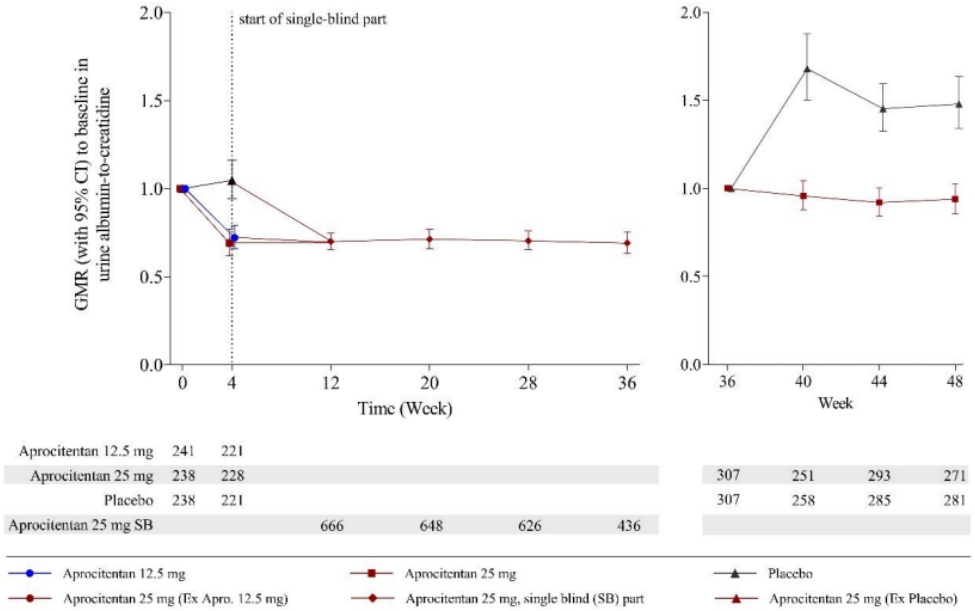
- **Ancillary analyses**

Ratios to baseline and DB-WD baseline of UACR

To assess a potential effect of aprocitentan on urine albumin excretion, UACR was assessed at defined time points. At baseline, 36.2% of subjects presented with significant albuminuria (UACR > 30 mg/g).

Figure 4-9 shows the change in UACR over time.

Figure 4-9 Change in UACR over time, expressed as a ratio of baseline

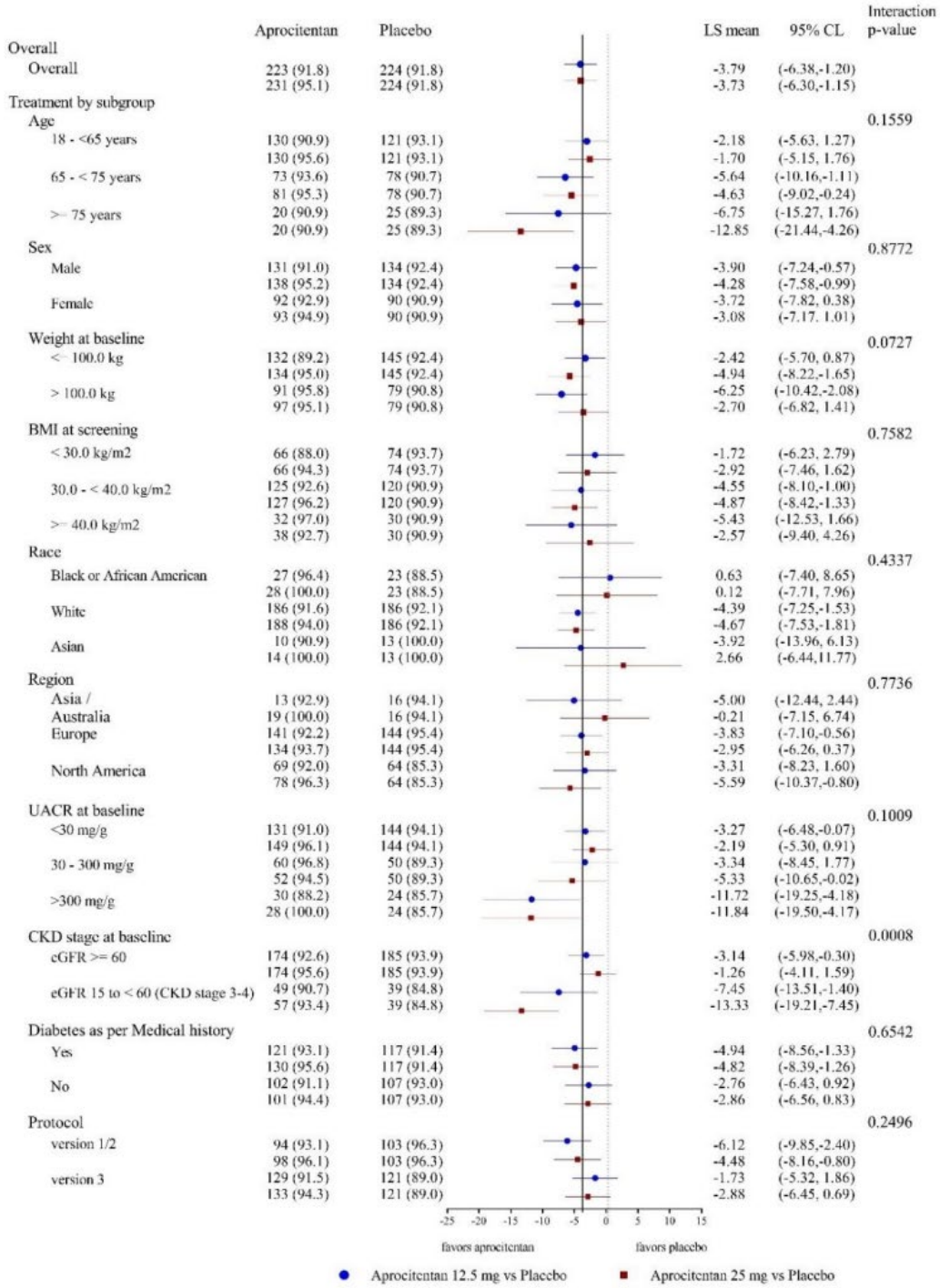


At the end of DB part 1 (Week 4), a similar decrease in UACR was observed in both aprocitentan groups, while UACR remained close to baseline in the placebo group. In the mixed model (Table 3-13), a difference to placebo in log-transformed UACR ratio (hereafter UACR ratio) to baseline at Week 4 was observed for both aprocitentan groups ($p < 0.0001$); the reduction in UACR compared to placebo was 30 and 34% for aprocitentan 12.5 mg and aprocitentan 25 mg, respectively. UACR ratio to baseline remained stable up to the end of SB part 2 (Week 36). At DB-WD baseline (Week 36), UACR was comparable across treatment groups. After withdrawal of aprocitentan, UACR in the placebo group increased between Week 36 and Week 40 and thereafter remained stable, indicating reversibility of the effect of aprocitentan on UACR. In contrast, in the aprocitentan 25 mg group UACR reduction was sustained until Week 48. In subjects with microalbuminuria (> 30–300 mg/g), a 4-week treatment with aprocitentan was associated with decreases in UACR from baseline of 43% in the 12.5 mg group and 45% in the 25 mg group, compared to placebo. In subjects with baseline macroalbuminuria (> 300 mg/g), the treatment effect was more pronounced, with a UACR reduction of 48% with aprocitentan 12.5 mg and of 61% with aprocitentan 25 mg, compared to placebo. In subjects with UACR < 30 mg/g the effect of aprocitentan was less pronounced than with the higher doses.

Pre-defined subgroup analyses

The results for pre-defined subgroup analyses on the primary efficacy endpoint are summarized in Figure 11-9.

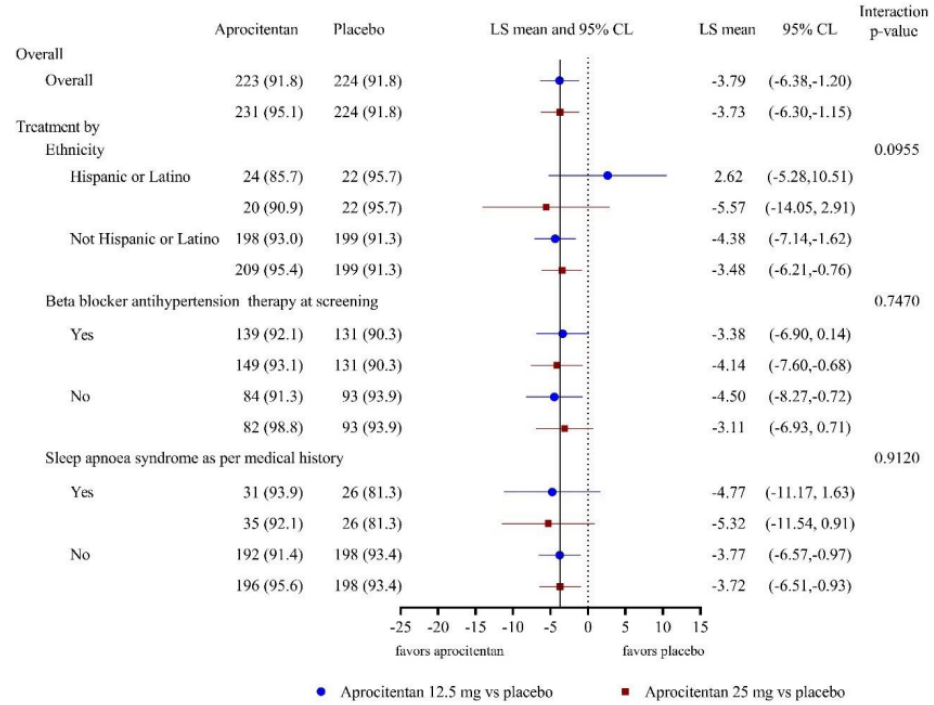
Figure 11-9 Subgroup analyses for change from baseline to Week 4 (DB part 1) in SiSBP: FAS



CL = confidence limits; DB = double-blind; FAS = Full analysis set; LS Mean = Least Squares mean; SiSBP = sitting systolic blood pressure.
Source: Figure 15.2.2-1.16

Additional subgroups:

Figure 11-11 Subgroup analyses for change from baseline to Week 4 (DB part 1) in SiSBP (mmHg) – additional subgroups: FAS



CL = confidence limits; DB = double-blind; FAS = Full analysis set; LS Mean = Least Squares mean; SiSBP = sitting systolic blood pressure.
Source: post-hoc Figure 15.2.2-5.1

A treatment-by-subgroup interaction (i.e., p-value < 0.1) was observed for the subgroups weight (p = 0.0727) and CKD stage (p = 0.0008). Numerically there was a consistent finding of lack of efficacy in Black or African American patients for both aprositentan doses.

Regarding weight the results were inconsistent for the two doses, not reflected in the analysis by BMI and did not challenge a beneficial effect over all weight groups. Further post hoc analyses were provided indicating that the lower/lack of efficacy in Black or African American patients and in patients with eGFR ≥ 60 mL/min/1.73 m2 was likely due to a large placebo effect in these small subgroups in the primary analysis. ABPM data and results from the DB-WD period did not indicate lack of efficacy in these sugbroups.

Table 3-13 Between-treatment analyses for ratios to baseline of UACR (mg/g) in the DB and DB-WD parts: FAS and mFAS

Treatment group	(DB-WD) Baseline (mg/g), Geom. Mean (SD of log)	Ratio to baseline LS Geom. Mean (95% CL)	Ratio to placebo LS Geom. Mean (95% CL)	p-value
Ratio to baseline at Week 4				
Aprocitentan 12.5 mg (N=243)	28.1 (1.8)	0.73 (0.66, 0.80)	0.70 (0.61, 0.80)	<0.0001
Aprocitentan 25 mg (N=243)	25.7 (1.7)	0.69 (0.63, 0.75)	0.66 (0.58, 0.75)	<0.0001
Placebo (N=244)	25.9 (1.7)	1.04 (0.95, 1.15)	-	
Ratio to DB-WD baseline at Week 40				
Aprocitentan 25 mg (N=307)	18.8 (1.6)	0.96 (0.87, 1.05)	0.58 (0.50, 0.66)	<0.0001
Placebo (N=307)	15.5 (1.4)	1.66 (1.50, 1.82)	-	

Mixed effects model for Repeated Measures: Change from baseline/ DB-WD baseline in log UACR = baseline/DB-WD baseline log UACR + treatment + visit + treatment x visit + baseline/DB-WD baseline x visit [+ stratum (i.e., randomized treatment in DB part) for modeling in DB-WD part].
CL = confidence limit; DB = double-blind; DB-WD = double-blind withdrawal; FAS = Full analysis set; LS = least squares; mFAS = modified Full analysis set; SD = standard deviation; UACR = urine albumin-to-creatinine ratio.
Source: Compiled from D-22.269 table 15.2.2-4.19, table 15.2.2-4.20, table 15.2.2-4.21 and table 15.2.2-4.22.

eGFR values decreased after administration of aprocitentan. (For discussion see safety).

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of efficacy for trial ID-080A301

Title: Multi-center, blinded, randomized, **P**a**R**all**E**l-group, Phase 3 study with apro**CI**tentan in **S**ubjects with Res**I**stant Hypertensi**ON** (RHT)		
Study identifier	ID-080A301 EudraCT Number: 2017-004393-33	
Design	Multi-center, randomized, parallel-group, blinded Phase 3 study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	48 weeks (4 weeks double-blind part 1, 32 weeks single-blind part 2, 12-week double-blind part 3) 4 weeks Not applicable
Hypothesis	Superiority	
Treatments groups Double-blind part 1	Aprocitentan 12.5 mg	Aprocitentan 12.5 mg once daily for 4 weeks, N=243
	Aprocitentan 25 mg	Aprocitentan 25 mg once daily for 4 weeks, N=243

	Placebo		Placebo once daily for 4 weeks, N=244
Treatments groups Single-blind part 2	Aprocitentan 25 mg		Aprocitentan 25 mg once daily for 32 weeks, N=704
Treatments groups Double-blind withdrawal part 3	Aprocitentan 25 mg		Aprocitentan 25 mg once daily for 12 weeks, N=307
	Placebo		Placebo once daily for 12 weeks, N=307
Endpoints and definitions	Primary endpoint	SiSBP at Week 4	Change from baseline to Week 4 of double-blind treatment in mean trough SiSBP, recorded via uAOBPM
	Key secondary endpoint	SiSBP at Week 40	Change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP, recorded via uAOBPM
	Secondary endpoints	SiDBP at Week 4	Change from baseline to Week 4 of double-blind treatment in mean trough SiDBP, recorded via uAOBPM
		SiDBP at Week 40	Change from DB-WD baseline (Week 36) to Week 40 in mean trough SiDBP, recorded via uAOBPM
		24h mean SBP and DBP at Week 4	Changes from baseline to Week 4 of double-blind treatment in 24 h mean SBP and DBP recorded via ABPM
		24h mean SBP and DBP at Week 40	Changes from DB-WD baseline (Week 36) to Week 40 in 24 h mean SBP and DBP recorded via ABPM
	Other efficacy endpoints	Daytime and night-time mean SBP and DBP at Week 4	Changes from baseline to Week 4 in daytime and night-time mean SBP and DBP recorded via ABPM
		Control rates at Week 4	BP control (yes/no) at Week 4 for mean trough SiSBP and SiDBP recorded via uAOBPM
		Response rates at Week 4	BP response (yes/no) at Week 4 for mean trough SiSBP and SiDBP recorded via uAOBPM
		Daytime and night-time mean SBP and DBP at Week 40	Changes from DB-WD baseline (Week 36) to Week 40 in daytime and night-time mean SBP and DBP recorded via ABPM
		Control rates at Week 40	BP control (yes/no) at Week 40 for mean trough SiSBP and SiDBP recorded via uAOBPM

		Loss of response rates at Week 40	BP response (yes/no) at Week 40 for mean trough SiSBP and SiDBP recorded via uAOBPM
		Ratio to baseline in UACR	Ratios to baseline for all assessed time points in DB part 1 and SB part 2, and ratios to DB-WD baseline (Week 36) for all assessed time points in DB-WD part 3, in UACR.
Database lock	12-May-2022		
Results and Analysis			
Analysis description	**Primary Analysis: primary endpoint**		
Analysis population and time point description	For the primary efficacy endpoint, analyses were performed on the Full analysis set (FAS) which comprised all subjects assigned (i.e., randomized) to a double-blind study treatment. Subjects were evaluated according to their assigned study treatment in double-blind part 1. All uAOBPM recordings, irrespective of any intercurrent event(s), were included in the main analysis. Changes from baseline to post-baseline visits up to Week 4 were analyzed using a mixed model with factors for treatment group, visit, and treatment-by-visit interaction, and covariates for baseline SiSBP and the interaction between baseline SiSBP and visit. An unstructured covariance matrix was used to account for the correlation between repeated BP measurements from the same subject. LS mean differences vs placebo at Week 4 and their 97.5% confidence intervals were obtained from the model.		

Descriptive statistics and estimate variability	Treatment group	Aprocitentan 12.5 mg	Aprocitentan 25 mg	Placebo
	Number of subjects	243	243	244
	Change from baseline to Week 4 in SiSBP (mmHg) Mean	-15.5	-14.9	-11.5

Effect estimate per comparison	Change from baseline to Week 4 in SiSBP (mmHg)	Comparison groups	Aprocitentan 12.5 mg vs placebo
		LS Mean difference	-3.79
		97.5% confidence limit	-6.76, -0.82
		P-value	0.0042
		Comparison groups	Aprocitentan 25 mg vs placebo
		LS Mean difference	-3.73
		97.5% confidence limit	-6.67, -0.78
		P-value	0.0046

<table>
<tr><td>Notes</td><td colspan="3">None.</td></tr>
<tr><td>Analysis description</td><td colspan="3">Primary analysis: key secondary endpoint</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">The main analysis for the change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP recorded via uAOBPM was conducted on the modified full analysis set (mFAS) for the 2 treatment groups (aprocitentan 25 mg and placebo). The analyses were adjusted for the stratum at re-randomization (i.e., randomized treatment in DB part 1).

Changes from DB-WD baseline (Week 36) to visits up to Week 40 were analyzed using a mixed model with factors for stratum (i.e., randomized treatment in DB part 1), treatment group, visit, and treatment by visit interaction, and covariates for DB-WD baseline SiSBP and the interaction between DB-WD baseline SiSBP and visit, and an unstructured covariance matrix.

LS mean differences vs placebo for the change from DB-WD baseline to Week 40 and their 95% CIs were obtained from the model.</td></tr>
<tr><td rowspan="4">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>Aprocitentan 25 mg</td><td>Placebo</td></tr>
<tr><td>Number of subjects</td><td>307</td><td>307</td></tr>
<tr><td>Change from DB-WD baseline to Week 40 in SiSBP (mmHg)

Mean</td><td>-1.2</td><td>4.0</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td rowspan="4">Effect estimate per comparison</td><td rowspan="4">Change from DB-WD baseline to Week 40 in SiSBP (mmHg)</td><td>Comparison groups</td><td>Aprocitentan 25 mg vs placebo</td></tr>
<tr><td>LS Mean difference</td><td>-5.87</td></tr>
<tr><td>95% confidence limit</td><td>-7.98, -3.76</td></tr>
<tr><td>P-value</td><td>< 0.0001</td></tr>
<tr><td>Notes</td><td colspan="3">None.</td></tr>
</table>

Analysis description	**Primary Analysis: other secondary endpoints**
Analysis population and time point description	Other secondary efficacy endpoints (summarized below) were tested at the two-sided significance level of 0.05. No correction for multiplicity was applied.

Endpoint	**Recorded via**	**Model**	**Analysis set**
Change from baseline to Week 4			
mean trough SiDBP	uAOBPM	mixed model	FAS
24 h mean SBP	ABPM	ANCOVA	aFAS
24 h mean DBP	ABPM	ANCOVA	aFAS
Change from DB-WD baseline to Week 40			
mean trough SiDBP	uAOBPM	mixed model	mFAS
24 h mean SBP	ABPM	ANCOVA	maFAS
24 h mean DBP	ABPM	ANCOVA	maFAS

FAS: Full analysis set (all subjects who were randomized and had a baseline SiSBP recorded via uAOBPM at trough); subjects were evaluated according to their assigned study treatment in DB part 1: aprocitentan 25 mg, aprocitentan 12.5 mg, or placebo.

mFAS: modified Full analysis set (all subjects from the FAS who were re-randomized in DB-WD part 3 and had a DB-WD baseline SiSBP recorded via uAOBPM at trough); subjects were evaluated according to their assigned study treatment in DB-WD part 3: aprocitentan 25 mg or placebo.

aFAS: Ambulatory blood pressure monitoring full analysis set (all subjects from the FAS with a baseline 24 h mean SBP value recorded via ABPM for a total duration of at least 21 h with at least 70% valid readings); subjects were evaluated according to their assigned study treatment in DB part 1.

maFAS: Modified ambulatory blood pressure monitoring full analysis set (all subjects from the mFAS with a DB-WD baseline 24 h mean SBP value recorded via ABPM for a total duration of at least 21 h with at least 70% valid readings); subjects were evaluated according to their assigned study treatment in DB-WD part 3.

Descriptive statistics and estimate variability	Treatment group	Aprocitentan 12.5 mg	Aprocitentan 25 mg	Placebo
	Number of subjects	243	243	244
	Change from baseline to Week 4 in SiDBP (mmHg) Mean	-10.8	-10.8	-6.3
	Number of subjects	206	207	220
	Change from baseline to Week 4 in 24 h mean SBP (mmHg) Mean	-6.74	-8.54	-2.43
	Change from baseline to Week 4 in 24 h mean DBP (mmHg) Mean	-6.50	-7.61	-1.80
	Number of subjects	-	307	307

	Change from DB-WD baseline to Week 40 in SiDBP (mmHg) Mean	-	-0.5	4.7
	Number of subjects	-	237	241
	Change from DB-WD baseline to Week 40 in 24 h mean SBP (mmHg) Mean	-	-0.10	6.56
	Change from DB-WD baseline to Week 40 in 24 h mean DBP (mmHg) Mean	-	-0.48	6.31

Effect estimate per comparison	Change from baseline to Week 4 in SiDBP (mmHg)	Comparison groups	Aprocitentan 12.5 mg vs placebo
		LS Mean difference	-3.94
		95% confidence limit	-5.57, -2.31
		P-value	< 0.0001
		Comparison groups	Aprocitentan 25 mg vs placebo
		LS Mean difference	-4.47
		95% confidence limit	-6.09, -2.85
		P-value	< 0.0001
	Change from baseline to Week 4 in 24 h mean SBP (mmHg)	Comparison groups	Aprocitentan 12.5 mg vs placebo
		LS Mean difference	-4.18
		95% confidence limit	-6.25, -2.12
		P-value	< 0.0001
		Comparison groups	Aprocitentan 25 mg vs placebo
		LS Mean difference	-5.90
		95% confidence limit	-7.94, -3.85
		P-value	< 0.0001
	Change from baseline to Week 4 in 24 h mean DBP (mmHg)	Comparison groups	Aprocitentan 12.5 mg vs placebo
		LS Mean difference	-4.32
		95% confidence limit	-5.66, -2.98
		P-value	< 0.0001

		Comparison groups	Aprocitentan 25 mg vs placebo
		LS Mean difference	-5.81
		95% confidence limit	-7.14, -4.49
		P-value	< 0.0001
	Change from DB-WD baseline to Week 40 in SiDBP (mmHg)	Comparison groups	Aprocitentan 25 mg vs placebo
		LS Mean difference	-5.29
		95% confidence limit	-6.72, -3.86
		P-value	< 0.0001
	Change from DB-WD baseline to Week 40 in 24 h mean SBP (mmHg)	Comparison groups	Aprocitentan 25 mg vs placebo
		LS Mean difference	-6.53
		95% confidence limit	-8.50, -4.56
		P-value	< 0.0001
	Change from DB-WD baseline to Week 40 in 24 h mean DBP (mmHg)	Comparison groups	Aprocitentan 25 mg vs placebo
		LS Mean difference	-6.75
		95% confidence limit	-7.98, -5.52
		P-value	< 0.0001
Notes	None.		

2.6.5.3. Clinical studies in special populations

Patients at the age of at least 65 were included in the primary analysis in the pivotal trial 301 (73/81/78 patients on aprocitentan 12.5 mg/25 mg/placebo). 20/20/25 patients of at least 75 years of age were included in the respective groups. There was no indication of a lower efficacy in these patients, numerically, based on these low numbers, the treatment effects of aprocitentan were larger in older patients but there was no treatment by age interaction (p=0.8772). No information is provided on patients 85 + years of age and about representation of age groups over the whole clinical development programme.

Number of subjects enrolled in clinical studies by age category

	Age 65–74 (Older subjects number / total number)	**Age 75–84 (Older subjects number / total number)**	**Age 85+ (Older subjects number / total number)**
Controlled Trials	Total: 330 / 1382 Phase 1[a]: 7 / 162 Phase 2: 74 / 490 Phase 3: 249 / 730	Total: 73 / 1382 Phase 1[a]: 1 / 162 Phase 2: 0 / 490 Phase 3: 72 / 730	Total: 0 / 1382
Non Controlled trials (only Phase 1[b])	7 / 120	0 / 120	0 / 120

[a] Phase 1 controlled trials include AC-080-101 (part B+C), AC-080-102, ID-080-107, and ID-080-108, from which only AC-080-101 contributed older subjects

2.6.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

The Application was mainly based on one pivotal trial in the target group of patients with RHT at least on triple antihypertensive standard therapy and a dose finding study in patients with mild to moderate arterial hypertension without treatment at the time of randomization. No Analyses across trials are provided.

2.6.5.6. Supportive study(ies)

N/A

2.6.6. Discussion on clinical efficacy

A clinical development programme has been set up to support the following indication:

JERAYGO is indicated for the treatment of resistant hypertension in adult patients in combination with other antihypertensive medications.

Dose selection

The dose selection for Phase 3 was based on the totality of data from previously performed studies, but wasmainly driven by dose-finding study 201 in HTN. A Phase 1 study (study AC-080-101) in healthy subjects investigated multiple doses ranging from 5 to 100 mg. After 10 days of treatment with 100 mg, there were frequent headaches and a signal of body weight increase, in particular in elderly subjects; therefore, the 100 mg dose was not carried forward to Phase 2. 50 mg was selected as the highest aprocitentan dose to be evaluated in study 201.

The Phase 2 study AC-080A201 (study 201) was a dose-finding study in subjects with essential hypertension (grade 1 and 2) designed to estimate the minimum effective dose and maximum tolerated dose of aprocitentan as monotherapy vs. placebo in subjects with HTN. It was a randomized, placebo- and actively (Lisinopril 20 mg) controlled study comparing aprocitentan 5, 10, 25, and 50 mg vs. placebo and vs. the active comparator Lisinopril. A dose-dependent reduction in BP (measured as SiDBP/SiSBP at Week 8) was observed over a dose range of 5 to 50 mg, 25 mg giving the largest decrease in BP. The effect of aprocitentan on BP values were less pronounced at the dose of 50 mg. The Applicant took this into account when concluding that a quadratic model was best to estimate the dose related treatment effect by applying kind of a u-shaped curve. Mechanistically one may speculate if the dose dependent increase in plasma ET-1 concentrations might counteract efficacy at higher doses. However, this is unlikely, according to data provided, irrespectively of dose there was no association between blood pressure and plasma-ET-1 levels. Whether the lower efficacy at 50 mg as observed is a true effect or a chance finding remains unclear.

The hemodilution effect (decrease in hemoglobin concentration and increase in ePV), which may signal a potential for fluid retention, was numerically larger at 50 mg than at 25 mg. This was consistent with the results of the clinical pharmacology mechanistic study to evaluate the effect of aprocitentan on body weight and fluid retention in healthy subjects on a high sodium diet (study AC-080-102) which showed lower weight increase (vs placebo) with 10 mg (+0.4 kg) than with 25 or 50 mg (+0.8 kg).

Based on these efficacy and safety considerations, the dose range of 10 to 25 mg was selected for further evaluation. It was assumed that data from the phase 2 population (monotherapy, stage 1 and 2 HTN) would sufficiently inform on dose relation of efficacy in the target population (resistant hypertension, add-on at least triple antihypertensive therapy). This led to selection of the doses of 12.5 and 25 mg o.d. for the Phase 3 program in subjects with difficult-to-control HTN. The dose of 12.5 mg was selected instead of 10 mg as it represented half of the expected maximum therapeutic dose.

Data over 4 weeks are available to assess the dose response in the target group of patients. In the single pivotal Phase 3 study (AC-080A301 (study 301)) 12.5 mg and 25 mg Aprocitentan were compared with placebo over 4 weeks. Only the 25 mg dose was carried foreward up to week 36 in an uncontrolled part of the study and thereafter investigated against placebo in a withdrawal design. For data on dose response see below. The Applicant proposes both doses as an option in the SmPC (4.2):

The recommended dose is 12.5 mg orally once daily. The dose can be increased to 25 mg once daily for patients tolerating the 12.5 mg dose and in need of tighter blood pressure (BP) control *(see section 4.4) .*

As discussed below, there was no difference in efficacy between the 25 mg dose and the 12.5 mg dose when uAOBPM (unattended automated office blood pressure measurement) was used, the assessment method for the primary and key secondary endpoints. Numerical dose related differences in efficacy were observed for ambulatory blood pressure measurements for systolic and diastolic blood pressure over 24 h, at day-time and night-time. Not all patients had evaluable ABPM values (90.2% in the double blind part 1, 77.9% in the DB-WD part 3, FAS respectively). Although a duration of 4 – 8 weeks was considered sufficient by the CHMP in the Scientific Advice (2017) in most cases the maximal BP lowering effect is not achieved within 4 weeks and it is not clear whether a longer period (e.g. 8 weeks) would have changed the outcome on dose relation of efficacy. After initiating a 25 mg dose in the open label phase, there was a decrease in BP, irrespectively of whether patients had received 12.5 mg or 25 mg before. SiSBP values decreased slightly more in patients initially treated with 12.5 mg, indicating a small additional add-on effect at the higher dose (difference between 1.0 and 1.7 mmHg up to week 20 with variable results thereafter).

An analysis on the impact of amendment 2 in study 201 that among others changed BP criteria for inclusion was provided and indicated that blood pressure responses after the amendment tended to be larger. This is kind of expected, considering e.g. that nonspecific blood pressure related effects are larger at higher baseline blood pressure levels. The result does not put a question mark on the overall results of study 201 and the conclusions drawn.

Design and conduct of clinical studies

The clinical program was mainly based on 1 controlled pivotal phase III study, study 301 (PRECISION) in patients with resistant arterial hypertension (RHT).

Design

The study consisted of a screening period (4–12 weeks), placebo run-in period (4 weeks), randomized treatment period (3 sequential parts, and safety follow-up (FU) period.

At least 4 weeks before the start of the placebo run-in period, individual background antihypertensive medications (except beta-blockers) were switched to a mandatory standardized background antihypertensive therapy (SBAT): a single pill fixed dose combination of a calcium channel blocker (amlodipine, 5 or 10 mg), an angiotensin receptor blocker (valsartan, 160 mg), and a diuretic (hydrochlorothiazide, 25 mg).

The purpose of the placebo run in period was to confirm that mean trough sitting systolic BP (SiSBP) remained ≥ 140 mmHg, to exclude potential placebo responders.

The randomized treatment period included 3 parts.

• Double-blind (DB) part 1 (4 weeks): subjects were randomized 1:1:1 to receive (qd) aprocitentan 25 mg, aprocitentan 12.5 mg, or placebo.

• SB part 2 (32 weeks): all subjects received aprocitentan 25 mg up to week 36

• DB withdrawal (DB-WD) part 3 (12 weeks): subjects were re-randomized 1:1 to receive aprocitentan 25 mg or placebo. EOT: Week 48

• Safety FU period (30–33 days)

Regarding efficacy the study design with a placebo controlled DB initial phase investigating the effect of different doses and a controlled withdrawal phase to investigate maintenance of efficacy was in line with the CHMP Scientific Advice (2017). However, as discussed below the design did not meet the strong CHMP recommendation on how to assess safety. In line with (EMA/CHMP/29947/2013/Rev. 4) the CHMP requested long term controlled data of at least 6 months in an actively controlled design in order to exclude a negative impact.

Endpoints

The primary and secondary endpoints focussed on systolic blood pressure as measured by uAOBPM.

Primary efficacy endpoint:

• Change from baseline to Week 4 of double-blind treatment in mean trough SiSBP (Unattended automated office blood pressure measurement (uAOBPM)).

Secondary efficacy endpoint:

• Change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP (uAOBPM).(“key secondary)

• Change from baseline to Week 4 of double-blind treatment in mean trough SiDBP (uAOBPM).

• Change from DB-WD baseline (Week 36) to Week 40 in mean trough SiDBP (uAOBPM).

• Changes from baseline to Week 4 of double-blind treatment in 24 h mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) recorded via ambulatory blood pressure monitoring (ABPM)).

• Changes from DB-WD baseline (Week 36) to Week 40 in 24 h mean SBP and DBP (ABPM).

Additional efficacy endpoints further characterizing BP response were predefined as well as urine albumin-to-creatinine ratio (UACR).

The design of the pivotal study was overall suitable to investigate short term efficacy (4 weeks) in a controlled fashion for both doses investigated (12.5 and 25 mg qd) and maintenance of efficacy of a 25 mg dose by the means of a randomized withdrawal part at the end of week 36.

Conduct

The rate of reported protocol violations was within the expected range. Quality control measures were in place. Relevant GCP non-compliance was detected in one clinical site leading to closure of this site (4204, Russian Federation). 9 randomized subjects prematurely discontinued study and sensitivity analyses were provided by excluding the 27 patients of this site. Other serious GCP issues were identified in 3 additional centres that were handled by corrective measures. In addition, there were several GCP issues identified during inspections in different countries that per se did not raise concerns. Information on the multilayer Quality assurance system in place revealed no indications that the findings at site 4204 were to be generalized for the area in question or for the whole study.

All participants in part 2 received aprocitentan 25mg (on top of SBAT), and this was a single-blind part of the study. Taking into account all the amendments made to the protocol during the study, it can be concluded that the study population was narrowed down, especially for safety reasons which is reflected in the SmPC.

Analyses covering the impact of the COVID19-pandemic and the Ukrainian war were provided. Overall, these issues are considered not to have had a relevant impact on the overall conclusions.

The way participants were presented in the Figure Disposition of randomized subjects were updated (see fig 4 above). Participants labelled as 'Other’ reason for treatment discontinuation who withdrew due to AE were added to the number of participants in the 'AE as reason for treatment discontinuation' as well as participants who discontinued the study treatment due to meeting study-specific treatment discontinuation criteria (SSDC) if considered an AE (fluid retention). In addition, analyses were provided by counting all SSDC as AEs. Based on this analysis the number of subjects who discontinued study treatment due to AEs increased across all study parts: DB part 1: aprocitentan 12.5 mg group (2.5% to 3.3%), aprocitentan 25mg (2.0% to 2.4%), placebo (remained the same 0.8%; SB part 2: aprocitentan 25mg 3.6% to 6.4%; DB-WD part 3: aprocitentan 25mg (2.9% to 4.8%), placebo (2.0% to 3.3%).

One patient who discontinued due to prolonged interruption due to an AE was not counted in the category AE and other prolonged interruptions were not due to AEs.

Study size

Out of 1965 screened subjects, 911 were included in the placebo RI period and 730 were randomized. 662 of 730 randomized subjects (90.7%) completed the study as per protocol with the EOS visit. European patients were sufficiently represented. The number of patients was considered sufficient to describe the treatment effect in the overall population and in relevant subgroups.

Study population

RHT was defined by a step-wise application of BP criteria: 1. Mean SiSBP ≥ 140 mmHg recorded via unattended automated office blood pressure measurement (uAOBPM) at the screening visit. 2. Mean trough SiSBP ≥ 140 mmHg (uAOBPM) at the switch from individual background antihypertensive medications (i.e., at least 3 medications from different pharmacological classes) to SBAT. Single blind placebo run in phase: 3. Mean trough SiSBP ≥ 140 mmHg (uAOBPM). At each of these steps patients were excluded when not meeting this criterion, respectively. However, despite of all these measures a large placebo effect was observed after randomization to phase 1 on the study. 40.6 % of patients in the placebo arm had sufficient BP control when defined by SiSBP < 140 mmHg and SiDBP< 90 mmHg by week 4.

There were 3 steps of preselection patients including a placebo run-in phase which does not correspond to the administration in clinical practice. However, the Applicant provided data on patient characteristics that indicated that the patients were sufficiently representative for a study population with RHT with risk factors as expected**.** On the other hand, 40.6 % of patients randomized to placebo had reached target BP values as proposed by the ESH/ESH 2018 after 4 weeks. This indicates that a large number of patients included were not in line with the assumption of RHT requiring treatment. At baseline, 24 h mean SBP values were approximately 137 mmHg in all groups. These values were significantly lower compared with baseline values measured with uAOBPM (above 153 mmHg in all treatment groups) and were below the cut-off value of 140 mmHg used as inclusion criteria. This is expected and not an issue. As the baseline 24 h mean SBP in study 301 (137 mmHg) corresponded to the 24 h mean SBP defined in the a.m. guideline (≥ 130 mmHg), and it can therefore be concluded that RHT in study 301 was confirmed by ABPM.

The applicant introduced inclusion and exclusion criteria to select subjects with true RHT, and exclude pseudo-RHT and secondary hypertension causes, including mainly primary hyperaldosteronism, renovascular disease and chronic kidney disease. Although obstructive sleep apnea (OSA) is one of the most common causes of secondary hypertension, patients with OSA were included in the study. There is evidence that specific targeted therapy such as CPAP improves systolic and diastolic blood pressure. The number of OSA patients treated with CPAP was 6/103 (5.8%). Although CPAP is the main treatment for OSA, the majority of included OSA patients (94.2%) were not treated with CPAP. It is considered that the use of CPAP in a small number of patients in this study does not affect the results and that the blood pressure lowering effect in OSA patients comes from the antihypertensive treatment.

Cushing's syndrome and hyperparathyroidism are also common causes of secondary hypertension. The applicant did not measure cortisol, Ca and PTH to exclude Cushing’s syndrome and hyperparathyroidism, but no single patient was reported with Cushing’s syndrome. A total of 10 patients (1.4%) with hyperparathyroidism were included. This number is accepted for a true RHT population.

Notable exclusion criteria were: participants with severe hypertension (grade 3, mean SiSBP ≥ 180 mmHg and/or SiDBP ≥ 110 mmHg), a history of TIA/stoke/MI/unstable angina in the 6 months prior to screening, severe renal insufficiency (eGFR < 15 mL/min/1.73 m2), Type 1 diabetes mellitus, hepatic impairment (ALT or AST > 3 × ULN, or severe hepatic impairment). These eligibility criteria are reflected in Section 5.1 of the SmPC.

Only in 5 patients (3 randomized) the dose of SBAT changed during the RI period.

The initially proposed indication was as follows: *aprocitentan is indicated for the treatment of resistant hypertension in adult patients in combination with other antihypertensive medications*. Upon request the Applicant amended the wording of the indication – ie. specified that aprocitentan is indicated for the treatment of resistant hypertension in combination with at least three antihypertensive medicinal products (see section 5.1).

The study allowed for a broad representation of patients with respect to underlying diseases. Not to be included were patients with transient ischemic attack, stroke, unstable angina, or myocardial infarction within 6 months prior to screening and some predefined conditions of clinically significant unstable cardiac disease including congestive heart failure NYHA stage III and IV, and excluding severe CKD (eGFR equation < 15 mL/min/1.73 m2) among others. Information on patients > 75 years is currently missing.

Statistical analysis

For defining the estimand attribute "target population of the clinical question", referring to the processes for selection of the analysis sets for primary and key secondary analysis is not appropriate as the definition of the target population of clinical interest aligned to the study objective (=part of the estimand) should be separated from the question how to appropriately identify and select a representative set of such patients (=part of study design). The objective of the study was "to demonstrate the BP-lowering effect of aprocitentan when added to standard-of-care in subjects with true RHT". An explicit definition of "true RHT" is not given. In order to be practically relevant, the target population should be patients that will be considered patients with RHT in clinical practice. As placebo non-responders are not identifiable in clinical practice, excluding these from the target population raises the question in how far results can be extrapolated to clinical practice.

The treatment policy strategy can be considered acceptable for treatment discontinuation and changes in background standard of care (such as change of diuretic). However, if antihypertensive rescue medication is taken after treatment discontinuation, the treatment effect in accordance with the treatment policy strategy may also incorporate the effect of rescue medication such that not only the effect irrespectively of rescue medication intake but also the hypothetical effect 'if rescue had not been available' is of interest (as already highlighted in the CHMP advice). Anyway, rescue medication intake was rare such that this issue is not of major relevance for the conclusions from the study. Adequacy of the methods, conduct, analysis and reporting of results from main studies, as appropriate. Discuss any particular issues raised regarding the study design.

All subjects who were randomized and had a baseline SiSBP and at least one post-baseline value were included in the analysis. Usually all treated patients should be included in the primary analysis, however, sensitivity analyses including all treated patients were provided.

The strategy for multiple testing provided control of the family-wise type 1 error rate for the hypothesis tests for the primary endpoint and the key secondary endpoint.

The baseline values were appropriately adjusted for in the primary and secondary analyses, as well as the re-randomisation stratification factor for the key secondary analysis.

Including all values irrespectively of the occurrence of intercurrent events in the analysis was appropriate in accordance with a treatment policy strategy. However, for the intercurrent event intake of anti-hypertensive rescue medication after withdrawal, the hypothetical strategy excluding values after the intercurrent event is also relevant.

Missing data handling should be aligned to the targeted estimand. Overall, due to the low proportion of patients with missing data, missing data handling may not be a critical issue. Nevertheless, the following remarks are made. The MMRM model which was applied for primary and key secondary analysis is not adequate when intercurrent events are accounted for by the treatment policy strategy. As already highlighted during CHMP scientific advice, a MMRM analysis is not appropriate for a data-set where some patients have complete on-treatment data, others incomplete data, and others a combination of on and off-treatment data. When trying to fit a variance structure to such data it would be anticipated that correlations between visits would be very different depending on the intercurrent events that took place between those visits.

Analyses replacing missing values by jump to reference (J2R) and copy reference (CR), respectively, were provided as sensitivity analyses (independently whether an intercurrent event was observed in the patient) and could be considered as more appropriate than MMRM. A decay to the reference profile as assumed by these methods is plausible for patients with missing values after treatment discontinuation; for patients with missing data for other reasons, these methods could be conservative (but missing data are not necessarily expected in these patients). The J2R analysis was not fully correctly specified but a relevant impact on the conclusions from the analysis is not expected. Additional sensitivity analyses were provided on request: (1) An analysis replacing missing data after treatment discontinuation by J2R, and missing data for other reasons under MAR; (2) An analysis replacing missing data after treatment discontinuation and rescue medication by J2R, and missing data for other reasons by MAR (to address the hypothetical effect if no rescue had been available under a more conservative assumption).

The sensitivity analysis excluding data after intercurrent events from the analysis, implicitly considering these to be missing at random (MAR), is not a sensitivity analysis but a supplementary analysis targeting the hypothetical effect 'if no intercurrent event had occurred', which is of questionable regulatory relevance. The tipping point analysis may be useful as supporting analysis because, as highlighted above, the MMRM analysis considering data to be MAR is not plausible. Sensitivity analyses replacing missing data using LOCF are of limited value as the assumption that the effect from last measurement is maintained is questionable, while BOCF analysis could be conservative depending on missing data patterns but underestimates variance as it is a single imputation method.

Efficacy data and additional analyses

The baseline characteristics of the randomized population were well balanced across treatment groups. Mean SiSBP/SiDBP values at baseline were 153.2 (8.8)/87.9 (9.4), 153.3 (9.0)/87.7 (9.7), and 153.3 (9.0)/87.1 (9.9) mmHg (SD) for Aprocitentan 12.5 and 25 mg qd and placebo, respectively. The randomized population was predominantly male (59.5%) and White (82.9%), and the mean age was 61.7 years. 44% of subjects were aged ≥ 65 years, including 9.9% aged ≥ 75 years. 11.2% of subjects were Black or African American, representing 33.6% of the randomized subjects in North America. Most subjects were enrolled in Europe (61.4%) or in North America (31.8%).

22.2% of subjects had CKD stage 3 or 4 (eGFR 15 – < 60 mL/min/1.73 m2 at screening and 14% had sleep apnea. Subjects with diabetes mellitus (Type II; 54.1%), ischemic heart disease (30.8%), stroke (7.8%), congestive heart failure (19.6%), and obesity (69.3%) were highly represented. 63.0% of randomized subjects were receiving ≥ 4 antihypertensive therapies at screening, with RAS blockers, diuretics, and CCBs being the most common treatments.

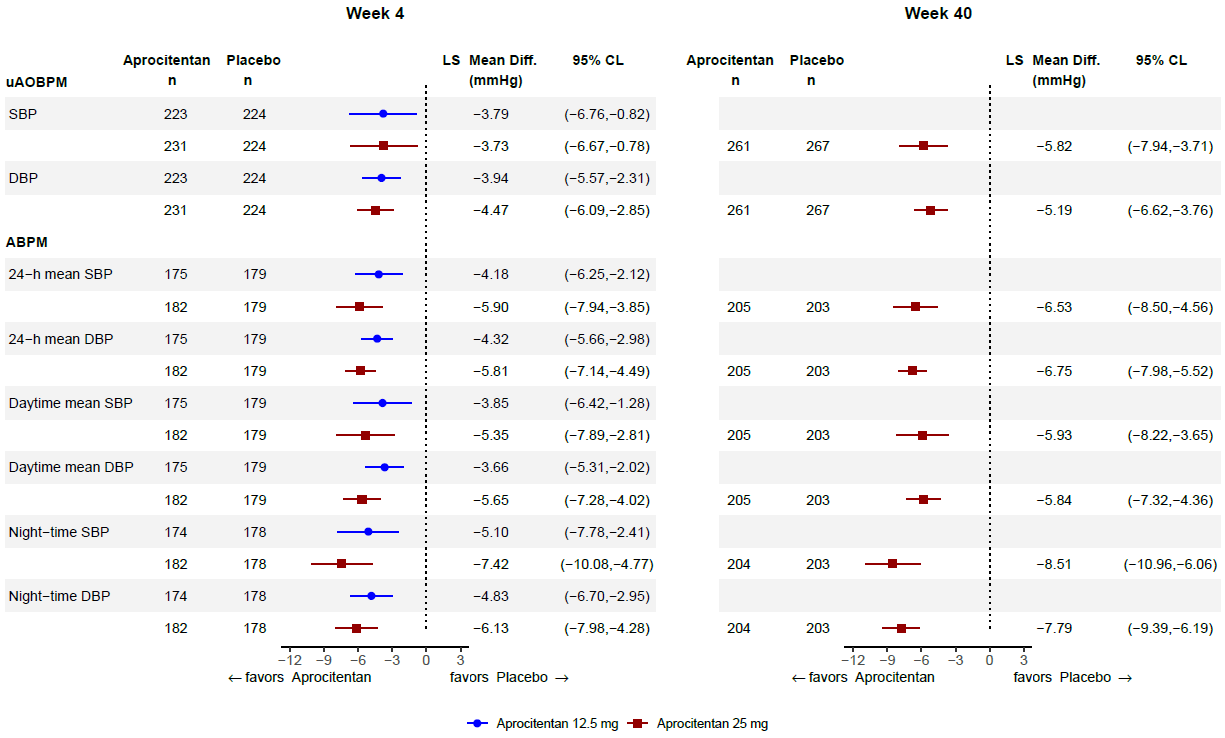
There is overall insufficient data on the administration of aprocitentan in patients within 6 months of a MACE event. Section 4.4 has been amended accordingly. Reference is also made in section 4.4. on considerations to be made whether aprocitentan should be discontinued or kept in case of one of these events.

Upon request it has been clarified that no data are available for patients at age 85 + years.

There was a statistically significant difference between aprocitentan 25 mg and placebo, and between aprocitentan 12.5 mg and placebo, in the mean change from baseline to Week 4 in SiSBP (primary efficacy endpoint) and for SiDBP (secondary endpoints), respectively. A treatment effect was observed already after 2 weeks. Change from DB-WD baseline to Week 40 in SiSBP (mmHg) and SiDBP was also significantly different between aprocitentan 25 mg and placebo after re-randomization.

An overview over key results on BP is provided in Figure 4-4.

Figure 4-4 Differences to placebo for changes from baseline in systolic and diastolic BP at Week 4 (DB part 1) and Week 40 (DB-WD part 3)



The data up to week 4 indicate a clinically relevant efficacy in the target group of patients. The results in the DB-WD trial demonstrate maintenance of efficacy over 40 and up to 48 weeks.

There were no relevant differences between the 12.5 and the 25 mg in efficacy dose for these endpoints.

For the primary endpoint efficacy was consistent over most subgroups as predefined. A possible treatment by weight interaction was not consistent for the two 12.5 and 25 mg aprocitentan strengths, was not equally represented in the analyses by BMI, and did not question a positive treatment effect irrespectively of weight. For Black or African American Patients the primary analysis did not indicate a treatment effect compared to placebo for both, the 12.5 and the 25 mg strength. This was possibly due to a chance high placebo effect at week 4. Other analyses performed consistently showed a treatment effect in this population, among these the analysis in the withdrawal part, and ABPM based measurements for systolic and diastolic blood pressure

(24 h, daytime, night-time) up to week 4 and during the DB-WD period. Subgroup analyses by CKD category at baseline revealed an interaction p-value of 0.0008 with a numerically higher efficacy in patients with eGFR 15 to < 60 mL/min/1.73 m2 (CKD stage 3–4). Analyses similar to those discussed above indicated that a clinically relevant efficacy can also be assumed n patients with eGFR ≥ 60 mL/min/1.73 m2. The data do not allow concluding on a higher efficacy in patients with CKD3/4.

Results for ambulatory blood pressure measurements (ABPM) were overall consistent with a significant decrease in systolic and diastolic BP over 24h, at daytime and at night-time. Numerically there was a tendency for a higher efficacy of the 25 mg dose as compared to the 12.5 mg dose. Several sensitivity analyses e.g. on missing values and the impact of diuretic use supported the robustness of the ambulatory blood pressure measurements and the conclusion on a somewhat higher efficacy of the 25 mg dose.

Considering the limited additional efficacy of the 25 mg over the 12.5 mg dose and the higher rate of AEs, in particular fluid retention and oedema, the 12.5 mg dose was considered the usual recommended dose. The dose can be increased to 25 mg once daily for patients tolerating the 12.5 mg dose and in need of tighter blood pressure (BP) control. It was reflected in the SmPC section 4.4 of the SmPC that when switching to 25 mg, the risk of increasing fluid retention, potentially aggravating heart failure or cardiovascular (CV) events, has to be taken into consideration in these patients.

UACR is a biomarker of renal dysfunction. After 4 weeks of treatment, a reduction of 30% (95% CL 20–39%) and 34% (95% CL 25–42%) in UACR was observed in aprocitentan 12.5 and 25 mg treatment groups compared to placebo group (p < 0.0001). 4 weeks after withdrawal of aprocitentan (Week 40), UACR in the placebo group increased and thereafter remained at a similar level, whereas the reduction in UACR was sustained in the aprocitentan group, corresponding to a reduction of 42% in the aprocitentan 25 mg group compared to placebo.

2.6.7. Conclusions on the clinical efficacy

In summary, a statistically significant and clinically relevant efficacy has been demonstrated for the target group of patients with RHT insufficiently treated with at least 3 antihypertensive medicinal products for the primary, secondary and other efficacy endpoints. The proposed indication sufficiently reflects the studied population and baseline treatment.

2.6.8. Clinical safety

The clinical Phase 3 study (PRECISION) and a dose-finding Phase 2 study, hereafter referred to as Study 301 and Study 201, contributed to the safety assessment of aprocitentan and are summarized in Table 1-1 below.

Table 1-1 Completed Phase 2/3 studies for the assessment of clinical safety

Study [Doc No]	Design	Number of randomized subjects	DB treatment / total daily dose / route / regimen	Treatment duration	Main efficacy endpoint(s)
Dose-finding Phase 2 study				**Monotherapy (Background antihypertensive treatment-naïve or treatment washed out)**	
Study 201 [D-17.023]	Prospective, multi-center, DB, double-dummy, randomized, placebo- and positive-reference, parallel-group dose-finding study in adult subjects (≥ 18 to ≤ 75 years) with HTN (grade 1 and 2)	N = 490	Aprocitentan 5 mg (N = 82) Aprocitentan 10 mg (N = 82) Aprocitentan 25 mg (N = 82) Aprocitentan 50 mg (N = 81) Lisinopril 20 mg (N = 81) Placebo (N = 82) Oral / once daily	4–6-week SB placebo RI period 8-week DB randomized treatment period 2-week SB placebo WD period	Change from baseline to Week 8 of DB treatment in: • mean trough SiSBP and SiDBP (uAOBP) • 24 h mean daytime and night-time SBP and DBP (ABPM)

Study [Doc No]	Design	Number of randomized subjects	DB treatment / total daily dose / route / regimen	Treatment duration	Main efficacy endpoint(s)
Phase 3 study				**Add-on therapy***	
Study 301 (PRECISION) [D-22.269]	Prospective, multi-center, blinded, randomized, parallel-group study in adult subjects (≥ 18 years) with HTN (grade 1 and 2) uncontrolled despite the use of 3 antihypertensive medications of different pharmacological classes	N = 730	Aprocitentan 12.5 mg (N = 243) Aprocitentan 25 mg (N = 243) Placebo (N = 244) Oral / once daily	4-week SB placebo RI period 48-week randomized treatment period in 3 parts: DB part 1 with aprocitentan 12.5 mg or 25 mg or placebo (4 weeks) SB part 2 with aprocitentan 25 mg (32 weeks) DB-WD part 3 with aprocitentan 25 mg or placebo (12 weeks)	Change from baseline to Week 4 of DB treatment in: • mean trough SiSBP and SiDBP (uAOBP) • 24 h mean daytime and night-time SBP and DBP (ABPM) Change from DB-WD baseline (Week 36) to Week 40 in: • mean trough SiSBP and SiDBP (uAOBP) • 24 h mean daytime and night-time SBP and DBP (ABPM)

* On top of an angiotensin receptor blocker (valsartan 160 mg), a calcium channel blocker (amlodipine 5 or 10 mg), and a diuretic (hydrochlorothiazide 25 mg).

ABPM = ambulatory blood pressure monitoring; DB = double-blind; DB-WD = double-blind withdrawal; HTN = hypertension; N = number of subjects in the Full analysis set; RI = Run-in; SB = single-blind; (Si)DBP = (sitting) diastolic blood pressure; (Si)SBP = (sitting) systolic blood pressure; uAOBP = unattended automatic office blood pressure; WD = withdrawal.

The safety of aprocitentan was evaluated as an add-on therapy at doses of 12.5 mg and 25 mg in Study 301 in 730 subjects with difficult-to-control HTN, and as monotherapy at doses of 5 mg, 10 mg, 25 mg, and 50 mg in Study 201 in 490 subjects with HTN. Long-term safety, for a treatment duration up to 48 weeks, was assessed for the 25 mg dose in Study 301.

However, duration of placebo-controlled patient exposure (aprocitentan vs. placebo) was limited during the Phase 2/3 programme to reliably assess long-term safety in a RHTN population. There are no placebo-controlled data above >12 weeks within the Phase 2/3 development programme.

2.6.8.1. Patient exposure

Exposure to study treatment within the Phase 2/3 development programme

Table 1-8 Combined exposure in Study 301 and Study 201

	Aprocitentan					Placebo[b]	Lisinopril
	5 mg	10 mg/12.5 mg	25 mg [a]	50 mg	Any dose		20 mg
Study 301							
N	NA	243	713	NA	724	444	NA
Subject-years	NA	19.5	486.4	NA	505.8	85.5	NA
At least 4 weeks	NA	191	687	NA	699	397	NA
At least 8 weeks	NA	1	671	NA	675	293	NA
At least 12 weeks	NA	NA	661	NA	667	171	NA
At least 24 weeks	NA	NA	633	NA	635	NA	NA
At least 26 weeks	NA	NA	630	NA	633	NA	NA
At least 32 weeks	NA	NA	536	NA	572	NA	NA
At least 34 weeks	NA	NA	419	NA	516	NA	NA
At least 35 weeks	NA	NA	409	NA	502	NA	NA
At least 36 weeks	NA	NA	391	NA	461	NA	NA
At least 39 weeks	NA	NA	304	NA	307	NA	NA
At least 40 weeks	NA	NA	297	NA	301	NA	NA
At least 44 weeks	NA	NA	183	NA	241	NA	NA
At least 46 weeks	NA	NA	104	NA	196	NA	NA
At least 47 weeks	NA	NA	100	NA	192	NA	NA
At least 48 weeks	NA	NA	50	NA	99	NA	NA

	Aprocitentan					Placebo[b]	Lisinopril
	5 mg	10 mg/12.5 mg	25 mg [a]	50 mg	Any dose		20 mg
Study 201							
N	82	82	82	81	327	82	81
Subject-years	12.1	12.2	12.2	11.7	48.2	11.8	12.0
At least 4 weeks	77	79	77	75	308	77	78
At least 8 weeks	56	54	57	54	221	52	53
Overall							
N	82	325	795	81	1051	526	81
Subject-years	12.1	31.7	498.6	11.7	554.0	97.3	12.0
At least 4 weeks	77	270	764	75	1007	474	78
At least 8 weeks	56	55	728	54	896	345	53
At least 12 weeks	NA	NA	662	NA	668	171	NA
At least 24 weeks	NA	NA	633	NA	635	NA	NA
At least 26 weeks	NA	NA	630	NA	633	NA	NA
At least 32 weeks	NA	NA	536	NA	572	NA	NA
At least 34 weeks	NA	NA	419	NA	516	NA	NA
At least 35 weeks	NA	NA	409	NA	502	NA	NA
At least 36 weeks	NA	NA	391	NA	461	NA	NA
At least 39 weeks	NA	NA	304	NA	307	NA	NA
At least 40 weeks	NA	NA	297	NA	301	NA	NA
At least 44 weeks	NA	NA	183	NA	241	NA	NA
At least 46 weeks	NA	NA	104	NA	196	NA	NA
At least 47 weeks	NA	NA	100	NA	192	NA	NA
At least 48 weeks	NA	NA	50	NA	99	NA	NA

[a] For study 301, exposure to aprocitentan 25 mg is the total exposure during the study regardless of study part.
[b] For study 301, total exposure to placebo in the study is regardless of study part (i.e., not continuous as treatment with placebo received in DB and DB-WD).
Of note, the difference in exposure of at least 47 weeks vs 48 weeks is explained by the fact that due to visit windows in study 301, many subjects had an exposure that was just few days less than 48 weeks.
DB = double-blind; DB-WD = double-blind withdrawal; NA = not applicable.

The safety profile of aprocitentan was characterized at doses of 12.5 mg and 25 mg in Study 301 and at doses of 5 mg, 10 mg, 25 mg, and 50 mg in Study 201.

Overall, 1220 subjects with HTN were included in the combined safety analyses of Study 301 (N=730) and Study 201 (N=490), of which 1051 subjects were exposed to aprocitentan: 81 subjects to aprocitentan 50 mg, 795 subjects to aprocitentan 25 mg, 325 subjects to aprocitentan 10/12.5 mg, and 82 subjects to

aprocitentan 5 mg [Table 1-8]. Please note that of those 1051 subjects, some were exposed to more than one dose level.

Of the 1051 subjects with HTN receiving aprocitentan, 633 subjects were treated for at least 26 weeks, 192 subjects for at least 47 weeks, and 99 subjects for at least 48 weeks. Due to the visit windows in Study 301, subjects completing the study as per protocol could have an exposure of just a few days less than 48 weeks, reflected by the considerably higher number of subjects with an exposure of at least 47 weeks (192 subjects) compared to 48 weeks (99 subjects). A total of 325 subjects and 795 subjects were exposed to aprocitentan 10 mg/12.5 mg or aprocitentan 25 mg, corresponding to 31.7 subject-years and 498.6 subject-years of exposure, respectively.

Exposure in clinical pharmacology Phase 1 studies

Table 1-9 Exposure to aprocitentan in Phase 1 clinical pharmacology studies

Study	N	Aprocitentan dose	Aprocitentan exposure
Single-dose			
AC-080-101 Part A	6	5 mg	Single dose
AC-080-101 Part B	24	25, 100, 300, or 600 mg	Single dose [a]
AC-080-104	6	25 mg	Single dose
AC-080-105 (renal impairment)	16	50 mg	Single dose
ID-080-109 (hepatic impairment)	17	25 mg	Single dose
ID-080-110	36	25 mg	Single dose [b]
Subtotal single dose	**105**		
Multiple or repeated dose			
AC-080-101 Part C	26	5, 25, or 100 mg o.d.	10 days
AC-080-102 (high sodium diet)	27[c]	10, 25, or 50 mg o.d.	9 days
AC-080-103	19	150 mg	1 day
		50 mg	4 days
AC-080-106	20	25 mg o.d.	13 days
ID-080-107	16	25 mg o.d.	10 days
ID-080-108 (TQT)	44	25 and 100 mg o.d.	10 days each
Subtotal multiple dose	**152**		
Total	**257**		

[a] Of the 6 subjects in the food effect group (100 mg dose group), 5 subjects received a second single dose of aprocitentan 100 mg after a washout-period of 14 days.
[b] All subjects received a second single dose of aprocitentan after a wash-out period of 19 days, except 2 subjects who prematurely discontinued the study and only took one single dose of study treatment.
[c] One additional subject received placebo in Period 1 of the study but discontinued the study prior to proceeding to Period 2; thus, the subject was not exposed to aprocitentan and is not counted in this table.
N = number of subjects who received aprocitentan; o.d. = once daily; TQT = thorough QT study.

Table 1-9 summarizes the exposure of the clinical pharmacology Phase 1 studies. In the 10 completed Phase 1 clinical pharmacology studies, a total of 257 subjects were exposed to aprocitentan, including 241 healthy subjects, 8 subjects with moderate hepatic impairment and 8 subjects with severe renal impairment. Of the 257 subjects, 105 subjects were exposed to single doses of aprocitentan (up to 600 mg) and 152 subjects received multiple doses of aprocitentan (up to 100 mg).

2.6.8.2. Adverse events

AEs during the 4-week DB part 1 of Study 301 (PRECISION), reported for ≥ 2% of subjects

Table 2-5 AEs occurring during the 4-week DB part 1 for ≥ 2% of subjects in any treatment group by Preferred Term; SAF (study 301)

	Aprocitentan		Placebo
	12.5 mg N = 243	25 mg N = 245	N = 242
Preferred Term	n (%)	n (%)	n (%)
Subjects with at least one event	**67 (27.6)**	**90 (36.7)**	**47 (19.4)**
Oedema peripheral [A]	16 (6.6)	35 (14.3)	5 (2.1)
Fluid retention [A]	4 (1.6)	7 (2.9)	0
Upper respiratory tract infection	0	6 (2.4)	4 (1.7)
Headache	0	5 (2.0)	3 (1.2)
Haemoglobin decreased [A]	6 (2.5)	0	0

Table shows Preferred Terms reported in ≥ 2% of subjects in any treatment group. AEs are sorted by descending frequency of Preferred Terms based on the aprocitentan 25 mg treatment group.

Percentages are based on the treatment group N; n = number of subjects with at least 1 row event; a subject can only be counted once per row but may be counted in more than one row.

Preferred Terms are based on MedDRA version 24.1.

[A] AE Preferred Term considered an AESI.

AE = adverse event; AESI = adverse event of special interest; DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; SAF = Safety analysis set.

Overall, AEs were reported in a numerically higher proportion of subjects in the aprocitentan groups compared to the placebo group during the 4-week DB part 1 of Study 301 [Table 2-5].

AEs were reported for 27.6% of subjects on aprocitentan 12.5 mg, 36.7% of subjects on aprocitentan 25 mg and 19.4% of subjects on placebo.

Peripheral oedema (aprocitentan 12.5 mg: 6.6%, aprocitentan 25 mg: 14.3% vs. placebo: 2.1%), fluid retention (aprocitentan 12.5 mg: 1.6%, aprocitentan 25 mg: 2.9% vs. placebo: 0%) and haemoglobin decreased (aprocitentan 12.5 mg: 2.5%, aprocitentan 25 mg: 0% vs. placebo: 0%) are well known adverse effects of endothelin receptor antagonists and were more frequent in the aprocitentan groups than in the placebo group.

AEs up to 48 weeks of treatment of Study 301, reported for ≥ 2% of subjects

Table 2-6 AEs occurring for ≥ 2% of subjects by time interval from the first dose of aprocitentan 25 mg and Preferred Term; Aprocitentan 25 mg set (study 301)

	Aprocitentan 25 mg				
	< 12 weeks N = 713	≥ 12- < 24 weeks N = 674	≥ 24- < 36 weeks N = 640	≥ 36 weeks N = 566	Overall N = 713
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least one event	**332 (46.6)**	**198 (29.4)**	**191 (29.8)**	**134 (23.7)**	**504 (70.7)**
Oedema peripheral [A]	96 (13.5)	29 (4.3)	9 (1.4)	7 (1.2)	133 (18.7)
Headache	16 (2.2)	10 (1.5)	8 (1.3)	2 (0.4)	34 (4.8)
Haemoglobin decreased [A]	19 (2.7)	6 (0.9)	6 (0.9)	3 (0.5)	33 (4.6)
COVID-19	10 (1.4)	7 (1.0)	5 (0.8)	9 (1.6)	31 (4.3)
Fluid retention [A]	24 (3.4)	2 (0.3)	3 (0.5)	0	28 (3.9)
COVID-19 pneumonia	8 (1.1)	8 (1.2)	5 (0.8)	4 (0.7)	25 (3.5)
Dyspnoea	14 (2.0)	5 (0.7)	0	2 (0.4)	21 (2.9)
Anaemia [A]	11 (1.5)	5 (0.7)	4 (0.6)	3 (0.5)	20 (2.8)
Glomerular filtration rate decreased	4 (0.6)	3 (0.4)	8 (1.3)	6 (1.1)	20 (2.8)
Dizziness	10 (1.4)	2 (0.3)	5 (0.8)	1 (0.2)	18 (2.5)
Nasopharyngitis	8 (1.1)	6 (0.9)	1 (0.2)	4 (0.7)	18 (2.5)
Hypotension	8 (1.1)	6 (0.9)	4 (0.6)	1 (0.2)	17 (2.4)
Pneumonia	8 (1.1)	0	3 (0.5)	6 (1.1)	17 (2.4)
Arthralgia	2 (0.3)	6 (0.9)	10 (1.6)	1 (0.2)	16 (2.2)
Hyperuricaemia	10 (1.4)	4 (0.6)	3 (0.5)	3 (0.5)	16 (2.2)
Upper respiratory tract infection	9 (1.3)	3 (0.4)	1 (0.2)	4 (0.7)	15 (2.1)
Atrial fibrillation	4 (0.6)	1 (0.1)	4 (0.6)	8 (1.4)	14 (2.0)

The % in each column displays the % of subjects reporting an AE in a certain exposure period. Subjects who had less than the exposure (either by design or because they prematurely discontinued treatment) are excluded.
A subject can be counted in more than one row.
A subject can be counted in more than one time interval in a row (a subject may experience multiple occurrences of the same AE at different time intervals whilst exposed to aprocitentan 25 mg).
A subject was only counted once in the overall column for a row where they experienced an AE.
AEs are sorted by descending frequency of Preferred Term based on the overall column.
[A] AE Preferred Term considered an AESI.
Preferred Terms are based on MedDRA dictionary version 24.1.
AE = adverse event; AESI = adverse event of special interest; COVID-19 = Coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities.

70.7% of the subjects in the aprocitentan 25 mg set had treatment-emergent AEs during Study 301.

The highest frequency of AEs was reported during the first 12 weeks of treatment with aprocitentan 25 mg (46.6%), with decreasing frequency over time thereafter [Table 2-6].

This pattern was observed mainly for the most common PT: Oedema peripheral, and also for the PTs: Fluid retention, Haemoglobin decreased, and Anaemia.

AEs during the 12-week DB-WD part 3 of Study 301, reported for ≥ 2% of subjects

Table 2-7 AEs occurring during DB-WD part 3 for ≥ 2% of subjects in either treatment group by Preferred Term; mSAF (study 301)

Preferred Term	Aprocitentan 25 mg N = 310 n (%)	Placebo N = 303 n (%)
Subjects with at least one event	**119 (38.4)**	**102 (33.7)**
COVID-19	9 (2.9)	8 (2.6)
Atrial fibrillation	8 (2.6)	1 (0.3)
Hypertension	4 (1.3)	6 (2.0)

Table shows Preferred Terms reported in ≥ 2% of subjects in either treatment group. AEs are sorted by descending frequency of Preferred Terms based on the aprocitentan 25 mg treatment group.
Percentages are based on the treatment group N; n = number of subjects with at least 1 row event; a subject can only be counted once per row but may be counted in more than one row.
Preferred Terms are based on MedDRA version 24.1.
AE = adverse event; COVID-19 = Coronavirus disease 2019; DB-WD = double-blind withdrawal; MedDRA = Medical Dictionary for Regulatory Activities; mSAF = modified safety analysis set.

During the 12-week DB-WD part 3 of Study 301, AEs were reported for 38.4% of the subjects in the aprocitentan 25 mg group and 33.7% of the subjects in the placebo group [Table 2-7].

AEs were reported at a low frequency and with no notable difference between aprocitentan 25 mg and placebo, except for atrial fibrillation which was reported in 8 subjects (2.6%) in the aprocitentan 25 mg group vs 1 subject (0.3%) in the placebo group. Of these 8 subjects reporting atrial fibrillation in the aprocitentan 25 mg group, 5 subjects experienced the adverse event of atrial fibrillation immediately after end of treatment during the 30-day safety follow-up phase (2 subjects within 2 days after the last dose of study treatment and 3 subjects between 22 and 30 days after last dose of study treatment). Even though all AEs of atrial fibrillation were assessed by the investigator as unrelated to study treatment, the fact that 5 cases of atrial fibrillation in the aprocitentan 25 mg group occurred during the 30-day safety FU phase immediately after stopping aprocitentan 25 mg therapy and 1 case of atrial fibrillation occurred when switching treatment with aprocitentan 25 mg to placebo merits some attention.

Burrell et al. demonstrated the occurrence of endothelin-1-induced arrhythmic contractions in human right atrial tissues obtained from patients undergoing cardiac surgery. Interestingly, arrhythmogenic effects in human atria were prevented by a dual endothelin (ETA/ETB) receptor antagonist (Burrell et al. Contractile and arrhythmic effects of endothelin receptor agonists in human heart in vitro: Blockade with SB 209670; Journal of Pharmacology and Experimental Therapeutics 2000, 292 (1) 449-459).

Thus, abrupt withdrawal after long-term therapy with aprocitentan 25 mg in RHTN patients might have triggered 5 adverse events of atrial fibrillation in Study 301.

Adverse Events (AEs) in Study 201

AEs during the 8-week double-blind treatment period of Study 201

Table 12-6 Double-blind treatment-emergent adverse events by system organ class and preferred term (≥ 2 subjects in any group), Safety Set

System Organ Class Preferred Term	Placebo N = 82 n (%)	ACT-132577 5 mg N = 82 n (%)	ACT-132577 10 mg N = 82 n (%)	ACT-132577 25 mg N = 82 n (%)	ACT-132577 50 mg N = 81 n (%)	Lisinopril 20 mg N = 81 n (%)
Subjects with at least one AE	30 (36.6)	18 (22.0)	24 (29.3)	33 (40.2)	22 (27.2)	26 (32.1)
Infections and infestations	3 (3.7)	6 (7.3)	9 (11.0)	7 (8.5)	6 (7.4)	8 (9.9)
Upper respiratory tract infection	1 (1.2)	0	4 (4.9)	1 (1.2)	2 (2.5)	1 (1.2)
Nasopharyngitis	1 (1.2)	1 (1.2)	2 (2.4)	2 (2.4)	0	4 (4.9)
Musculoskeletal and connective tissue disorders	3 (3.7)	3 (3.7)	1 (1.2)	7 (8.5)	6 (7.4)	2 (2.5)
Arthralgia	2 (2.4)	0	1 (1.2)	1 (1.2)	3 (3.7)	0
Pain in extremity	1 (1.2)	1 (1.2)	0	1 (1.2)	2 (2.5)	0
Gastrointestinal disorders	1 (1.2)	1 (1.2)	6 (7.3)	3 (3.7)	4 (4.9)	3 (3.7)
Constipation	0	0	3 (3.7)	0	1 (1.2)	0
General disorders & admin site conditions	1 (1.2)	0	1 (1.2)	2 (2.4)	4 (4.9)	0
Oedema peripheral	0	0	0	2 (2.4)	2 (2.5)	0
Vascular disorders	6 (7.3)	1 (1.2)	0	3 (3.7)	3 (3.7)	5 (6.2)
Hypertension	4 (4.9)	1 (1.2)	0	2 (2.4)	3 (3.7)	3 (3.7)
Orthostatic hypotension	1 (1.2)	0	0	1 (1.2)	0	2 (2.5)
Blood and lymphatic system disorders	1 (1.2)	1 (1.2)	0	3 (3.7)	2 (2.5)	1 (1.2)
Anaemia	0	0	0	2 (2.4)	1 (1.2)	0
Injury, poisoning and procedural complications	1 (1.2)	1 (1.2)	5 (6.1)	1 (1.2)	2 (2.5)	2 (2.5)
Nervous system disorders	4 (4.9)	3 (3.7)	2 (2.4)	4 (4.9)	2 (2.5)	5 (6.2)
Headache	1 (1.2)	1 (1.2)	2 (2.4)	2 (2.4)	2 (2.5)	4 (4.9)
Skin and subcutaneous tissue disorders	1 (1.2)	1 (1.2)	0	2 (2.4)	2 (2.5)	1 (1.2)
Cardiac disorders	0	2 (2.4)	1 (1.2)	1 (1.2)	1 (1.2)	2 (2.5)
Ear and labyrinth disorders	4 (4.9)	0	1 (1.2)	0	1 (1.2)	0
Eye disorders	0	0	1 (1.2)	2 (2.4)	1 (1.2)	1 (1.2)
Investigations	10 (12.2)	2 (2.4)	5 (6.1)	3 (3.7)	0	2 (2.5)
Haemoglobin decreased	0	0	2 (2.4)	1 (1.2)	0	1 (1.2)
Blood glucose increased	2 (2.4)	0	0	0	0	0
Blood pressure increased	3 (3.7)	0	0	0	0	0
Metabolism and nutrition disorders	0	0	2 (2.4)	1 (1.2)	0	0
Renal and urinary disorders	0	0	1 (1.2)	0	0	2 (2.5)
Reproductive system and breast disorders	0	0	1 (1.2)	0	0	2 (2.5)
Erectile dysfunction	0	0	0	0	0	2 (2.5)
Respiratory, thoracic & mediastinal disorders	3 (3.7)	2 (2.4)	1 (1.2)	5 (6.1)	0	2 (2.5)
Nasal congestion	0	0	0	2 (2.4)	0	0
Rhinorrhoea	0	0	0	2 (2.4)	0	0

Overall, during the 8-week DB treatment period of Study 201, no apparent dose response was observed for AEs in the aprocitentan groups, and the proportion of subjects with AEs in the aprocitentan groups (22.0–40.2%) was comparable with the placebo group (36.6%) [Table 12-6].

2.6.8.3. Serious adverse event/deaths/other significant events

SAEs during the 4-week DB part 1 of Study 301

Table 2-8 SAEs with onset during the 4-week DB part 1 by Preferred Term; SAF (study 301)

Preferred Term	Aprocitentan 12.5 mg N = 243 n (%)	Aprocitentan 25 mg N = 245 n (%)	Placebo N = 242 n (%)
Subjects with at least one event	**8 (3.3)**	**8 (3.3)**	**3 (1.2)**
Cellulitis	0	2 (0.8)	0
Pneumonia	1 (0.4)	1 (0.4)[a]	0
Abscess jaw	0	1 (0.4)	0
Blood pressure increased	0	1 (0.4)[b]	0
Cardiac failure [A,M]	0	1 (0.4)[b]	0
Cardiac failure chronic [A,M]	0	1 (0.4)[a]	0
Cerebrovascular accident [M]	0	1 (0.4)	0
Chest pain	0	1 (0.4)[b]	0
Meniere's disease	0	1 (0.4)	0
Oedema peripheral [A]	0	1 (0.4)[b]	0
Pancreatitis chronic	0	1 (0.4)	0
Pulmonary oedema [A]	0	1 (0.4)[b]	0
COVID-19 pneumonia [F]	2 (0.8)	0	1 (0.4)[e]
Ischaemic stroke [M]	1 (0.4)[c]	0	1 (0.4)[e]
Cerebral infarction [M]	1 (0.4)	0	0
Cholecystitis acute	1 (0.4)	0	0
Deep vein thrombosis	1 (0.4)[d]	0	0
Hip arthroplasty	1 (0.4)	0	0
Myocardial infarction [M]	1 (0.4)	0	0
Pulmonary embolism	1 (0.4)[d]	0	0
Peritonsillar abscess	0	0	1 (0.4)
Pyelonephritis acute	0	0	1 (0.4)[f]
Sepsis	0	0	1 (0.4)[f]

AEs are sorted by descending frequency of Preferred Terms based on the aprocitentan 25 mg treatment group.
Percentages are based on the treatment group N; n = number of subjects with at least 1 row event; a subject can only be counted once per row but may be counted in more than one row.

[A] AE Preferred Term considered an AESI.

[M] AE Preferred Term adjudicated as MACE-plus (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure).

[F] COVID-19 pneumonia had a fatal outcome for 1 subject during DB part 1 (Subject [redacted] aprocitentan 12.5 mg).

[a] Same subject had SAEs of Cardiac failure chronic and Pneumonia.

[b] Same subject had SAEs of Cardiac failure, Pulmonary oedema, Blood pressure increased, Chest pain, and Oedema peripheral.

[c] SAE was reported as related to study treatment by the investigator.

[d] Same subject had SAEs of Pulmonary embolism and Deep vein thrombosis.

[e] Same subject had SAEs of Ischaemic stroke and COVID-19 pneumonia.

[f] Same subject had SAEs of Pyelonephritis acute (2) and Sepsis (1).

Overall, 19 subjects had SAEs with onset during the 4-week double-blind part 1 of Study 301.

8 subjects (3.3%) in each aprocitentan group (12.5 mg and 25 mg) and 3 subjects (1.2%) in the placebo group [Table 2-8]. 5 subjects had SAEs leading to premature discontinuation of study treatment. Three in the aprocitentan 12.5 mg group (ischaemic stroke, assessed as related to study treatment by the investigator, COVID-19 pneumonia, fatal, and pulmonary embolism), one in the aprocitentan 25 mg group (cerebrovascular accident), and one in the placebo group (ischaemic stroke).

SAEs up to 48 weeks of treatment in Study 301

Table 2-9 SAEs reported in > 1 subject overall, by time interval from first dose of aprocitentan 25 mg and Preferred Term; Aprocitentan 25 mg set (study 301)

	Aprocitentan 25 mg				
	< 12 weeks	≥ 12- < 24 weeks	≥ 24- < 36 weeks	≥ 36 weeks	Overall
	N = 713	N = 674	N = 640	N = 566	N = 713
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least one event	**39 (5.5)**	**30 (4.5)**	**29 (4.5)**	**17 (3.0)**	**104 (14.6)**
COVID-19 pneumonia [F]	5 (0.7)	7 (1.0)	4 (0.6)	3 (0.5)	19 (2.7)
Angina unstable [M*]	2 (0.3)	1 (0.1)	2 (0.3)	1 (0.2)	6 (0.8)
Atrial fibrillation	1 (0.1)	1 (0.1)	1 (0.2)	3 (0.5)	5 (0.7)
Pneumonia	3 (0.4)	0	0	2 (0.4)	5 (0.7)
Cardiac failure congestive [A, M]	2 (0.3)	1 (0.1)	0	0	3 (0.4)
Cerebrovascular accident [M, F]	2 (0.3)	0	1 (0.2)	0	3 (0.4)
Myocardial infarction [M]	2 (0.3)	0	0	1 (0.2)	3 (0.4)
Acute myocardial infarction [M]	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Calculus urinary	1 (0.1)	0	1 (0.2)	0	2 (0.3)
Cardiac failure [A, M]	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Cardiac failure chronic [A, M]	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Cellulitis	2 (0.3)	0	0	0	2 (0.3)
Chest pain	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Coronary artery disease	1 (0.1)	0	1 (0.2)	0	2 (0.3)
Dyspnoea	0	1 (0.1)	0	1 (0.2)	2 (0.3)
Hyperkalaemia	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Pancreatitis chronic	1 (0.1)	0	0	1 (0.2)	2 (0.3)
Pulmonary oedema [A]	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Syncope	1 (0.1)	0	1 (0.2)	0	2 (0.3)
Transient ischaemic attack	0	1 (0.1)	0	1 (0.2)	2 (0.3)

The % in each column displays the % of subjects reporting an AE in a certain exposure period. Subjects who had less than the exposure (either by design or because they prematurely discontinued treatment) are excluded.
A subject can be counted in more than one row.
A subject can be counted in more than one time interval in a row (a subject may experience multiple occurrences of the same AE at different time intervals whilst exposed to aprocitentan 25 mg).
A subject will only be counted once in the overall column for a row where they experience an AE.
AEs are sorted by descending frequency of Preferred Term based on the overall column.
[A] AE Preferred Term considered an AESI.
[M] AE Preferred Term adjudicated as MACE-plus (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure) for at least 1 subject.
[F] COVID-19 pneumonia had a fatal outcome for 4 subjects: < 12 weeks in 2 subjects ([redacted] [redacted]) ≥ 12 – < 24 weeks in 1 subject ([redacted]) and ≥ 36 weeks in 1 subject ([redacted]) Cerebrovascular accident had a fatal outcome for 2 subjects: < 12 weeks in 1 subject ([redacted]) and ≥ 24 – < 36 weeks in 1 subject ([redacted])
Preferred Terms are based on MedDRA dictionary version 24.1.
* 1 of 6 subjects ([redacted]) with Angina unstable was adjudicated as non-fatal MI during DB-WD part 3.

The most frequently reported SAE PT overall was COVID-19 pneumonia (19 subjects; 2.7%), followed by angina unstable (6 subjects; 0.8%), atrial fibrillation and pneumonia (both 5 subjects; 0.7%) and cardiac failure congestive, cerebrovascular accident and myocardial infarction (all 3 subjects; 0.4%). Of the 104 subjects (14.6%) with SAEs up to 48 weeks of treatment with aprocitentan 25 mg, 18 subjects had SAEs leading to premature discontinuation of study treatment. For 1 of these 18 subjects, the event of cardiac failure chronic was assessed as related to study treatment by the investigator. There was an SAE of allergic dermatitis requiring hospitalization and medical treatment in a 73-year-old female (4819020) with no relevant medical history. The subject was on placebo during the DB part 1 and developed the SAE two days after starting aprocitentan 25 mg in SB part 2. There was a positive dechallenge and positive rechallenge

with the study medication which was permanently discontinued. The investigator assessed allergic dermatitis as related to aprocitentan.

SAEs during the 12-week DB-WD part 3 of Study 301 and the 30-day safety FU period

Table 2-11 SAEs during DB-WD part 3 by Preferred Term, mSAF (study 301)

Preferred Term	Aprocitentan 25 mg N = 310 n (%)	Placebo N = 303 n (%)
Subjects with at least one event	**18 (5.8)**	**9 (3.0)**
COVID-19 pneumonia [F]	4 (1.3)[a]	2 (0.7)*
Atrial fibrillation	3 (1.0)[b] *	0
Pneumonia	2 (0.6)[c] *	0
Acute left ventricular failure [A, M]	1 (0.3)	0
Angina unstable [M]	1 (0.3)[d]	0
Aortic stenosis	1 (0.3)[d]	0
COVID-19	1 (0.3)	0
Cardiogenic shock [A]	1 (0.3)[e] *	0
Cholecystitis infective	1 (0.3)	0
Dyspnoea [M]	1 (0.3)	0
Facial paresis	1 (0.3)[b] *	0
Hypertension	1 (0.3)[c] *	0
Multiple organ dysfunction syndrome [F]	1 (0.3)[a]	0
Myocardial infarction [M]	1 (0.3)[e] *	0
Pancreatitis chronic	1 (0.3)	0
Skin ulcer	1 (0.3) *	0
Transient ischaemic attack	1 (0.3) *	0
Angioedema	0	1 (0.3)
Cardiac failure acute [M]	0	1 (0.3)*
Coronary artery dissection	0	1 (0.3)
Endometrial hyperplasia	0	1 (0.3)*
Haemorrhage intracranial [M]	0	1 (0.3)
Ischaemic stroke [M]	0	1 (0.3)
Renal cancer	0	1 (0.3)

AEs are sorted by descending frequency of Preferred Terms based on the aprocitentan 25 mg treatment group.
Percentages are based on the treatment group N; n = number of subjects with at least 1 row event; a subject can only be counted once per row but may be counted in more than one row.
[A] AE Preferred Term considered an AESI.
[M] AE Preferred Term adjudicated as MACE-plus (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure).
[F] AE had a fatal outcome in at least 1 subject (see below).
[a] One subject had SAEs of COVID-19 pneumonia and Multiple organ dysfunction syndrome (both with fatal outcome).
[b] One subject had SAEs of Atrial fibrillation and Facial paresis.
[c] One subject had SAEs of Pneumonia and Hypertension.
[d] One subject had SAEs of Angina unstable and Aortic stenosis.
[e] One subject had SAEs of Cardiogenic shock and Myocardial infarction.
*1 subject experienced the event during the 30-day safety FU period.

During the 12-week DB-WD part 3 of Study 301 and the 30-day safety FU period, the overall incidence of SAEs was numerically higher in the aprocitentan 25 mg group (18 subjects; 5.8%) than in the placebo group (9 subjects, 3.0%), but most events were reported for single subjects [Table 2-11].

Slight numerical differences between the aprocitentan 25 mg group and placebo group were observed for: COVID-19 pneumonia (4 subjects vs 2 subjects), atrial fibrillation (3 subjects vs 0 subjects), and pneumonia (2 subjects vs 0 subjects) without clear evidence of a causal association with aprocitentan treatment. One subject with atrial fibrillation and one subject with pneumonia in the aprocitentan 25 mg group experienced the event during the 30-day safety FU period. Of the 27 subjects with SAEs during DB-WD part 3 of Study

301, 6 subjects had SAEs leading to premature discontinuation of study treatment, including 3 subjects on aprocitentan 25 mg and 3 subjects on placebo.

Treatment-emergent deaths during Study 301

Deaths

Across the aprocitentan clinical development program, a total of 13 death cases were reported (all in Study 301). Two of these 13 death cases were not considered treatment emergent: One subject (1144001) experienced an MI (confirmed MACE), exacerbated congestive heart failure and arteriosclerosis during screening (primary cause of death: atherosclerotic CV disease) and another subject (1066050), with COVID-19 pneumonia, died due to pharyngeal hemorrhage (primary cause of death) and concurrent respiratory failure, 42 days after the last dose of study treatment (SB part 2, aprocitentan 25 mg). The remaining 11 death cases were treatment-emergent and are presented in Table 12-11 below.

Table 12-11 Treatment-emergent deaths by primary cause of death (preferred term), by study part

Study part (analysis set) Primary cause of death (Preferred Term)			
DB part 1 (SAF)	**Aprocitentan 12.5 mg N = 243 n (%)**	**Aprocitentan 25 mg N = 245 n (%)**	**Placebo N = 242 n (%)**
Subjects who died	1 (0.4)	0	0
COVID-19 pneumonia	1 (0.4)	0	0
SB part 2 (rSAF)		**Aprocitentan 25 mg N = 704 n (%)**	
Subjects who died		9 (1.3)	
COVID-19 pneumonia		3 (0.4)	
Cerebrovascular accident (M)		2 (0.3)	
Death (M)		1 (0.1)	
Invasive breast carcinoma[a] (M)		1 (0.1)	
Procedural intestinal perforation		1 (0.1)	
Sudden cardiac death (M)		1 (0.1)	
DB-WD part 3 (mSAF)		**Aprocitentan 25 mg N = 310 n (%)**	**Placebo N = 303 n (%)**
Subjects who died		1 (0.3)	0
Multiple organ dysfunction syndrome[b]		1 (0.3)	0

Deaths are those occurring during the applicable treatment period up to 30 days after the last dose of study treatment in each subject's last treatment period.
'M': Adjudicated as MACE (cardiovascular death) [Section 12.3.6.4].
[a] Primary cause of death reported for Subject [redacted] was invasive breast carcinoma; the case was adjudicated as MACE, due to concurrent SAEs of brain oedema and subdural haemorrhage.
[b] Subject [redacted] had a concurrent SAE of COVID-19 pneumonia with fatal outcome.
DB = double-blind, DB-WD = double-blind withdrawal, MACE = major adverse cardiovascular event; mSAF = modified Safety analysis set, rSAF = restricted Safety analysis set, SAE = serious adverse event; SAF = Safety analysis set, SB = single-blind.

11 death cases were treatment-emergent during Study 301. None of these treatment-emergent deaths was considered related to study treatment by the investigator. It is understood that a rather sick population with RHTN and pre-existing comorbidities was included in Study 301. However, with a limited duration of 48 weeks and a limited number of 730 patients included in Study 301 and without placebo-controlled data across the whole study duration, the treatment-emergent 11 death cases observed during Study 301 are

difficult to interpret and a numerical imbalance and/or safety signal for deaths cases in subjects treated with aprocitentan can not be excluded with certainty.

Given the challenge posed by the long (32 weeks) uncontrolled treatment period, a comparison of the incidence rate observed in Study 301 with what has been reported in the literature was performed, showing that the observed incidence is in line with what is expected in this heavily comorbid population at high CV risk.

Treatment-emergent adverse events of special interest (AESI) in Study 301

Table 3-1 Overview of AESIs during the placebo-controlled study parts by category; (study 301)

Study part / Idorsia MedDRA Query name	*Safety analysis set*	Aprocitentan 12.5 mg n (%)	Aprocitentan 25 mg n (%)	Placebo n (%)
DB part 1	*Safety analysis set*			
N		243	245	242
Hepatic disorders		0	1 (0.4)	2 (0.8)
Anaemia		9 (3.7)	3 (1.2)	0
Oedema / fluid retention		22 (9.1)	45 (18.4)	5 (2.1)
Heart failure		1 (0.4)	2 (0.8)	0
DB-WD part 3	*Modified safety analysis set*			
N		-	310	303
Hepatic disorders		-	4 (1.3)	7 (2.3)
Anaemia		-	6 (1.9)	4 (1.3)
Oedema / fluid retention		-	8 (2.6)	4 (1.3)
Heart failure		-	3 (1.0)	1 (0.3)

A subject could only be counted once per row but could be counted in more than one row.
AESI = adverse event of special interest; DB = double-blind; DB-WD = double-blind withdrawal; MedDRA = Medical Dictionary for Regulatory Activities.

Adverse events of special interest (AESI) were oedema/ fluid retention, cases of heart failure, anaemia and hepatic disorders [Table 3-1]. For more details on anaemia (changes in hemoglobin, hematocrit and estimated plasma volume) and laboratory abnormalities in liver enzymes (e.g. ALT, AST, total bilirubin) please refer to section 3.3.7.4 Laboratory findings of this report.

Table 3-27 Overview of edema / fluid retention AEs during the 4-week DB part 1; SAF (study 301)

	Aprocitentan 12.5 mg N = 243 n (%)	Aprocitentan 25 mg N = 245 n (%)	Placebo N = 242 n (%)
Subjects with at least one event			
Edema / fluid retention	22 (9.1)	45 (18.4)	5 (2.1)
SAE	0	1 (0.4)	0
Leading to premature discontinuation of study treatment	0	1 (0.4)	0
Mild	11 (4.5)	27 (11)	4 (1.7)
Moderate	11 (4.5)	15 (6.1)	1 (0.4)
Severe	0	3 (1.2)	0
Recovered	17 (7.0)	34 (13.9)	1 (0.4)
Fatal outcome	0	0	0

If a subject had more than one event only the most severe event is counted.
If a subject had more than one edema, only the most severe outcome was counted (e.g., Fatal, Not Recovered or Recovered).
AE = adverse event; DB = double-blind; EOS =End of Study; SAF = safety analysis set.

During the 4-week double-blind part 1 of Study 301, AEs denoting edema/ fluid retention were reported in 22 subjects (9.1%) in the aprocitentan 12.5 mg group, 45 subjects (18.4%) in the aprocitentan 25 mg group, and 5 subjects (2.1%) in the placebo group [Table 3-27].

Most subjects with edema/ fluid retention AEs had events that were mild or moderate in intensity. Severe events were reported in only 3 subjects, all of them treated with aprocitentan 25 mg.

No edema/ fluid retention AE during DB part 1 had a fatal outcome.

Table 3-30 Overview of use of diuretics to manage edema / fluid retention events during the 4-week DB part 1; SAF (study 301)

	Aprocitentan 12.5 mg N = 243 n (%)	Aprocitentan 25 mg N = 245 n (%)	Placebo N = 242 n (%)
Subjects with at least one edema / fluid retention event	**22 (9.1) [a]**	**45 (18.4) [a]**	**5 (2.1) [a]**
Receiving additional diuretic treatment	10 (45.5)	20 (44.4)	2 (40.0)
Recovered with additional diuretic treatment [b]	8 (80.0)	15 (75.0)	0
Not recovered at EOS despite diuretic treatment [b]	2 (20.0)	5 (25.0)	2 (100)

[a] Percentage calculated based on total number of subjects per treatment group.
If not otherwise stated, the percentages are calculated based on the number of subjects with at least one event of edema / fluid retention per respective treatment group.
[b] Percentage calculated based on number of subjects who received additional diuretics.
DB = double-blind; EOS = End of Study; SAF = safety analysis set.

Overall, 32 subjects, including 10/22 subjects (45.5%) in the aprocitentan 12.5 mg group, 20/45 subjects (44.4%) in the aprocitentan 25 mg group, and 2/5 subjects (40%) in the placebo group received additional diuretics for treating edema/ fluid retention AEs with onset during DB part 1 [Table 3-30]. 28/32 subjects (87.5%) received loop diuretics, mainly furosemide. With the additional diuretic treatment, 8/10 subjects (80%) in the aprocitentan 12.5 mg group and 15/20 subjects (75.0%) in the aprocitentan 25 mg group recovered, but none (0%) of the 2 subjects in the placebo group did.

Table 3-2 Overview of AESIs up to 48 weeks of treatment by time interval from first dose of aprocitentan 25 mg and by category; Aprocitentan 25 mg set (study 301)

	Aprocitentan 25 mg				
Idorsia MedDRA Query name	<12 weeks N = 713 n (%)	≥ 12- < 24 weeks N = 674 n (%)	≥ 24- < 36 weeks N = 640 n (%)	≥ 36 weeks N = 566 n (%)	Overall N = 713 n (%)
Hepatic disorders	3 (0.4)	6 (0.9)	8 (1.3)	7 (1.2)	20 (2.8)
Anaemia	38 (5.3)	19 (2.8)	15 (2.3)	6 (1.1)	73 (10.2)
Oedema / fluid retention	130 (18.2)	33 (4.9)	17 (2.7)	8 (1.4)	170 (23.8)
Heart failure	9 (1.3)	4 (0.6)	1 (0.2)	4 (0.7)	16 (2.2)

A subject can be counted in more than one row.
A subject can be counted in more than one time interval in a row (a subject may experience multiple occurrences of the same AE at different time intervals whilst exposed to aprocitentan 25 mg).
A subject was only counted once in the overall column for a row where they experienced an AE.
Idorsia MedDRA query name is based on MedDRA dictionary version 24.1.
AE = adverse event; AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities.

For oedema/ fluid retention, anaemia and the few cases of heart failure, the majority of events occurred during the first 12 weeks of treatment with aprocitentan 25 mg, whereas for hepatic disorders, the frequency of new events was overall low and similar across all time intervals [Table 3-2].

Table 3-31 Overview of edema / fluid retention AEs up to 48 weeks of treatment; Aprocitentan 25 mg set (study 301)

	Aprocitentan 25 mg N = 713 n (%)
Subjects with at least one event	**170 (23.8)**
Serious	3 (0.4)
Leading to premature discontinuation of study treatment	6 (0.8) [a]
Mild	106 (14.9)
Moderate	57 (8.0)
Severe	7 (1.0)
Fatal outcome *	1 (0.1) [b]

If a subject has more than one event only the most severe event is counted. If a subject has events with different outcomes (i.e., Fatal, Not Recovered or Recovered) the most severe outcome will be counted.
If a subject had more than one edema only the most severe outcome was counted
[a] One additional subject prematurely discontinued study treatment due to meeting the study-specific study treatment discontinuation criterion for persistent fluid retention.
[b] Subject [redacted] primary cause of death infiltrative carcinoma of the left breast.
*Fatality is derived from outcome of an AE and does not necessary show the primary cause of death.
AE = adverse event; EOS = End of Study.

Overall, 170 of 713 subjects (23.8%) receiving aprocitentan 25 mg at any time during Study 301 had at least one AE of edema/ fluid retention [Table 3-31]. In most of the subjects experiencing edema/ fluid retention, the AEs were mild (106/170; 62.4%) or moderate (57/170; 33.5%) in intensity. Severe AEs of edema/ fluid retention were reported in 7 of 170 subjects (4.1%). 6 subjects discontinued study treatment prematurely due to edema/ fluid retention (not treated with diuretics before discontinuation).

Table 3-35 Overview of use of diuretics to manage edema / fluid retention events up to 48 weeks of treatment; Aprocitentan 25 mg set (study 301)

	Aprocitentan 25 mg N = 713 n (%)
Subjects with at least one edema / fluid retention event	170 (23.8) [a]
Receiving additional diuretic treatment	73 (42.9)
Recovered with additional diuretic treatment [b]	55 (75.3)
Not recovered at EOS despite diuretic treatment [b]	18 (24.7)

If a subject has events with different outcomes (i.e., Fatal, Not Recovered or Recovered) the most severe outcome will be counted.
If not otherwise stated, the percentages are calculated based on the number of subjects with at least one event of edema / fluid retention.
[a] Percentage calculated based on total number of subjects.
[b] Percentage calculated based on number of subjects who received additional diuretics.
EOS = End-of-Study.

73/170 subjects (42.9%) with AEs of edema/ fluid retention received additional diuretic treatment for the event [Table 3-35]. The most used diuretics (86%) were loop diuretics, mainly furosemide (55%).

Most of them (55/73 subjects; 75.3%) recovered. However, a considerable part of subjects 18/73 (24.7%) did not recover at end of study despite strong loop diuretic treatment. It is unclear, how to manage AEs of

edema/ fluid retention under aprocitentan treatment in subjects, who develop tolerance to chronic therapy with loop diuretics, which is a well-known problem for e.g. furosemide or when thiazide-like diuretics lose their efficacy in subjects with declining kidney function.

MACE during the 4-week DB part 1 of Study 301

Table 3-53 Adjudication-confirmed MACE during the 4-week DB part 1; SAF (study 301)

	Aprocitentan		Placebo
MACE category Preferred Term	12.5 mg N = 243 n (%)	25 mg N = 245 n (%)	N = 242 n (%)
Subjects with at least one event	**3 (1.2)**	**1 (0.4)**	**1 (0.4)**
Cardiovascular death	0	0	0
Non-fatal myocardial infarction	1 (0.4)[a]	0	0
Myocardial infarction	1 (0.4)[a]	0	0
Non-fatal stroke	2 (0.8)	1 (0.4)	1 (0.4)
Cerebrovascular accident	0	1 (0.4)	0
Ischaemic stroke	1 (0.4)[b]	0	1 (0.4)
Cerebral infarction	1 (0.4)	0	0

[a] 1 subject had an event of non-fatal myocardial infarction during DB part 1 and a second event during SB part 2 ([redacted]).
[b] Ischaemic stroke was reported as related to study treatment by the investigator (Subject [redacted]).
- A subject could only be counted once per row but could be counted in more than one row.
- Preferred Terms are based on MedDRA dictionary version 24.1.
- Preferred Terms are sorted within the MACE category by descending frequency based on the aprocitentan 25 mg treatment group.
DB = double-blind; MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; SAF = safety analysis set; SB = single-blind.

Overall, 5 subjects had MACE with onset during DB part 1 of Study 301. The AE of MI occurred in a subject on aprocitentan 12.5 mg with multiple risk factors for MACE, who had recurrent episodes of cardiac ischemia, including 2 MIs and 1 unstable angina during different parts of the study. All 4 AEs of non-fatal stroke (2 in the aprocitentan 12.5 mg group), 1 in the aprocitentan 25 mg group and 1 in the placebo group were ischemic in nature. Neither hypotension nor hypertension was recorded for any of the 4 subjects with stroke. 2 of the 4 subjects were aged ≥ 75 years, all were overweight or obese, and 3 of the 4 subjects had a medical history of diabetes. No CV deaths were reported during DB part 1 of Study 301.

MACE up to 48 weeks of treatment in Study 301

Table 3-54 Adjudication-confirmed MACE by time interval from first dose of aprocitentan 25 mg; Aprocitentan 25 mg set (study 301)

	Aprocitentan 25 mg				
MACE category Preferred Term	<12 weeks N = 713 n (%)	≥ 12- < 24 weeks N = 674 n (%)	≥ 24- < 36 weeks N = 640 n (%)	≥ 36 weeks N = 566 n (%)	Overall N = 713 n (%)
Subjects with at least one event	**5 (0.7)**	**1 (0.2)**	**4 (0.6)**	**2 (0.4)**	**12 (1.7)**
Cardiovascular death	2 (0.3)	0	3 (0.5)	0	5 (0.7)
Non-fatal myocardial infarction	2 (0.3)	1 (0.1)	0	2 (0.4)[b]	5 (0.7)
Non-fatal stroke	1 (0.1)	0	1 (0.2)[a]	0	2 (0.3)

A subject can be counted in more than one row.
A subject can be counted in more than one time interval in a row (a subject may experience multiple occurrences of the same AE at different time intervals whilst exposed to aprocitentan 25 mg).
A subject is only counted once in the overall column for a row where they experience an AE.
[a] Subject [redacted] had an Ischaemic stroke 24 days after last dose of aprocitentan 25 mg (re-randomized to placebo in DB-WD part 3).
[b] Subject [redacted] had a non-fatal myocardial infarction 22 days after end-of-treatment (DB-WD part 3).
AE= adverse event; DB-WD = double-blind withdrawal; MACE = major adverse cardiovascular event.

Overall, 12 of 713 subjects (1.7%) in the aprocitentan 25 mg set had MACE up to 48 weeks of treatment. The proportion of subjects with MACE for different time intervals during treatment with aprocitentan 25 mg was low and no notable trend was observed over time [Table 3-54]. All subjects had a pertinent cardiovascular medical history, i.e. chronic heart failure, stroke, angina pectoris, cerebral or aortic atherosclerosis, or vascular encephalopathy.

MACE during DB-WD part 3 of Study 301

Table 3-55 Adjudication-confirmed MACE during DB-WD part 3; mSAF (study 301)

MACE category Preferred Term	Aprocitentan 25 mg N = 310 n (%)	Placebo N = 303 n (%)
Subjects with at least one event	**2 (0.6)**	**2 (0.7)**
Cardiovascular death	0	0
Non-fatal myocardial infarction	2 (0.6)	0
Angina unstable	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
Non-fatal stroke	0	2 (0.7)
Haemorrhage intracranial	0	1 (0.3)
Ischaemic stroke	0	1 (0.3)

A subject could only be counted once per row but could be counted in more than one row.
Note: both events of non-fatal stroke occurred more than 20 days after the last dose of aprocitentan.
Preferred Terms are based on MedDRA dictionary version 24.1.
Preferred Terms are sorted within the MACE category by descending frequency based on the aprocitentan 25 mg treatment group.
DB-WD = double-blind withdrawal; MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; mSAF = modified safety analysis set.

4 subjects had adjudication-confirmed MACE with onset during DB-WD part 3 of Study 301. Two subjects in the aprocitentan 25 mg group had non-fatal MI and 2 subjects in the placebo group had non-fatal stroke. No cardiovascular deaths were reported with onset during DB-WD part 3 [Table 3-55]. All events were reported as unrelated to study treatment.

As for the MACE cases observed in the other parts of the study, the subjects who experienced MACE during DB-WD part 3 of Study 301 had a significant CV medical background, i.e. left ventricular hypertrophy, carotid

arteriosclerosis, chronic cerebral ischemia, aortic valve stenosis, MI, coronary artery disease, and/or a medical history of diabetes.

MACE in Study 201

No MACE were reported in any randomized subjects during Study 201.

MACE in clinical pharmacology studies

No MACE were reported in clinical pharmacology Phase 1 studies.

Heart failure adverse events of special interest (AESI) in Study 301

Table 3-47 Treatment-emergent AEs denoting heart failure in study 301, by study part

Study part (analysis set) Preferred Term			
DB part 1 (SAF)	**Aprocitentan 12.5 mg N = 243 n (%)**	**Aprocitentan 25 mg N = 245 n (%)**	**Placebo N = 242 n (%)**
Subjects with at least one event	1 (0.4)	2 (0.8)	0
AEs (non-serious)	1 (0.4)	0	0
Cardiac failure chronic	1 (0.4)	0	0
SAEs (hospitalization for heart failure)	0	2 (0.8)	0
Cardiac failure[a]	0	1 (0.4)	0
Cardiac failure chronic[a]	0	1 (0.4)	0
SB part 2 (rSAF)		**Aprocitentan 25 mg N = 704 n (%)**	
Subjects with at least one event		12 (1.7)	
AEs (non-serious)		6 (0.9)	
Cardiac failure congestive		3 (0.4)	
Cardiac failure		3 (0.4)	
Pulmonary oedema*		1 (0.1)	
Chronic left ventricular failure		1 (0.1)	
SAEs (hospitalization for heart failure)		6 (0.9)	
Cardiac failure congestive[a]		3 (0.4)	
Cardiac failure		1 (0.1)	
Cardiac failure chronic		1 (0.1)	
Left ventricular dysfunction[c]		1 (0.1)	
DB-WD part 3 (mSAF)		**Aprocitentan 25 mg N = 310 n (%)**	**Placebo N = 303 n (%)**
Subjects with at least one event		3 (1.0)	1 (0.3)
AEs (non-serious)		1 (0.3)	0
Cardiac failure		1 (0.3)	0
SAEs (hospitalization for heart failure)[b]		2 (0.6)	1 (0.3)
Acute left ventricular failure		1 (0.3)	0
Dyspnoea[c]		1 (0.3)	0
Cardiac failure acute[a]		0	1 (0.3)

Heart failure AEs are presented by study part and Preferred Terms. Non-serious AEs were categorized as 'Heart failure' AESI, and SAEs were categorized as MACE-plus.
Percentages are based on the treatment group N; n = number of subjects with at least 1 row event; a subject can only be counted once per row but may be counted in more than one row.
* Pulmonary oedema (Subject [redacted]) is counted in both AESI categories 'edema / fluid retention' and 'heart failure'.
[a] Subjects had additional AEs: Subject [redacted] (serious pulmonary edema), Subject [redacted] (non-serious cardiac failure chronic), Subject [redacted] (non-serious cardiac failure congestive and serious pulmonary edema), Subject [redacted] (non-serious acute left ventricular failure), Subject [redacted] (non-serious cardiac failure chronic).
[b] Subject [redacted] had concurrent SAEs of cardiogenic shock and myocardial infarction. The case was reviewed by the CAC and adjudicated as non-fatal myocardial infarction (MACE). Therefore, the case was categorized as MACE and not as hospitalization for heart failure. Consequently, the event was not included in this table.
[c] The events of left ventricular dysfunction ([redacted]) and dyspnoea ([redacted]) were not categorized as 'Heart failure' AESI, however were adjudicated as hospitalization for heart failure by the CAC.
Preferred Terms are based on MedDRA version 24.1.

In the population of 730 subjects with difficult-to-control HTN in Study 301, treated for up to 48 weeks, there were 19 subjects (2.6%) with treatment-emergent events of heart failure:

Eight (8) subjects with non-serious AEs (as per AESI definition) and 11 subjects with at least one SAE of heart failure requiring hospitalization as per CAC adjudication [Table 3-47].

Non-serious heart failure adverse events of special interest (AESI) in Study 301

Table 3-48 Characteristics of subjects with non-serious AEs of heart failure in study 301

	DB part 1	SB part 2	DB-WD part 3	Total
Subjects with at least 1 event	**1**	**6**	**1**	**8**
Aprocitentan 12.5 mg	**1**	**NA**	**NA**	**1**
Aprocitentan 25 mg	**0**	**6**	**1**	**7**
Placebo	**0**	**NA**	**0**	**0**
Baseline characteristics				
Age > 65 years	1	4	1	6 (75%)
BMI > 35 kg/m^2	0	4	1	5 (63%)
MH of diabetes	0	5	0	5 (63%)
MH of cardiac failure	0	2	1	3 (38%)
MH of Oedema / fluid retention	0	2	0	2 (25%)
Baseline eGFR 15-< 60 mL/min/1.73 m^2	1	1	1	3 (38%)
Beta-blocker*	0	4	1	5 (63%)
Loop diuretic or more than 1 diuretic before switch to SBAT	0	4	0	4 (50%)
Post randomization				
Oedema / fluid retention	0	5	0	5 (63%)
Prior to event	0	2	0	2 (25%)
Need for diuretic	1	3	1	5 (63%)
Study treatment discontinuation	0	0	0	0

*Subjects on beta-blocker at screening (as per protocol these medications were not switched to SBAT and were continued during the study).
AE = adverse event; BMI = body mass index; DB = double-blind, DB-WD = double-blind withdrawal, eGFR = estimated glomerular filtration rate, MH = medical history, NA = not applicable; SB = single blind, SBAT = standardized background antihypertensive therapy.

Most of the subjects with non-serious AEs of heart failure in Study 301 had multiple risk factors, including pre-existing edema (25%), heart failure (38%), baseline eGFR 15 – < 60 mL/min/1.73 m2 (38%), diabetes (63%), BMI > 35 kg/m2 (63%), and age > 65 years (75%) [Table 3-48].

At screening, 50% of the subjects were receiving loop diuretics or more than 1 diuretic before switching to SBAT and 63% of the subjects were receiving beta-blockers.

Hospitalization for heart failure (SAEs) in Study 301

Table 3-50 Characteristics of subjects with hospitalization for heart failure in study 301

	DB part 1	SB part 2	DB-WD part 3	Total
Subjects with at least 1 event	**2**	**6**	**3**	**11**
Aprocitentan 12.5 mg	**0**	**NA**	**NA**	**0**
Aprocitentan 25 mg	**2**	**6**	**2**	**10**
Placebo	**0**	**NA**	**1[a]**	**1**
Baseline characteristics				
Age > 65 years	2	4	1	7 (64%)
BMI > 35 kg/m^2	2	4	0	6 (55%)
MH of diabetes	2	6	3	11 (100%)
MH of cardiac failure	1	3	1	5 (45%)
MH of Oedema / fluid retention	1	3	0	4 (36%)
Baseline eGFR 15- < 60 mL/min/1.73 m^2	1	4	1	6 (55%)
Beta-blocker [b]	2	6	2	10 (91%)
Loop diuretic or more than 1 diuretic before switch to SBAT	1	4	1	6 (55%)
Post randomization				
Oedema / fluid retention	2	6[c]	3[c]	11 (100%)
prior to event	1	4	2	7 (64%)
Need for diuretic	1	5	3	9 (82%)
Study treatment discontinuation	0	2	0	2 (18%)

[a] Last study drug intake (placebo) was 24 days before the event.
[b] Subjects on beta-blocker at screening (as per protocol these medications were not switched to SBAT and were continued during the study).
[c] Oedema / fluid retention was reported to Global Drug Safety only, not captured in the clinical database (Subject [redacted] Pulmonary oedema; Subject [redacted] Oedema peripheral).
AE = adverse event; BMI = body mass index; DB = double-blind; DB-WD = double-blind withdrawal; eGFR = estimated glomerular filtration rate; FU = follow-up; MH = medical history; NA = not applicable; SB = single blind; SBAT = standardized background antihypertensive therapy.

Following CAC adjudication, a total of 11 subjects had confirmed treatment-emergent hospitalization for heart failure (10 subjects on aprocitentan 25 mg, 1 subject on placebo).

Most of the 11 subjects had multiple risk factors, including pre-existing edema (36%), heart failure (45%), baseline eGFR 15 – < 60 mL/min/1.73 m2 (55%), BMI > 35 kg/m2 (55%), age > 65 years (64%) and diabetes (100%) [Table 3-50].

At screening, 55% of the subjects were receiving loop diuretics or more than 1 diuretic before switching to SBAT and 91% of the subjects were receiving beta-blockers.

Deaths and SAEs during the 8-week double-blind treatment period of Study 201

Deaths

No subject died during Study 201.

SAEs during the 8-week double-blind treatment period of Study 201

A total of 2 subjects on aprocitentan, both in the 25 mg group, vs no subject on placebo experienced SAEs in Study 201 [Table 12-7]: One subject (1.2%) with Bundle branch block left and one subject (1.2%) with Neoplasm malignant. Both SAEs led to premature discontinuation of DB study treatment. The Bundle branch block left SAE was asymptomatic, mild in intensity, did not require hospitalization, and was considered not clinically significant by the cardiologist. The subject with the SAE of malignant neoplasm prematurely discontinued DB study treatment due to an increase in size of a pre-existing neck neoplasm (diagnosed based on a biopsy before entering the study).

Table 12-7 Double-blind treatment-emergent serious adverse events by preferred term

ACT-132577
Protocol: AC-080A201
Double-blind treatment-emergent serious adverse events (SAEs) by preferred term
Analysis Set: Safety Set

Preferred Term	Placebo N = 82 n (%)	ACT-132577 5 mg N = 82 n (%)	ACT-132577 10 mg N = 82 n (%)	ACT-132577 25 mg N = 82 n (%)	ACT-132577 50 mg N = 81 n (%)	Lisinopril 20 mg N = 81 n (%)
Subjects with at least one SAE	0	0	0	2 (2.4)	0	1 (1.2)
Bundle branch block left	0	0	0	1 (1.2)	0	0
Fall	0	0	0	0	0	1 (1.2)
Jaw fracture	0	0	0	0	0	1 (1.2)
Neoplasm malignant	0	0	0	1 (1.2)	0	0

In Study 201, SAEs were reported in only 2 subjects (both in the aprocitentan 25 mg group). None of the reported treatment-emergent SAEs during Study 201 (1 asymptomatic left bundle branch block and 1 malignant neoplasm) was considered by the investigator to be related to the DB study treatment.

Treatment-emergent adverse events of special interest (AESI) in Study 201

Table 3-3 AESIs occurring during the 8-week DB treatment period by category and Preferred Term; SAF (study 201)

Idorsia MedDRA Query name	Aprocitentan 5 mg N = 82	Aprocitentan 10 mg N = 82	Aprocitentan 25 mg N = 82	Aprocitentan 50 mg N = 81	Placebo N = 82	Lisinopril 20 mg N = 81
Hepatic disorders	2 (2.4)	0	1 (1.2)	1 (1.2)[a]	2 (2.4)	0
Anaemia	0	2 (2.4)	3 (3.7)	1 (1.2)[a]	0	1 (1.2)
Oedema / fluid retention	0	0	2 (2.4)	2 (2.5)	0	0
Heart failure	0	0	0	0	0	0

Subjects could have events in more than one row.
AESI = adverse event of special interest; DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SAF= safety set.

Overall, the frequency of AESIs in Study 201 was low. Most frequently reported adverse events of special interest (AESI) in the aprocitentan groups were anaemia and oedema/ fluid retention [Table 3-3].

2.6.8.4. Laboratory findings

Hematology

Table 3-12 Mean and median changes from baseline to Week 4 in hemoglobin, hematocrit, and ePV during DB part 1; SAF (study 301)

Parameter Statistics	Aprocitentan 12.5 mg N = 243	Aprocitentan 25 mg N = 245	Placebo N = 243
Hemoglobin (g/L)			
n	208	217	213
Mean (SD) value at BL	139.1 (15.4)	138.5 (14.0)	141.0 (15.1)
Mean (SD) change from BL	–8.0 (7.6)	–8.5 (7.2)	–0.4 (7.7)
Median (Min, Max) change from BL	–8 (–33, 13)	–9 (–32, 20)	–1 (–23, 48)
Hematocrit (L/L)			
n	203	212	210
Mean (SD) value at BL	0.410 (0.042)	0.408 (0.038)	0.413 (0.042)
Mean (SD) change from BL	–0.021 (0.025)	–0.023 (0.024)	+0.001 (0.026)
Median (Min, Max) change from BL	–0.02 (–0.09, 0.04)	–0.02 (–0.09, 0.08)	0 (–0.10, 0.15)
ePV (% change)			
n	203	212	210
Mean % (SD) change from BL	+10.45 (10.79)	+11.22 (9.97)	+0.51 (9.23)
Median (min., max.) change from BL	+9.9 (–15.0, 50.4)	+10.8 (–26.6, 41.5)	+0.6 (–45.1, 40.1)

ePV was indirectly estimated using the Strauss formula [Strauss 1951] based on changes in both hemoglobin and hematocrit.
BL = baseline; DB = double-blind; ePV = estimated plasma volume; max. = maximum; min. = minimum; SAF = Safety analysis set; SD = standard deviation.

Mean hemoglobin and hematocrit decreased from baseline to Week 4 in both aprocitentan groups (mean decrease in hemoglobin of 8.0–8.5 g/L), but not in the placebo group [Table 3-12].

Mean increases in estimated plasma volume (ePV) of approximately 10–11% were observed for both aprocitentan groups, but not in the placebo group [Table 3-12].

Consistent with experience with other endothelin receptor antagonists, decreases in hemoglobin and haematocrit observed for subjects on aprocitentan 12.5 mg and 25 mg may be attributed in most cases to hemodilution due to plasma volume expansion or fluid redistribution.

Table 3-13 Marked decreases in hemoglobin and hematocrit during the 4-week DB part 1; SAF (study 301)

Parameter Marked laboratory abnormality	Aprocitentan 12.5 mg N = 243 n / Nn (%)	Aprocitentan 25 mg N = 245 n / Nn (%)	Placebo N = 242 n / Nn (%)
Hemoglobin (g/L)			
< 80	0 / 222	0 / 230	0 / 226
< 100	7 / 221 (3.2)	3 / 229 (1.3)	0 / 226
Hematocrit (%)			
< 20%	0 / 217	0 / 224	0 / 224
< 28% in women, < 32% in men	5 / 214 (2.3)	8 / 224 (3.6)	0 / 223

Thresholds for marked abnormalities as defined in the CSR SAP [D-22.269 appendix 16.1.9 section 14.2].
DB = double-blind; CSR = clinical study report; SAF = safety analysis set; SAP = statistical analysis plan.

Marked decreases in hemoglobin and hematocrit only occurred in the aprocitentan groups. No subjects had hemoglobin values < 80 g/L or hematocrit < 20% during the 4-week DB part 1 [Table 3-13].

Table 3-15 Overview of anemia AEs during the 4-week DB part 1; SAF (study 301)

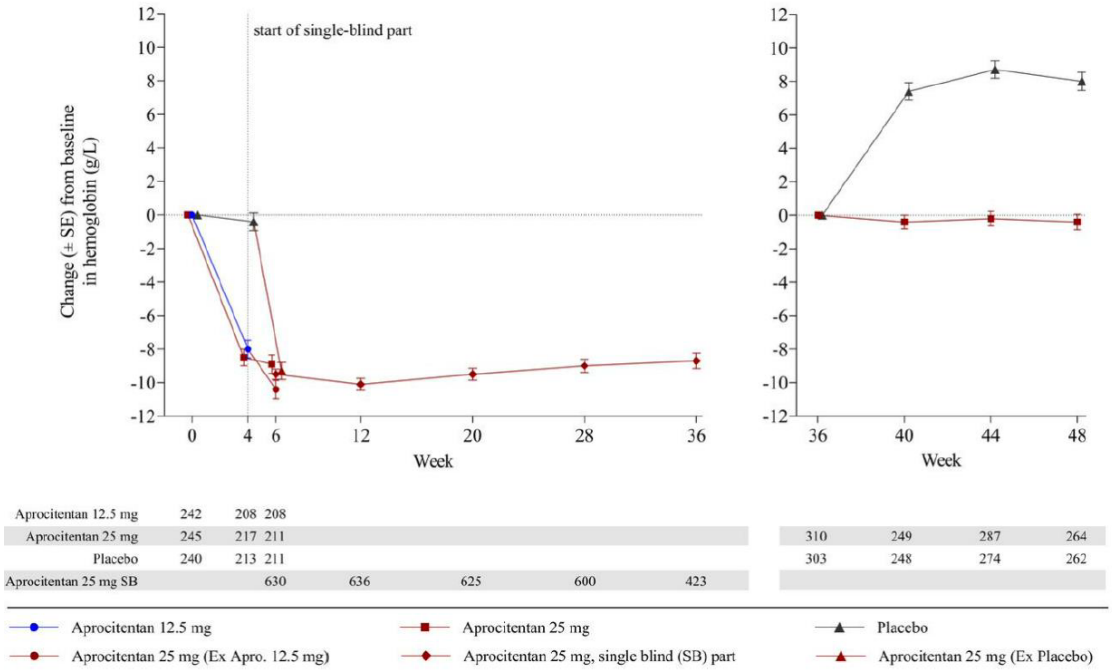
	Aprocitentan		Placebo
	12.5 mg N = 243 n (%)	25 mg N = 245 n (%)	N = 242 n (%)
Subjects with at least one event			
Anemia	9 (3.7)	3 (1.2)	0
Serious	0	0	0
Leading to premature discontinuation of study treatment	0	0	0
Mild	8 (3.3)	3 (1.2)	0
Moderate	0	0	0
Severe	1 (0.4)	0	0
Fatal outcome	0	0	0

If a subject has more than one event only the most severe event is counted.
AE = adverse event; DB = double-blind; SAE = serious adverse event, SAF =Safety analysis set.

All cases of anemia were mild in intensity, except for 1 case of severe anemia in the aprocitentan 12.5 mg group. Subject 1133004 had an unrelated event of severe anemia due to gastrointestinal blood loss (Hb = 4.3 g/dl) and required a blood transfusion. There were no AEs leading to premature discontinuation of study treatment [Table 3-15].

Mean hemoglobin over 48 weeks in Study 301 (across all study parts)

Figure 3-1 Hemoglobin: Mean (±SE) change from baseline to visits in DB part 1, SB part 2, and DB-WD part 3: SAF, mSAF (study 301)



DB = double blind; DB-WD = double-blind withdrawal; mSAF = modified safety analysis set; SAF = safety analysis set; SB = single blind; SE = standard error.

Mean changes from baseline in hemoglobin across all parts of Study 301 are shown in Figure 3-1.

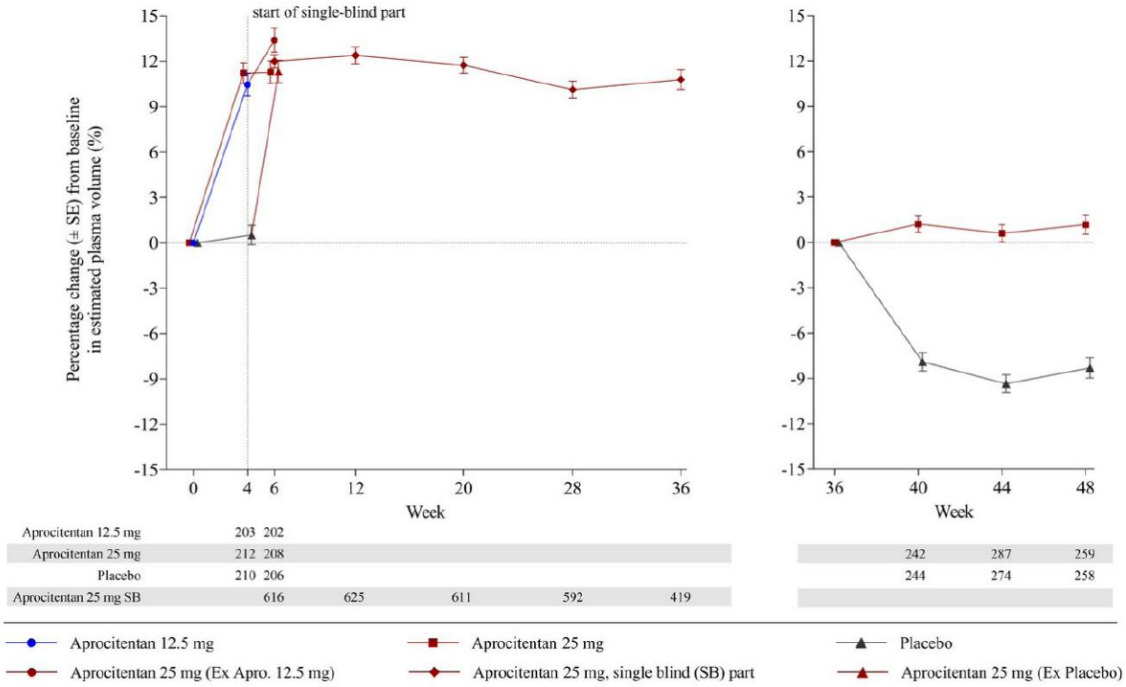
By the end of the 4-week DB part 1 of Study 301, mean decreases in hemoglobin of 8.0–8.5 g/L were observed for subjects on aprocitentan 12.5 mg and 25 mg, but not for subjects on placebo.

By Week 6 (i.e. 2 weeks after switching all subjects to aprocitentan 25 mg) mean hemoglobin values had decreased for subjects who were initially on placebo to the same level as for the subjects who received aprocitentan right from the beginning [Figure 3-1].

During the 12-week DB-WD part 3, mean hemoglobin values for subjects who continued to receive aprocitentan 25 mg remained unchanged until Week 48, whereas for subjects re-randomized to placebo the mean hemoglobin values returned back by Week 48 to similar values as those observed at baseline.

Mean estimated plasma volume (ePV) over 48 weeks in Study 301 (across all study parts)

Figure 3-2 ePV: Mean (±SE) change from baseline to visits in DB part 1, SB part 2, and DB-WD part 3: SAF, mSAF (study 301)



ePV was indirectly estimated using the Strauss formula [Strauss 1951] based on changes in both hemoglobin and hematocrit.
DB = double blind; DB-WD = double-blind withdrawal; ePV = estimated plasma volume; mSAF = modified safety analysis set; SAF = safety analysis set; SB = single blind; SE = standard error.

Mean percentage changes from baseline in estimated plasma volume (ePV) across all parts of Study 301 are shown in Figure 3-2. By the end of the 4-week double-blind part 1 of Study 301, mean increases of 10% to < 12% in estimated plasma volume (ePV) were observed in both aprocitentan groups, but not in the placebo group.

By Week 6 (i.e. 2 weeks after switching all subjects to aprocitentan 25 mg) the mean estimated plasma volume (ePV) had increased for subjects who were initially on placebo to the same level as for subjects who received aprocitentan right from the beginning [Figure 3-2].

During the 12-week DB-WD part 3, mean estimated plasma volume (ePV) for subjects who continued to receive aprocitentan 25 mg remained unchanged until Week 48, whereas for subjects re-randomized to placebo mean estimated plasma volume (ePV) decreased by Week 48 to similar values as those observed at baseline.

Other hematology variables (leukocytes, lymphocytes, neutrophils, and platelets)

Table 4-2 Hematology: marked laboratory abnormalities (study 301, DB part 1): SAF

Variable Marked laboratory abnormality	Aprocitentan 12.5 mg N = 243 n / Nn (%)	Aprocitentan 25 mg N = 245 n / Nn (%)	Placebo N = 242 n / Nn (%)
Hemoglobin (g/L)			
< 80	0 / 222	0 / 230	0 / 226
< 100	7 / 221 (3.2)	3 / 229 (1.3)	0 / 226
Hematocrit (%)			
< 20%	0 / 217	0 / 224	0 / 224
< 28% in women, < 32% in men	5 / 214 (2.3)	8 / 224 (3.6)	0 / 223
> 55% in women, > 60% in men	0 / 217	0 / 224	1 / 224 (0.4)
> 65%	0 / 217	0 / 224	0 / 224
Leukocytes (10^9/L)			
< 2.0	0 / 222	0 / 230	0 / 226
< 3.0	0 / 221	0 / 229	2 / 224 (0.9)
Lymphocytes (10^9/L)			
< 0.5	0 / 221	1 / 229 (0.4)	1 / 225 (0.4)
< 0.8	3 / 221 (1.4)	1 / 228 (0.4)	6 / 224 (2.7)
Neutrophils (10^9/L)			
< 1.0	0 / 221	1 / 230 (0.4)	0 / 226
< 1.5	0 / 219	1 / 226 (0.4)	1 / 225 (0.4)

n = number of subjects with at least 1 marked abnormality; Nn = number of subjects at risk: those not meeting the criterion at baseline (or having a missing baseline value) and having at least 1 post-baseline value for a given variable. A subject is only counted once, but may be reported in more than 1 marked laboratory abnormality criterion of a given variable.

Variables with no marked laboratory abnormalities are not displayed: platelets, eosinophils, hemoglobin high, leukocytes high, and lymphocytes high.

Thresholds for marked abnormalities as defined in the CSR SAP [D-22.269 appendix 16.1.9.1.1, section 14.2].

CSR = clinical study report; DB = double-blind; SAF = safety analysis set; SAP = statistical analysis plan.

Table 4-3 Hematology: marked laboratory abnormalities by time interval since the first dose of aprocitentan 25 mg; Aprocitentan 25 mg set (study 301)

	Aprocitentan 25 mg				
	< 12 weeks N=713 n / Nn (%)	≥ 12- < 24 weeks N=674 n / Nn (%)	≥ 24- < 36 weeks N=640 n / Nn (%)	≥ 36 weeks N=566 n / Nn (%)	Overall N=713 n / Nn (%)
Hemoglobin (g/L)					
< 80	0 / 700	1 / 644 (0.2)	0 / 620	0 / 473	1 / 709 (0.1)
< 100	22 / 698 (3.2)	22 / 643 (3.4)	13 / 619 (2.1)	11 / 473 (2.3)	45 / 707 (6.4)
Hematocrit (%)					
< 20%	0 / 698	0 / 636	0 / 617	0 / 471	0 / 709
< 28% in women, < 32% in men	23 / 694 (3.3)	15 / 633 (2.4)	14 / 616 (2.3)	10 / 470 (2.1)	38 / 705 (5.4)
Leukocytes (10^9/L)					
< 2.0	0 / 700	0 / 644	0 / 620	0 / 471	0 / 709
< 3.0	7 / 696 (1.0)	3 / 641 (0.5)	3 / 617 (0.5)	3 / 469 (0.6)	13 / 705 (1.8)
Platelets (10^9/L)					
< 50	0 / 694	0 / 639	0 / 615	0 / 468	0 / 707
< 75	0 / 694	0 / 639	0 / 615	1 / 468 (0.2)*	1 / 707 (0.1)
> 600	1 / 694 (0.1)	0 / 639	0 / 615	0 / 469	1 / 707 (0.1)
> 999	0 / 695	0 / 640	0 / 616	0 / 469	0 / 708
Lymphocytes (10^9/L)					
< 0.5	1 / 698 (0.1)	1 / 642 (0.2)	0 / 618	1 / 469 (0.2)	3 / 707 (0.4)
< 0.8	18 / 696 (2.6)	10 / 641 (1.6)	8 / 617 (1.3)	13 / 469 (2.8)	30 / 705 (4.3)
> 4.0	3 / 697 (0.4)	2 / 641 (0.3)	3 / 617 (0.5)	5 / 469 (1.1)	9 / 706 (1.3)
> 20	0 / 700	0 / 644	0 / 620	0 / 471	0 / 709
Neutrophils (10^9/L)					
< 1.0	3 / 699 (0.4)	2 / 644 (0.3)	3 / 619 (0.5)	3 / 470 (0.6)	8 / 708 (1.1)
< 1.5	12 / 692 (1.7)	3 / 637 (0.5)	8 / 612 (1.3)	6 / 464 (1.3)	23 / 701 (3.3)

n is the number of subjects with at least one treatment-emergent marked abnormality worse than baseline.
Nn is the number of subjects at risk: those not meeting the criterion at baseline (or having a missing baseline value) and having at least one post-baseline value prior to EOT+30 days for a given variable.
A subject was counted only once, but may be reported in more than one marked laboratory abnormality criterion of a given variable.
A subject can be included in more than one time interval according to treatment duration.
Variables with no marked laboratory abnormalities are not displayed: eosinophils, hemoglobin high, hematocrit high, and leukocytes high.
Thresholds for marked abnormalities as defined in the CSR SAP [D-22.269 appendix 16.1.9.1.1 section 14.2].
* Subject [redacted] (aprocitentan 25 mg during all 3 study parts) with COVID-19 pneumonia (Days 247–252) had platelets 74 × 10^9/L on Day 281; values were within normal range at all other measurements (reference range 130–394 × 10^9/L).
COVID-19 = Coronavirus disease 2019; CSR = clinical study report; SAP = statistical analysis plan.

Table 4-4 Hematology: marked laboratory abnormalities (study 301, DB-WD part 3): mSAF

Variable Marked laboratory abnormality	Aprocitentan 25 mg N = 310 n / Nn (%)	Placebo N = 303 n / Nn (%)
Hemoglobin (g/L)		
< 80	0 / 307	0 / 297
< 100	4 / 303 (1.3)	4 / 292 (1.4)
ULN + > 20 or > baseline if baseline > ULN	0 / 307	1 / 297 (0.3)
ULN + > 40 or > baseline if baseline > ULN	0 / 307	0 / 297
Hematocrit (%)		
< 20%	0 / 307	0 / 297
< 28% in women, < 32% in men	5 / 299 (1.7)	2 / 292 (0.7)
> 55% in women, > 60% in men	0 / 307	1 / 297 (0.3)
> 65%	0 / 307	0 / 297
Leukocytes (10^9/L)		
< 2.0	0 / 307	0 / 297
< 3.0	4 / 306 (1.3)	0 / 297
Platelets (10^9/L)		
< 50	0 / 307	0 / 295
< 75	1 / 307 (0.3)	0 / 295
> 600	0 / 307	1 / 295 (0.3)
> 999	0 / 307	0 / 295
Lymphocytes (10^9/L)		
< 0.5	1 / 307 (0.3)	1 / 297 (0.3)
< 0.8	7 / 303 (2.3)	3 / 294 (1.0)
> 4.0	7 / 307 (2.3)	1 / 297 (0.3)
> 20	0 / 307	0 / 297
Neutrophils (10^9/L)		
< 1.0	1 / 307 (0.3)	2 / 296 (0.7)
< 1.5	3 / 305 (1.0)	7 / 293 (2.4)

n = number of subjects with at least 1 marked abnormality; Nn = number of subjects at risk: those not meeting the criterion at DB-WD baseline (or having a missing DB-WD baseline value) and having at least 1 post-baseline value for a given variable.
A subject is only counted once, but may be reported in more than 1 marked laboratory abnormality criterion of a given variable.
Variables with no marked laboratory abnormalities are not displayed: eosinophils and leukocytes high.
Thresholds for marked abnormalities as defined in the CSR SAP [D-22.269 appendix 16.1.9.1.1, section 14.2].
CSR = clinical study report; DB-WD = double-blind withdrawal; mSAF = restricted safety analysis set; SAP = statistical analysis plan ;ULN = upper limit of normal.

Besides changes in hemoglobin and haematocrit (decrease) and estimated plasma volume (ePV) (increase), no clinically relevant differences between aprocitentan groups and placebo were noted for other hematology variables (leukocytes, lymphocytes, neutrophils, and platelets) across all parts of Study 301.

Study 201: Mean changes in hemoglobin, hematocrit, and estimated plasma volume (ePV) from baseline to Week 8 (end of DB treatment period)

Table 3-25 Mean change baseline to Week 8 (end of DB treatment period) in hemoglobin, hematocrit, and ePV

Parameter Statistics	Aprocitentan 5 mg N = 82	Aprocitentan 10 mg N = 82	Aprocitentan 25 mg N = 82	Aprocitentan 50 mg N = 81	Placebo N = 82	Lisinopril 20 mg N = 81
Hemoglobin (g/L)						
n	72	73	67	67	69	68
Mean (SD) change from BL	–1.3 (6.8)	–2.7 (8.7)	–3.8 (10.0)	–6.7 (7.2)	2.2 (8.0)	0.1 (7.5)
Median (Min. Max) change from BL	–1 (–17, 16)	–3 (–36, 31)	–3 (–29, 22)	–7 (–22, 13)	2 (–21, 28)	–1 (–20, 19)
Hematocrit (L/L)						
n	72	73	66	67	69	67
Mean (SD) change from BL	–0.009 (0.023)	–0.014 (0.030)	–0.018 (0.032)	–0.022 (0.027)	–0.004 (0.030)	–0.007 (0.027)
Median (Min. Max) change from BL	–0.01 (–0.07, 0.04)	–0.01 (–0.10, 0.06)	–0.02 (–0.10, 0.06)	–0.02 (–0.10, 0.06)	–0.01 (–0.09, 0.07)	–0.01 (–0.06, 0.07)
ePV (% change)						
n	72	73	66	67	69	67
Mean % (SD) change from BL	3.002 (8.913)	5.059 (11.825)	6.911 (13.031)	9.528 (10.393)	-0.285 (10.545)	1.610 (9.857)
Median % (Min. Max) change from BL	2.61 (–15.83, 26.98)	3.92 (–28.85, 55.76)	6.40 (–22.56, 42.33)	11.18 (–17.40, 41.78)	–1.10 (–27.36, 35.51)	1.37 (–22.53, 28.08)

BL = baseline; DB = double-blind; ePV = estimated plasma volume; Max = maximum; Min = minimum; SD = standard deviation.

Results of Study 201 showed a dose-dependent decrease in mean hemoglobin and hematocrit for the aprocitentan groups during the 8-week double-blind treatment period [Table 3-25].

Mean changes for hemoglobin and hematocrit (decrease) and estimated plasma volume (ePV) (increase) are slightly less pronounced but overall consistent with the changes observed in Study 301.

At Week 10, two weeks after withdrawal of aprocitentan, the observed changes returned back to almost baseline values. Mean and median changes from baseline to Week 8 (end of DB treatment period) for other hematology variables (leukocytes, lymphocytes, neutrophils, and platelets) were small and not clinically relevant.

Hematology in clinical pharmacology Phase 1 studies

The clinical pharmacology Phase 1 studies were single dose studies and the multiple dose studies of limited duration (up to 13 days of treatment). In most clinical pharmacology studies, small decreases were observed for hemoglobin and hematocrit. No clinically significant treatment-related patterns were observed for any other hematology variables. Anemia was only reported during the thorough QT study (ID-080-108), where 2 subjects (4.8%) in the aprocitentan 25 mg group had AEs of anaemia. Both events were mild in intensity and resolved by end of study (EOS).

Clinical Chemistry

Liver enzyme abnormalities (AST, ALT, total bilirubin)

Table 3-4 Marked liver enzyme abnormalities during the 4-week DB part 1: SAF (study 301)

Marked liver abnormality	Aprocitentan 12.5 mg N = 243 n / Nn (%)	Aprocitentan 25 mg N = 245 n / Nn (%)	Placebo N = 242 n / Nn (%)
AST and/or ALT > 3 × ULN	0 / 235	1 / 239 (0.4)	2 / 228 (0.9)
AST and/or ALT > 5 × ULN	0 / 235	0 / 240	1 / 230 (0.4)
AST and/or ALT > 10 × ULN	0 / 235	0 / 240	1 / 230 (0.4)
TBIL > 2 × ULN	0 / 236	1 / 239 (0.4)[a]	0 / 232
(ALT and/or AST > 3 × ULN) and (TBIL > 2 × ULN)	0 / 235	0 / 240	0 / 230

[a] The same subject had elevated TBIL (> 2 × ULN) during SB part 2 and at the end of the safety follow-up period (Subject [redacted]).
n is the number of subjects meeting the abnormality criterion.
Nn is the number of subjects at risk: those not meeting the criterion at baseline within a given central laboratory sample (or having a missing baseline value) and having at least one post-baseline value for all parameters within the given parameter.
A subject was counted only once but could be reported in more than one elevated liver abnormality criterion of a given criteria group.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; DB = double-blind; SAF = safety analysis set; SB = single-blind; TBIL= total bilirubin; ULN = upper limit of normal.

Frequencies of marked liver enzyme abnormalities (AST, ALT, total bilirubin) were low (<1%) and comparable between the aprocitentan treatment groups (12.5 mg and 25 mg) and the placebo group during the 4-week DB part 1 of Study 301 [Table 3-4]. No subject in any treatment group had concomitant ALT and/or AST > 3 × ULN and TBIL > 2 × ULN.

Table 3-6 Marked liver enzyme abnormalities by time interval from the first dose of aprocitentan 25 mg; Aprocitentan 25 mg set (study 301)

	Aprocitentan 25 mg				
	< 12 weeks N = 713 n / Nn (%)	≥ 12- < 24 weeks N = 674 n / Nn (%)	≥ 24- < 36 weeks N = 640 n / Nn (%)	≥ 36 weeks N = 566 n / Nn (%)	Overall N = 713 n / Nn (%)
AST and/or ALT > 3 × ULN	2/703 (0.3)	6/648 (0.9)	4/622 (0.6)	6/475 (1.3)	13/708 (1.8)
AST and/or ALT > 5 × ULN	0/704	2/648 (0.3)	2/622 (0.3)	3/475 (0.6)	6/709 (0.8)
AST and/or ALT > 10 × ULN	0/704	1/648 (0.2)	1/622 (0.2)	0/475	2/709 (0.3)
TBIL > 2 x ULN	1/703 (0.1)	0/647	0/621	1/474 (0.2)	1/708 (0.1)
(ALT and/or AST > 3 × ULN) and (TBIL > 2 × ULN)	0/704	0/648	0/622	0/475	0/709

n is the number of subjects meeting the abnormality criterion.
Nn is the number of subjects at risk: those not meeting the criterion at baseline within a given central laboratory sample (or having a missing baseline value) and having at least one post-baseline value for all variables within the given category.
A subject will be counted only once but may be reported in more than one elevated liver abnormality criterion of a given criteria group.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; TBIL = total bilirubin, ULN = upper limit of normal.

Marked laboratory abnormalities for AST, ALT, and total bilirubin up to 48 weeks of treatment during Study 301 are summarized in Table 3-6. Overall, 13 subjects in the aprocitentan 25 mg set had ALT and/or AST > 3 × ULN. No subjects had a concomitant ALT and/or AST > 3 × ULN and TBIL > 2 × ULN.

There was no evidence of drug-induced hepatotoxicity.

Table 3-9 Marked liver enzyme abnormalities during DB-WD part 3; mSAF (study 301)

Marked liver abnormality	Aprocitentan 25 mg N = 310 n / Nn (%)	Placebo N = 303 n / Nn (%)
AST and/or ALT > 3 × ULN	4 / 305 (1.3)	3 / 296 (1.0)
AST and/or ALT > 5 × ULN	1 / 306 (0.3)	1 / 296 (0.3)
AST and/or ALT > 10 × ULN	0 / 306	1 / 297 (0.3)
TBIL > 2 × ULN	0 / 306	0 / 295
(ALT and/or AST > 3 × ULN) and (TBIL > 2 × ULN)	0 / 306	0 / 297

n is the number of subjects meeting the abnormality criterion.
Nn is the number of subjects at risk: those not meeting the criterion at double-blind withdrawal baseline within a given central laboratory sample (or having a missing double-blind withdrawal baseline value) and having at least one post-baseline value for all variables within the given variable.
A subject was counted only once but could be reported in more than one elevated liver abnormality criterion of a given criteria group.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; DB-WD = double-blind withdrawal; Msaf = modified safety analysis set: TBIL = total bilirubin; ULN = upper limit of normal.

Frequencies of marked liver enzyme abnormalities (AST, ALT, total bilirubin) were low and comparable between the aprocitentan 25 mg and the placebo group during DB-WD part 3 of Study 301.

No subject in either treatment group had ALT and/or AST > 3 × ULN and TBIL > 2 × ULN.

Liver abnormalities in Study 201

There were 2 subjects overall, 1 subject in the aprocitentan 5 mg group and 1 subject in the placebo group, with elevations in ALT and/or AST to > 3×ULN (but less than 5 × ULN) during the DB treatment period of Study 201. The subject in the aprocitentan 5 mg group had a normal ALT baseline value and an elevation to > 3 × ULN at the end of the DB treatment period (Week 8). Values returned to within normal range at Week 10. No subject in any treatment group had an elevation in bilirubin to > 2 × ULN during the DB treatment period.

In Study 201, marked liver enzyme abnormalities were infrequent and balanced between aprocitentan and placebo groups (1 subject with ALT and/or AST > 3 × ULN on aprocitentan 5 mg and 1 subject on placebo).

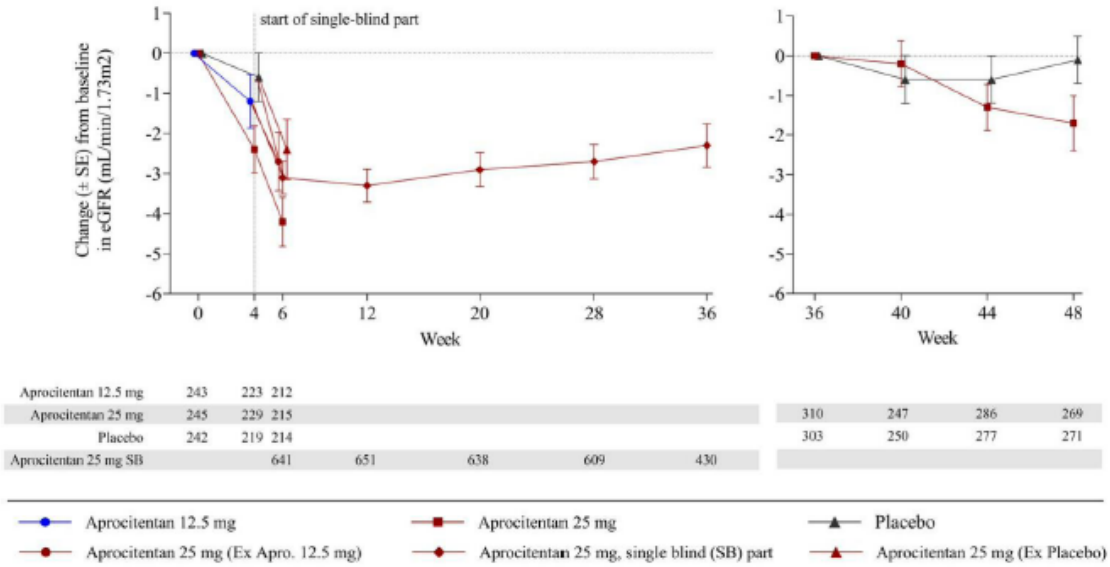
Liver abnormalities in clinical pharmacology Phase 1 studies

The only occurrence of any liver abnormality AEs in clinical pharmacology Phase 1 studies was in study AC-080-101, where the effect of food on aprocitentan was investigated after administration of a single dose of aprocitentan 100 mg in a small number of subjects (6 subjects fasted, 5 subjects fed). One elderly subject in the aprocitentan 100 mg group had AE of ALT increased and AST increased at Day 8; corresponding laboratory values (measured at Day 10) were ALT 3.8 × ULN and AST 2.5 × ULN.

ALT and AST levels were below 3 × ULN at end of study and returned to baseline values approximately 2.5 weeks after last dosing. The subject's total bilirubin remained within the normal range.

Kidney function in Study 301

Figure 3-7 eGFR: mean (± SE) change from baseline to visits in DB part 1, SB part 2, and DB-WD part 3: SAF, mSAF (study 301)



DB = double blind; DB-WD = double-blind withdrawal; eGFR = estimated glomerular filtration rate; mSAF = modified safety analysis set; SAF = safety analysis set; SB = single blind; SE = standard error.

At baseline, mean eGFR values were similar across treatment groups (means of 76-77 mL/min/1.73 m2). The mean eGFR change from baseline in Study 301 over time is shown in Figure 3-7.

As expected, because of the decrease in BP and possible intraglomerular effects of aprocitentan, a small, dose-dependent decrease in mean eGFR was observed (–1.2 mL/min for aprocitentan 12.5 mg and –2.4 mL/min for aprocitentan 25 mg vs –0.6 mL/min for placebo) during DB part 1 of Study 301. This decrease continued to a nadir of –4.2 mL/min at Week 6 in those subjects who had received 25 mg from Day 1, and similarly, decreased further in subjects who were switched to 25 mg at Week 4, to reach −2.7 mL/min in ex-12.5 mg subjects and −2.4 mL/min in ex-placebo subjects at Week 6. Thereafter, during SB part 2, the mean decrease in eGFR in the whole group stabilized at –3.3 mL/min at Week 12 and −2.3 mL/min by the end of SB part 2 at Week 36. During DB-WD part 3, eGFR values from Week 36 to Week 48 remained basically unchanged in the placebo group (−0.1 mL/min) and slightly decreased in the aprocitentan 25 mg group (−1.7 mL/min).

Laboratory abnormalities for eGFR, creatinine and potassium during Study 301

Table 3-61 Kidney function: Marked abnormalities for eGFR, creatinine, and potassium during study 301

Parameter Marked laboratory abnormality	Aprocitentan 12.5 mg n / Nn (%)	Aprocitentan 25 mg n / Nn (%)	Placebo n / Nn (%)
eGFR (mL/min/1.73 m²)			
DB part 1 (SAF)			
< 30	4 / 230 (1.7)	6 / 233 (2.6)	2 / 227 (0.9)
< 60	15 / 185 (8.1)	8 / 180 (4.4)	14 / 190 (7.4)
DB-WD part 3 (mSAF)			
< 30	-	14 / 296 (4.7)	2 / 288 (0.7)
< 60	-	28 / 228 (12.3)	28 / 237 (11.8)
Total up to 48 weeks of treatment (Aprocitentan 25 mg set)			
< 30	-	44 / 692 (6.4)	-
< 60	-	124 / 557 (22.3)	-
Creatinine (µmol/L)			
DB part 1 (SAF)			
> 1.5 × ULN or 1.5 × baseline if baseline > ULN	1 / 225 (0.4)	4 / 231 (1.7)	2 / 228 (0.9)
> 3 × ULN or 3 × baseline if baseline > ULN	0 / 236	0 / 241	0 / 233
DB-WD part 3 (mSAF)			
> 1.5 × ULN or 1.5 × baseline if baseline > ULN	-	9 / 293 (3.1)	2 / 289 (0.7)
> 3 × ULN or 3 × baseline if baseline > ULN	-	1 / 305 (0.3)	0 / 297
Total up to 48 weeks of treatment (Aprocitentan 25 mg set)			
> 1.5 × ULN or 1.5 × baseline if baseline > ULN	-	33 / 685 (4.8)	-
> 3 × ULN or 3 × baseline if baseline > ULN	-	3 / 709 (0.4) [a]	-
Potassium (mmol/L)			
DB part 1 (SAF)			
> 5.5	6 / 233 (2.6)	3 / 237 (1.3)	2 / 230 (0.9)
> 6.0	0 / 235	0 / 241	0 / 231
DB-WD part 3 (mSAF)			
> 5.5		8 / 297 (2.7)	13 / 291 (4.5)
> 6.0		2 / 304 (0.7)	1 / 297 (0.3)
Total up to 48 weeks of treatment (Aprocitentan 25 mg set)			
> 5.5		43 / 702 (6.1)	
> 6.0		11 / 709 (1.6)	

[a] 2 additional subjects (Subjects [redacted] and [redacted]) with baseline creatinine within normal range had an increase to > 3 × baseline values.

n is the number of subjects with at least one treatment-emergent marked abnormality worse than baseline/DB-WD baseline.

Nn is the number of subjects at risk: those not meeting the criterion at baseline/DB-WD baseline (or having a missing baseline/DB-WD baseline value) and having at least one post-baseline/post-DB-WD baseline value prior to EOT + 30 days for a given parameter.

DB = double-blind; DB-WD = double-blind withdrawal; eGFR = estimated glomerular filtration rate; EOT = end-of-treatment; rSAF = restricted safety analysis set; SAF = safety analysis set; ULN = upper limit of normal.

eGFR

eGFR values < 30 mL/min/1.73 m2 were newly reported during DB part 1 of Study 301 for 4/230 subjects (1.7%) in the aprocitentan 12.5 mg group, 6/233 subjects (2.6%) in the aprocitentan 25 mg group, and 2/227 subjects (0.9%) in the placebo group. Likewise, a higher proportion of subjects had newly reported eGFR values < 30 mL/min during DB-WD part 3 of Study 301 in the aprocitentan 25 mg group than in the placebo group (4.7% vs 0.7%). In total, 44 of 692 subjects (6.4%) exposed to aprocitentan 25 mg for up to 48 weeks had newly reported eGFR values < 30 mL/min/1.73 m2 [Table 3-61].

The applicant argued that almost all of these subjects had a low eGFR at baseline and the reduced eGFR during the Study 3 reflected a blood pressure lowering effect of aprocitentan on renal hemodynamics but not an acute kidney injury.

Creatinine

3/709 subjects (0.4%) had a creatinine > 3 × ULN at any time during the study: 2 of these subjects had a creatinine value > ULN at baseline which increased to > 3 × ULN; and the third subject had a single value of creatinine > 3 × ULN, however the investigator repeated the blood test in a local laboratory on the same day and the creatinine value was normal, i.e., the initial result may have been a laboratory error.

In addition, 2/709 (0.3%) subjects with baseline creatinine values within normal range had an increase to > 3 × baseline values: one subject was discontinued due to meeting renal study-specific study treatment discontinuation criteria, and one subject had a baseline eGFR ≥ 60 mL/min which decreased to < 30 mL/min.

Hyperkalemia

In the aprocitentan 25 mg set, marked laboratory abnormalities of hyperkalemia occurred with an incidence of 1.6% (for potassium values > 6 mmol/L) and 6.1% (for values > 5.5 mmol/L) during up to 48 weeks of treatment with aprocitentan 25 mg [Table 3-61]. None of the cases > 6 mmol/L occurred during DB part 1, and of the three cases occurring during DB-WD part 3, two cases were on aprocitentan 25 mg and one on placebo. Thus, no imbalance with placebo treatment and no dose-dependency were detected, and there was no sign of connection to aprocitentan therapy. Two subjects discontinued study treatment due to hyperkalemia, one with a potassium level > 6 mmol/L and the other with a potassium value > 5.5 but < 6 mmol/L. The applicant concluded that the incidence of hyperkalemia in Study 301 is likely due to valsartan administered in subjects with a combination of CKD, diabetes, and betablockers.

Discontinuations due to renal function during Study 301

In total, 18 subjects discontinued study treatment due to kidney effects during the study (two subjects while on placebo):

• 4 subjects discontinued due to AEs: Two subjects during SB part 2 and two subjects during DB-WD part 3, all on aprocitentan 25 mg.

• 12 subjects met the study-specific study treatment discontinuation criteria: 11 subjects on aprocitentan 25 mg (9 during SB part 2 and 2 during DB-WD part 3) and 1 subject on placebo (DB-WD part 3).

• 2 subjects were withdrawn by the investigator due to their eGFR levels: One subject on placebo during DB part 1, and one subject on aprocitentan 25 mg during SB part 2.

In conclusion, aprocitentan induces a small, dose-dependent initial decline in eGFR, followed by stabilization, in a pattern comparable to hemodynamic renal effects of other antihypertensive treatments such as RAS blockers or SGLT2 inhibitors. Subjects with eGFR 15 – < 60 mL/min/1.73 m2, or with diabetic nephropathy, were at higher risk of renal events, but this may be due primarily to their underlying disease and/or the hemodynamic effect of aprocitentan, rather than any harmful effect of the drug on the kidney.

Biomarker for heart failure and heart disease in Study 301

NT-proBNP and troponin I

Throughout Study 301, there were no clinically relevant mean changes for NT-proBNP and troponin I in any treatment group.

ECG in Study 301

Table 12-52 12-lead ECG: marked abnormalities, by study part

Study part (analysis set) Variable Marked ECG abnormality			
DB part 1 (SAF)	**Aprocitentan 12.5 mg N = 243 n / Nn (%)**	**Aprocitentan 25 mg N = 245 n / Nn (%)**	**Placebo N = 242 n / Nn (%)**
QTcF Interval, Aggregate (msec)			
> 450	7 / 188 (3.7)	25 / 192 (13.0)	17 / 189 (9.0)
> 480	1 / 219 (0.5)	3 / 224 (1.3)	2 / 216 (0.9)
> 500	0 / 224	0 / 229	1 / 221 (0.5)
> 30 increase from baseline	6 / 221 (2.7)	11 / 226 (4.9)	9 / 221 (4.1)
> 60 increase from baseline	1 / 221 (0.5)	1 / 226 (0.4)	1 / 221 (0.5)
SB part 2 (rSAF)		**Aprocitentan 25 mg N = 704 n / Nn (%)**	
QTcF Interval, Aggregate (msec)			
> 450		119 / 573 (20.8)	
> 480		22 / 660 (3.3)	
> 500		6 / 676 (0.9)	
> 30 increase from baseline		74 / 665 (11.1)	
> 60 increase from baseline		7 / 665 (1.1)	
DB-WD part 3 (mSAF)		**Aprocitentan 25 mg N = 310 n / Nn (%)**	**Placebo N = 303 n / Nn (%)**
QTcF Interval, Aggregate (msec)			
> 450		31 / 230 (13.5)	27 / 219 (12.3)
> 480		4 / 266 (1.5)	8 / 270 (3.0)
> 500		1 / 273 (0.4)	0 / 274
> 30 increase from baseline		17 / 274 (6.2)	17 / 275 (6.2)
> 60 increase from baseline		1 / 274 (0.4)	0 / 275

n = number of subjects with at least 1 marked abnormality; Nn = number of subjects at risk: those not meeting the criterion at baseline (or DB-WD baseline), or having a missing baseline (or DB-WD baseline) value, and having at least 1 post-baseline value for a given variable. A subject is only counted once, but may be reported in more than 1 marked ECG abnormality criterion of a given variable.

DB = double-blind; DB-WD = double-blind withdrawal; mSAF = modified Safety analysis set; QTcF = QT interval corrected for heart rate using Fridericia's formula; rSAF = restricted Safety analysis set; SAF = Safety analysis set; SB = single-blind

Marked ECG abnormalities are presented in Table 12-52.

In all 3 study parts, the most common marked abnormalities were QTcF interval prolongation to > 450 ms and/or an increase of > 30 ms from baseline.

During DB part 1 (4 weeks) QTcF prolongation to > 450 ms was reported for 3.7%, 13.0%, and 9.0% of subjects in the aprocitentan 12.5 mg, aprocitentan 25 mg, and placebo groups, respectively, and an increase of > 30 ms from baseline for 2.7%, 4.9%, and 4.1% of subjects, respectively.

QTcF interval prolongation to > 500 ms was not reported in any aprocitentan groups but was reported for 1 subject (0.5%) in the placebo group during DB part 1.

During SB part 2 (32 weeks), QTcF interval prolongation to > 450 ms, > 480 ms or > 500 ms were reported for 20.8%, 3.3% and 0.9% respectively and increase of > 30 ms and > 60 ms from baseline, were reported for 11.1 % and 1.1%, respectively.

During DB-WD part 3 (12 weeks), QTcF prolongation to > 450 ms was reported for 13.5% and 12.3% of subjects in the aprocitentan 25 mg and placebo groups, respectively, and an increase of > 30 ms from baseline for 6.2% of subjects in both groups. 1 subject (0.4%) in the aprocitentan 25 mg group and no subjects in the placebo group had a QTcF interval prolongation to > 500 ms during DB-WD part 3.

The proportion of subjects with ECG findings was similar across treatment groups in the placebo-controlled double-blind (DB) part 1 and double-blind withdrawal (DB-WD) part 3 of Study 301.

ECG analysis up to 48 weeks of treatment during Study 301

Table 5-2 ECG: Marked abnormalities by time interval since first dose of aprocitentan 25 mg; Aprocitentan 25 mg set (study 301)

	Aprocitentan 25 mg				
Variable Marked ECG abnormality	<12 weeks N=713 n / Nn (%)	≥ 12- < 24 weeks N=674 n / Nn (%)	≥ 24- < 36 weeks N=640 n / Nn (%)	≥ 36 weeks N=566 n / Nn (%)	Overall N=713 n / Nn (%)
QTcF Interval, Aggregate (ms)					
> 450	70 / 559 (12.5)	55 / 518 (10.6)	38 / 367 (10.4)	40 / 309 (12.9)	138 / 591 (23.4)
> 480	9 / 649 (1.4)	11 / 597 (1.8)	8 / 423 (1.9)	4 / 354 (1.1)	26 / 683 (3.8)
> 500	2 / 664 (0.3)	3 / 608 (0.5)	1 / 429 (0.2)	2 / 360 (0.6)	7 / 699 (1.0)
> 30 increase from BL	34 / 654 (5.2)	32 / 600 (5.3)	24 / 425 (5.6)	22 / 354 (6.2)	87 / 687 (12.7)
> 60 increase from BL	3 / 654 (0.5)	4 / 600 (0.7)	2 / 425 (0.5)	2 / 354 (0.6)	8 / 687 (1.2)

n = number of subjects with at least one treatment-emergent marked abnormality worse than baseline; Nn = number of subjects at risk: not meeting the criterion at baseline (or having a missing baseline value) and having at least one post-baseline value prior to EOT + 30 days for a given variable.
A subject is only counted once but may be reported in more than one marked ECG abnormality criterion of a given variable.
A subject can be included in more than one time interval according to treatment duration.
BL= baseline; ECG = electrocardiography; EOT = end-of-treatment; QTcF = QT interval corrected for heart rate using Fridericia's formula.

Up to 48 weeks of treatment with aprocitentan 25 mg, the proportion of subjects with marked ECG abnormalities by time interval was stable over time [Table 5-2].

ECG in Study 201

For the aprocitentan groups, changes from baseline to Week 4 and Week 8 of the DB treatment period in the ECG variables of heart rate and the PR, QRS, QT, QTcB, and QTcF intervals were unremarkable.

ECG in the TQT Phase 1 study

Results of the TQT study (ID-080-108) concluded that administration of aprocitentan was associated with a dose related increase in QTcF that exceeded the threshold of regulatory concern (upper bound of the 90% CI for ΔΔQTcF > 10 ms) at supratherapeutic doses of aprocitentan (100 mg) and at an aprocitentan concentration of 16.1 µg/mL. Outlier analyses did not reveal a signal of concern. The results of the high exposure scenario that was simulated for the highest therapeutic dose of aprocitentan (25 mg) using the population PK model estimated that Cmax at steady-state conditions in a high exposure scenario was 7 µg/mL, less than half the threshold concentration of 16.1 µg/mL, providing some reassurance. However, it is not entirely clear whether in vulnerable patients (e.g. patients with heart failure or electrolyte imbalances), or when co-prescribed with other drugs with the potential for QT prolongation, the observed effect might become clinically relevant.

In addition, aprocitentan is highly bound to plasma proteins (> 99%). Plasma protein binding is essential for drug-drug interactions, since substances can displace each other from plasma protein binding and thus the effective concentration of a drug can suddenly increase. A DDI study between aprocitentan and drugs with high plasma protein binding was not conducted. Some drugs that are highly bound to plasma proteins may also be frequently used in a RHTN population and include among others e.g. Spironolactone, Furosemide, Ibuprofen, Propranolol, Amiodarone, Verapamil, Rivaroxaban, Warfarin. Displacement of aprocitentan from its plasma protein binding by other plasma protein binding medications is not considered to affect the safety margin for QT interval prolongation.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

Intrinsic factors

Subgroup analyses by intrinsic factors were performed in Study 301 for the placebo-controlled 4-week DB part 1 and during up to 48 weeks of treatment with aprocitentan 25 mg. The subgroups of interest were based on age, gender, race/ethnicity, BMI, baseline eGFR, medical history of cardiac failure and medical history of diabetes [Table 5-16].

Table 5-16 Subgroup results for AESI in the 4-week DB part 1 by treatment group, and up to 48 weeks in the aprocitentan 25 mg set (study 301)

	DB part 1 (4 weeks)			Aprocitentan 25 mg set (up to 48 weeks)
	Aprocitentan		Placebo	Aprocitentan
Category Subgroup	12.5 mg n/N (%)	25 mg n/N (%)	n/N (%)	25 mg n/N (%)
Hepatic disorders – Total	**0/243**	**1/245 (0.4)**	**2/242 (0.8)**	**20/713 (2.8)**
Age				
18 – < 65 years	0/143	1/138 (0.7)	0/128	11/399 (2.8)
65 – < 75 years	0/78	0/85	1/86 (1.2)	6/244 (2.5)
≥ 75 years	0/22	0/22	1/28 (3.6)	3/70 (4.3)
eGFR (mL/min/1.73 m²)				
≥ 60	0/188	1/183 (0.5)	1/197 (0.5)	18/559 (3.2)
15 – < 60	0/55	0/62	1/45 (0.5)	2/154 (1.3)
Medical history of cardiac failure				
Yes	0/49	0/51	0/44	4/143 (2.8)
No	0/194	1/194 (0.5)	2/198 (1.0)	16/570 (2.8)
BMI (kg/m²)				
< 30	0/75	0/71	0/78	5/217 (2.3)
30 – < 40	0/135	0/132	2/132 (1.5)	11/391 (2.8)
≥ 40	0/33	1/42 (2.4)	0/32	4/105 (3.8)
Medical history of diabetes				
Yes	0/131	0/137	2/127 (1.6)	6/384 (1.6)
No	0/112	1/108 (0.9)	0/115	14/329 (4.3)
Anaemia – Total	**9/243 (3.7)**	**3/245 (1.2)**	**0/242**	**73/713 (10.2)**
Age				
18 – < 65 years	5/143 (3.5)	1/138 (0.7)	0/128	28/399 (7.0)
65 – < 75 years	4/78 (5.1)	0/85	0/86	33/244 (13.5)
≥ 75 years	0/22	2/22 (9.1)	0/28	12/70 (17.1)
eGFR (mL/min/1.73 m²)				
≥ 60	6/188 (3.2)	1/183 (0.5)	0/197	49/559 (8.8)
15 – < 60	3/55 (5.5)	2/62 (3.2)	0/45	24/154 (15.6)
Medical history of cardiac failure				
Yes	4/49 (8.2)	2/51 (3.9)	0/44	21/143 (14.7)
No	5/194 (2.6)	1/194 (0.5)	0/198	52/570 (9.1)
BMI (kg/m²)				
< 30	1/75 (1.3)	2/71 (2.8)	0/78	28/217 (12.9)
30 – < 40	8/135 (5.9)	1/132 (0.8)	0/132	35/391 (9.0)
≥ 40	0/33	0/42	0/32	10/105 (9.5)
Medical history of diabetes				
Yes	5/131 (3.8)	3/137 (2.2)	0/127	43/384 (11.2)
No	4/112 (3.6)	0/108	0/115	30/329 (9.1)
Oedema/fluid retention – Total	**22/243 (9.1)**	**45/245 (18.4)**	**5/242 (2.1)**	**170/713 (23.8)**
Age				

18 – < 65 years	6/143 (4.2)	22/138 (15.9)	2/128 (1.6)	81/399 (20.3)
65 – < 75 years	12/78 (15.4)	15/85 (17.6)	2/86 (2.3)	64/244 (26.2)
≥ 75 years	4/22 (18.2)	8/22 (36.4)	1/28 (3.6)	25/70 (35.7)
Sex				
Male	12/144 (8.3)	29/147 (19.7)	3/143 (2.1)	114/424 (26.9)
Female	10/99 (10.1)	16/98 (16.3)	2/99 (2.0)	56/289 (19.4)
eGFR (mL/min/1.73 m^2)				
≥ 60	12/188 (6.4)	30/183 (16.4)	4/197 (2.0)	117/559 (20.9)
15 – < 60	10/55 (18.2)	15/62 (24.2)	1/45 (2.2)	53/154 (34.4)
Medical history of cardiac failure				
Yes	5/49 (10.2)	13/51 (25.5)	2/44 (4.5)	30/143 (21.0)
No	17/194 (8.8)	32/194 (16.5)	3/198 (1.5)	140/570 (24.6)
BMI (kg/m^2)				
< 30	5/75 (6.7)	13/71 (18.3)	1/78 (1.3)	41/217 (18.9)
30 – < 40	16/135 (11.9)	24/132 (18.2)	3/132 (2.3)	95/391 (24.3)
≥ 40	1/33 (3.0)	8/42 (19.0)	1/32 (3.1)	34/105 (32.4)
Medical history of diabetes				
Yes	12/131 (9.2)	31/137 (22.6)	3/127 (2.4)	112/384 (29.2)
No	10/112 (8.9)	14/108 (13.0)	2/115 (1.7)	58/329 (17.6)
Heart Failure – Total	**1/243 (0.4)**	**2/245 (0.8)**	**0/242**	**17/713 (2.4)***
Age				
18 – < 65 years	0/143	0/138	0/128	5/399 (1.3)
65 – < 75 years	1/78 (1.3)	1/85 (1.2)	0/86	6/244 (2.5)
≥ 75 years	0/22	1/22 (4.5)	0/28	6/70 (8.6)
eGFR (mL/min/1.73 m^2)				
≥ 60	0/188	1/183 (0.5)	0/197	10/559 (1.8)
15 – < 60	1/55 (1.8)	1/62 (1.6)	0/45	7/154 (4.5)
Medical history of cardiac failure				
Yes	0/49	1/51 (2.0)	0/44	6/143 (4.2)
No	1/194 (0.5)	1/194 (0.5)	0/198	11/570 (1.9)
BMI (kg/m^2)				
< 30	1/75 (1.3)	0/71	0/78	1/217 (0.5)
30 – < 40	0/135	2/132 (1.5)	0/132	11/391 (2.8)
≥ 40	0/33	0/42	0/32	5/105 (4.8)
Medical history of diabetes				
Yes	0/131	2/137 (1.5)	0/127	14/384 (3.6)
No	1/112 (0.9)	0/108	0/115	3/329 (0.9)

*Source Abridged from table iss-2.7.1. One subject ([redacted]) with 2 events (cardiogenic shock and myocardial infarction) adjudicated as MACE. Therefore, the case was categorized as MACE and excluded from AESI heart failure. Two other subjects ([redacted] with left ventricular dysfunction and [redacted] with dyspnoea) were added to AESI heart failure because they were not categorized as AESI heart failure but adjudicated as hospitalization for heart failure.

AESI = adverse event of special interest, BMI = body mass index, DB = double-blind, eGFR = estimated glomerular filtration rate; MACE = major adverse cardiovascular event.

Age

As expected, increased incidence rates were observed in elderly subjects for anaemia, oedema / fluid retention and heart failure.

Gender

During the 4-week DB part 1 of Study 301, no difference was seen between gender subgroups in any treatment group, whereas with prolonged treatment up to 48 weeks, an increased incidence was observed in male subjects for oedema / fluid retention but the difference was considered possibly linked to other factors such as high BMI and history of heart failure.

Race/ethnicity

Subgroup analyses did not reveal any clinically relevant differences between races.

Population PK modeling, investigating race/ethnicity data from all studies, did not indicate a clinically relevant impact of race/ethnicity on PK. Thus, no dose adjustment is needed based on race/ethnicity.

BMI

BMI > 40 kg/m2 was linked to an increased incidence of oedema / fluid retention and heart failure.

eGFR
Increased incidences were observed in subjects with baseline eGFR 15 – < 60 mL/min/1.73 m2 for anaemia, oedema / fluid retention and heart failure. The incidence of oedema / fluid retention was consistently lower with aprocitentan 12.5 mg (compared to 25 mg) across eGFR subgroups.

Medical history of diabetes
Increased incidences were observed in subjects with a medical history of diabetes for oedema / fluid retention: the incidence of oedema / fluid retention events was higher for diabetic subjects treated with aprocitentan, particularly with aprocitentan 25 mg.

Medical history of cardiac failure
Increased incidences were observed in subjects with medical history of cardiac failure for anaemia and heart failure. Of interest, during the 4-week DB part 1, the incidence of oedema / fluid retention events was higher in subjects with a medical history of cardiac failure receiving 25 mg aprocitentan, compared to those without medical history of cardiac failure, while in subjects on aprocitentan 12.5 mg the incidence was significantly lower (compared to aprocitentan 25 mg) with no imbalance observed between subjects with vs subjects without medical history of cardiac failure.

Extrinsic factors

For extrinsic factors (food effect, drug-drug interactions) reference is made to the corresponding clinical pharmacology sections of this report.

2.6.8.7. Immunological events

Antibody formation was not reported during the clinical Phase 2/3 studies.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Please refer to the corresponding assessment in the pharmacokinetics section of this report.

2.6.8.9. Discontinuation due to adverse events

AEs leading to premature discontinuation of study treatment with onset during the 4-week DB part 1 of Study 301

Table 2-12 AEs leading to premature discontinuation of DB study treatment during the 4-week DB part 1 by Preferred Term; SAF (study 301)

Preferred Term	Aprocitentan		Placebo
	12.5 mg N = 243 n (%)	25 mg N = 245 n (%)	N = 242 n (%)
Subjects with at least one event	**7 (2.9)**	**5 (2.0)**	**2 (0.8)**
Cerebrovascular accident[M]	0	1 (0.4)	0
Face oedema[A]	0	1 (0.4)	0
Pollakiuria	0	1 (0.4)	0
Root canal infection	0	1 (0.4)	0
Transaminases increased	0	1 (0.4)	0
Allergic oedema	1 (0.4)	0	0
COVID-19 pneumonia	1 (0.4)	0	0
Hyperkalaemia	1 (0.4)	0	0
Hypotension	1 (0.4)	0	1 (0.4)
Ischaemic stroke[M]	1 (0.4)	0	1 (0.4)
Pulmonary embolism	1 (0.4)	0	0
Ventricular extrasystoles	1 (0.4)	0	0

Preferred Terms are sorted by descending frequency in the aprocitentan 25 mg group, and alphabetically thereafter.
A subject can only be counted once per row but may be counted in more than one row.
[A] AE Preferred Term considered an AESI.
[M] AE Preferred Term adjudicated as MACE-plus (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure).
Preferred Terms are based on MedDRA version 24.1.
AE = adverse event; AESI = adverse event of special interest; COVID-19 = Coronavirus disease 2019; DB = double-blind; MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; SAF = Safety analysis set.

The overall proportion of subjects with an AE leading to premature discontinuation of study treatment during the 4-week DB part 1 of Study 301 was low, with a numerically higher incidence in the aprocitentan 12.5 mg and 25 mg groups than in the placebo group but without any dose relationship (2.9% and 2.0% vs 0.8%, respectively). Across the treatment groups, each of these AEs occurred in only a single subject [Table 2-12].

AEs leading to premature discontinuation of study treatment during up to 48 weeks of treatment with aprocitentan 25 mg

Table 2-13 AEs leading to premature discontinuation of study treatment by time interval from first dose of aprocitentan 25 mg and Preferred Term; Aprocitentan 25 mg set (study 301)

	Aprocitentan 25 mg				
Preferred Term	<12 weeks N = 713 n (%)	≥ 12- < 24 weeks N = 674 n (%)	≥ 24- < 36 weeks N = 640 n (%)	≥ 36 weeks N = 566 n (%)	Overall N = 713 n (%)
Subjects with at least one event	**20 (2.8)**	**7 (1.0)**	**9 (1.4)**	**5 (0.9)**	**41 (5.8)**
COVID-19 pneumonia	1 (0.1)	2 (0.3)	0	1 (0.2)	4 (0.6)
Oedema peripheral[A]	2 (0.3)	1 (0.1)	0	0	3 (0.4)
Angina unstable[M,*]	0	0	1 (0.2)	1 (0.2)	2 (0.3)
Cerebrovascular accident[M]	2 (0.3)	0	0	0	2 (0.3)
Transaminases increased[A]	1 (0.1)	0	0	1 (0.2)	2 (0.3)
Acute kidney injury	1 (0.1)	0	0	0	1 (0.1)
Alanine aminotransferase increased[A]	0	0	1 (0.2)	0	1 (0.1)
Blood pressure decreased	0	0	0	1 (0.2)	1 (0.1)
Cardiac failure chronic[A,M]	0	1 (0.1)	0	0	1 (0.1)
Cardiac failure congestive[A,M]	1 (0.1)	0	0	0	1 (0.1)
Coronary artery disease	0	0	1 (0.2)	0	1 (0.1)
Dermatitis allergic	1 (0.1)	0	0	0	1 (0.1)
Dry mouth	1 (0.1)	0	0	0	1 (0.1)
Dysgeusia	1 (0.1)	0	0	0	1 (0.1)
Dyspnoea[M]	1 (0.1)	0	0	0	1 (0.1)
Face oedema[A]	1 (0.1)	0	0	0	1 (0.1)
Fluid retention[A]	1 (0.1)	0	0	0	1 (0.1)
Glomerular filtration rate decreased	0	0	1 (0.2)	0	1 (0.1)
Hepatic enzyme increased[A]	0	0	1 (0.2)	0	1 (0.1)
Hyperkalaemia	0	1 (0.1)	0	0	1 (0.1)
Hypertension	0	0	1 (0.2)	0	1 (0.1)
Hypervolaemia	0	0	0	1 (0.2)	1 (0.1)
Ischaemic stroke[M]	0	0	1 (0.2)	0	1 (0.1)
Metastatic neoplasm	0	0	1 (0.2)	0	1 (0.1)
Multiple organ dysfunction syndrome	0	0	0	1 (0.2)	1 (0.1)
Myocardial infarction[M]	1 (0.1)	0	0	0	1 (0.1)
Pollakiuria	1 (0.1)	0	0	0	1 (0.1)
Pregnancy	0	1 (0.1)	0	0	1 (0.1)
Procedural intestinal perforation	1 (0.1)	0	0	0	1 (0.1)

Renal failure	0	1 (0.1)	0	0	1 (0.1)
Renal impairment	0	0	1 (0.2)	0	1 (0.1)
Respiratory failure	1 (0.1)	0	0	0	1 (0.1)
Root canal infection	1 (0.1)	0	0	0	1 (0.1)
Syncope	1 (0.1)	0	0	0	1 (0.1)
Vasomotor rhinitis	1 (0.1)	0	0	0	1 (0.1)

The % in each column displays the % of subjects reporting an AE in a certain exposure period. Subjects who had less than the exposure (either by design or because they prematurely discontinued treatment) are excluded.
A subject can be counted in more than one row.
A subject can be counted in more than one time interval in a row (a subject may experience multiple occurrences of the same AE at different time intervals whilst exposed to aprocitentan 25 mg).
A subject will only be counted once in the overall column for a row where they experience an AE.
AEs are sorted by descending frequency of Preferred Term based on the overall column.
[A] AE Preferred Term considered an AESI.
[M] AE Preferred Term adjudicated as MACE-plus (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure) for at least 1 subject.
* Angina unstable was adjudicated by the CAC for 2 subjects: confirmed as non-fatal myocardial infarction in Subject [redacted] (≥ 36 weeks interval) and not confirmed as myocardial infarction based on troponin I values in Subject [redacted] (≥ 24 – < 36 weeks interval).
Preferred Terms are based on MedDRA dictionary version 24.1.
AE = adverse event; AESI = adverse event of special interest; CAC = Central Adjudication Committee; COVID-19 = Coronavirus disease 2019; MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities.

AEs leading to premature discontinuation of study treatment occurred in 41 subjects (5.8%) during up to 48 weeks of treatment with aprocitentan 25 mg. Approximately half of these subjects (20 subjects; 2.8%) had the events during the first 12 weeks of treatment [Table 2-13]. Of note, discontinuation was not linked to any particular type of AE.

Table 2-14 Subjects with premature discontinuation of study treatment due to study-specific study treatment discontinuation criteria up to 48 weeks of treatment with aprocitentan 25 mg, by study part; Aprocitentan 25 mg set (study 301)

Criterion	Aprocitentan 25 mg			
	DB part 1 N = 245 n (%)	SB part 2 N = 704 n (%)	DB-WD part 3 N = 310 n (%)	Total N = 713 n (%)
Renal failure	0	9 (1.3)	2 (0.6)	11 (1.5)
Hemoglobin abnormalities	0	4 (0.6)	0	4 (0.6)
Liver transaminase abnormalities	0	1 (0.1)	1 (0.3)	2 (0.3)
Persistent fluid retention	0	1 (0.1)	0	1 (0.1)

N = number of subjects with event.
Study-specific study treatment discontinuation criteria as defined in the CSR [D-22.269 section 9.3.6.3].
CSR= clinical study report; DB = double-blind; DB-WD = double-blind withdrawal; SB = single-blind.

18 subjects on aprocitentan 25 mg prematurely discontinued study treatment up to 48 weeks of treatment due to study-specific treatment discontinuation criteria [Table 2-14]. Of note, 8 of the 11 subjects meeting the "renal failure" criterion had a baseline eGFR 15 – < 60 mL/min/1.73 m2. "Renal failure" was defined for this purpose as confirmed eGFR < 15 mL/min/1.73 m2 or confirmed decrease of ≥ 30% from baseline in eGFR based on the CKD-EPI equation. Since the second part of this criterion (eGFR decrease > 30%) was found to be too strict and not medically relevant because it reflects a PD effect of the drug, it was changed to "confirmed increase of > 2 × from baseline in serum creatinine" in Global Protocol Amendment 2.

AEs leading to premature discontinuation of study treatment during DB-WD part 3 by Preferred Term, mSAF (Study 301)

Table 2-15 AEs leading to premature discontinuation of study treatment during DB-WD part 3 by Preferred Term, mSAF (study 301)

Preferred Term	Aprocitentan 25 mg N = 310 n (%)	Placebo N = 303 n (%)
Subjects with at least one event	**7 (2.3)**	**5 (1.7)**
Angina unstable[M]	1 (0.3)	0
Blood pressure decreased	1 (0.3)	0
COVID-19 pneumonia	1 (0.3)[a]	0
Glomerular filtration rate decreased	1 (0.3)	0
Hypervolaemia[A]	1 (0.3)	0
Multiple organ dysfunction syndrome	1 (0.3)[a]	0
Renal impairment	1 (0.3)	0
Transaminases increased	1 (0.3)	0
Alanine aminotransferase increased	0	1 (0.3)
Angioedema	0	1 (0.3)
Haemorrhage intracranial[M]	0	1 (0.3)
Hypertension	0	1 (0.3)
Ischaemic stroke[M]	0	1 (0.3)

A subject can only be counted once per row but may be counted in more than one row.
AEs are sorted by descending frequency of System Organ Class and Preferred Terms based on the aprocitentan 25 mg treatment group.
[A] AE Preferred Term considered an AESI.
[M] AE Preferred Term adjudicated as MACE-plus (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure).
[a] One subject had COVID-19 pneumonia and Multiple organ dysfunction syndrome.
System Organ Class and Preferred Terms are based on MedDRA version 24.1.
AE = adverse event; AESI = adverse event of special interest; COVID-19 = Coronavirus disease 2019; DB-WD = double-blind withdrawal; MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; mSAF = modified safety analysis set.

Table 2-16 Subjects with premature discontinuation of study treatment due to study-specific study treatment discontinuation criteria during DB-WD part 3; mSAF (study 301)

Criterion	Aprocitentan 25 mg N = 310 n (%)	Placebo N = 303 n (%)
Renal failure	2 (0.6)	1 (0.3)
Hemoglobin abnormalities	0	0
Liver transaminase abnormalities	1 (0.3)	1 (0.3)
Persistent fluid retention	0	0

N = number of subjects with event.
Study-specific study treatment discontinuation criteria as defined in the CSR [D-22.269 section 9.3.6.3].
Note: subjects in the aprocitentan 25 mg group are also contained in Table 2-14.
CSR= clinical study report; DB-WD = double-blind withdrawal, mSAF = modified safety analysis set.

During the 12-week DB-WD part 3, a similar proportion of subjects in the aprocitentan 25 mg group and the placebo group had AEs leading to premature discontinuation of study treatment (2.3% and 1.7%); all PTs were reported for single subjects in either treatment group [Table 2-15].

In addition, 5 subjects prematurely discontinued study treatment due to study-specific study treatment discontinuation criteria during DB-WD part 3. Of note, the 2 subjects in the aprocitentan 25 mg group meeting the "renal failure" criterion had a baseline eGFR 15 – < 60 mL/min/1.73 m2 [Table 2-16].

AEs leading to premature discontinuation of study treatment during the 8-week DB period of Study 201

Table 12-8 Double-blind treatment-emergent adverse events (AEs) leading to premature discontinuation of study treatment by preferred term, Safety Set

ACT-132577
Protocol: AC-080A201
Double-blind treatment-emergent adverse events (AEs) leading to premature discontinuation of study treatment by preferred term
Analysis Set: Safety Set

Preferred Term	Placebo N = 82 n (%)	ACT-132577 5 mg N = 82 n (%)	ACT-132577 10 mg N = 82 n (%)	ACT-132577 25 mg N = 82 n (%)	ACT-132577 50 mg N = 81 n (%)	Lisinopril 20 mg N = 81 n (%)
Subjects with at least one AE	5 (6.1)	1 (1.2)	2 (2.4)	3 (3.7)	3 (3.7)	3 (3.7)
Hypertension	2 (2.4)	0	0	1 (1.2)	2 (2.5)	1 (1.2)
Face oedema	0	0	0	0	1 (1.2)	0
Anxiety	1 (1.2)	0	0	0	0	0
Blood pressure increased	2 (2.4)	0	0	0	0	0
Bundle branch block left	0	0	0	1 (1.2)	0	0
Erectile dysfunction	0	0	0	0	0	1 (1.2)
Neoplasm malignant	0	0	0	1 (1.2)	0	0
Palpitations	0	0	0	0	0	1 (1.2)
Rib fracture	0	0	1 (1.2)	0	0	0
Supraventricular tachycardia	0	0	1 (1.2)	0	0	0
Viral infection	0	1 (1.2)	0	0	0	0

AEs leading to premature discontinuation of study treatment during the 8-week DB period of Study 201 were reported in a lower proportion of subjects in all aprocitentan groups (1.2%–3.7%) than in the placebo group

(6.1%) [Table 12-8]. Apart from Hypertension and Blood pressure increased, all PTs were reported for single subjects in any treatment group.

AEs leading to premature discontinuation of study treatment in the clinical pharmacology Phase 1 studies

AEs leading to premature discontinuation of study treatment were reported in a total of 9 subjects on aprocitentan in clinical pharmacology studies; of these, 5 subjects received aprocitentan at supratherapeutic dose (100 mg), 3 subjects received aprocitentan 25 mg and 1 subject aprocitentan 10 mg.

AEs PTs leading to premature discontinuation of study treatment were as follows:

• **100 mg aprocitentan:**
1) Upper respiratory tract infection (1 subject in study AC-080-101).
2) Cardiac discomfort and Palpitations, as well as a QTcB prolongation from baseline of > 60 ms (1 subject in study ID-080-108).
3) Asthenia, Bradycardia, Restlessness, Nausea, Feeling hot, and Paraesthesia (1 subject in study ID-080-108).
4) Dizziness, Nausea, Vomiting, Headache, Ear discomfort, and Nasal congestion (1 subject in study ID-080-108).
5) Oedema peripheral, Face oedema, and Seasonal allergy (1 subject in study ID-080-108).

• **25 mg aprocitentan:**
6) Vomiting and Headache (1 subject in study AC-080-102).
7) Influenza like illness and Headache (1 subject in study AC-080-106).
8) Pharyngitis (1 subject in study AC-080-106).

• **10 mg aprocitentan:**
9) Musculoskeletal chest pain and Blood creatine phosphokinase increased (1 subject in study AC-080-102).

None of these AEs leading to premature discontinuation of study treatment in the clinical pharmacology Phase 1 studies were an AESI, except for 1 subject who discontinued aprocitentan 100 mg due to peripheral edema and face edema in study ID-080-108. The events resolved without sequelae between the EOS and post-study safety follow-up visit.

2.6.8.10. Post marketing experience

Aprocitentan has not yet received marketing approval in any region.

2.6.9. Discussion on clinical safety

Phase 3 development programme

The application consists of only one pivotal study. Although this may be acceptable under specific circumstances (Points to consider on application with 1. Meta-analyses; 2. One pivotal study; CPMP/EWP/2330/99), the pivotal Study 301 is not deemed sufficiently controlled and is of limited duration

(less than one year). Considering that dual ET antagonism represent a new pharmacological principle as there is no clinical experience with ERAs in the treatment of resistant hypertension, as a rule at least two well controlled studies with long-term follow up would be expected.

In the submitted pivotal study, the safety analysis is additionally heavily hindered by the fact that the only true placebo controlled data come from the DB part 1 of the study which lasted only 4 weeks. The second placebo controlled period was the DB-WD part 3 which lasted 12 weeks, however all patients re-randomised to placebo received and tolerated aprocitentan 25 mg during the preceeding 32 weeks (in SB part 2) and therefore this group does not entirely match the target group of patients.

Exposure

The main focus of the safety assessment is on data from patients with resistant hypertension who received aprocitentan 12.5 mg dose (exposure up to maximal 4 weeks) and aprocitentan 25 mg dose (exposure varied from 32 weeks to 48 weeks). Exposure to doses intended for clinical use in subjects with resistant hypertension is as follows:

12.5 mg dose: 191 subjects were treated for a maximum of 4 weeks.

25 mg dose: 630 subjects were treated for at least 6 months, 100 subjects for at least 47 weeks, and 50 subjects for at least 48 weeks.

Any dose of 12.5 mg and/or 25 mg: 192 subjects were treated for at least 47 weeks, and 99 subjects for at least 48 weeks.

*Note: Due to the visit windows in Study 301, subjects completing the study as per protocol could have an exposure of just a few days less than 48 weeks, reflected by the considerably higher number of subjects with an exposure of at least 47 weeks compared to 48 weeks.

In the context of ICH1 guideline, the safety database is borderline due to limited exposure to aprocitentan where only 100 patients with resistant hypertension for at least 47 weeks and 50 patients with resistant hypertension for 48 weeks received the highest target dose (aprocitentan 25 mg) and no patient was exposed for longer than 48 weeks (11 months). There is no ongoing or open-label extension (OLE) study planned with aprocitentan in rHTN.

Representativeness of the population studied

Study 301 was conducted in the target population with difficult-to-control HTN. Mean SiSBP (SD) was 156.9 (11.6) mmHg and SiDBP was 88.5 (10.6) mmHg at screening and 460 subjects (63.0%) were receiving ≥ 4 antihypertensive therapies.

Demographic characteristics of the 730 randomized subjects were balanced across treatment groups.

The majority of subjects were male (434 subjects, 59.5%) and White (605 subjects, 82.9%). 82 subjects (11.2%) were Black or African American. The median age was 63 years (range 24–84 years): 44.0% of subjects were aged ≥ 65 years, including 9.9% aged ≥ 75 years.

Mean body mass index (SD) was 33.7 (6.2) kg/m2; the majority of subjects were obese (BMI ≥ 30 kg/m2; 506 subjects, 69.3%), including 107 subjects (14.7%) with a BMI ≥ 40 kg/m2. 284 subjects (38.9%) had a baseline body weight > 100 kg.

At baseline, 90 subjects (12.6%) had UACR > 300 mg/g and 162 subjects (22.2%) had chronic kidney disease (CKD) stage 3–4, defined as eGFR < 60 mL/min/1.73 m2. Of these, 21 subjects (2.9%) had CKD stage 4 (i.e., eGFR ≥ 15 to 30 mL/min/1.73 m2).

Over half of the subjects had diabetes (395 subjects, 54.1%). Other prevalent comorbidities were ischaemic heart disease (225 subjects, 30.8%), heart failure (143 subjects, 19.6%), and sleep apnoea syndrome (103 subjects, 14.1%).

In conclusion, the safety population studied, and relevant subgroups are considered representative of the target population of difficult-to control HTN, a population that is enriched for patients at high CV risk.

On the other hand, 40.6 % of patients randomized to placebo had reached target BP values as proposed by the ESH/ESH 2018 after 4 weeks. This indicates that a large number of patients included were not in line with the assumption of RHT requiring treatment.

Overall safety profile

DB part 1

The most common TEAE during DB part 1 was **oedema peripheral** in all 3 treatment groups.

Other PTs that were reported for ≥2% of subjects were **fluid retention**, **upper respiratory tract infection**, **headache** and **haemoglobin decreased.** All were consistently reported more frequently in the aprocitentan groups compared to placebo and in a dose dependent manner, except for haemoglobin decreased which was reported only in the 12.5 mg group. The Applicant included oedema/fluid retention (very common) and haemoglobin decreased (common) in SmPC as ADRs, which is supported.

Other common TEAE reported for more than 1% of subject during DB part 1 were **dyspnoea, face oedema and arthralgia**. All were reported only in the aprocitentan groups except one case of dyspnoea in the placebo group (0.4%). Due to very low number of events, any conclusion on causality based on comparison of frequencies is limited, especially with regards to PTs occurring in less than 1% of subjects. However, some PT's occurred clearly more frequently or exclusively in the aprocitentan groups, like **fatigue** (3 vs 0), **dizziness** (4 vs 1, plus one additional case of dizziness postural), **dyspnoea** (5 vs 1, plus 3 additional cases of dyspnoea exertional), **angina pectoris** (3 vs 0), **hypotension** (4 vs 1) and **acute kidney injury** (3 vs 0).

ADRs of dysponoea (common) and hypotension (uncommon) were included in SmPC part 4.8. Not including the other of the above mentioned AEs was sufficiently justified by the Applicant and accepted.

The majority of TEAEs reported during the DB part 1 were of mild or moderate intensity, while 17 subjects reported severe events (15 of which were in aprocitentan groups), most commonly oedema peripheral. Overall, 12 subjects discontinued during the DB part 1 due to AEs in the aprocitentan groups (2.5%) compared to 2 subjects in the placebo group (0.8%).

SB part 2

The assessment of AEs occurring during the SB part 2 is heavily hindered by the fact that this part of the study was uncontrolled, making a causality assessment difficult. Nevertheless, overall 27 subjects (3.8%) discontinued due to AEs, 188 subjects (26.7%) reported AESIs, and 14 subjects (2.0%) had adjudication-confirmed MACE-plus. The most common TEAE PTs during the SB part 2 were infections, primarily related to COVID-19, and oedema peripheral (13.5%).

The majority of TEAEs during the SB part 2 were of mild or moderate intensity, while 47 subjects (6.7%) reported severe events, again most commonly related to COVID-19.

9 subjects (1.3%) died during the SB part 2.

Although a causality assessment is difficult, further discussion and assessment of causality was provided for AEs of interest including dyspnoea, hypotension, dizziness, arthralgia, fatigue and syncope. ADRs of dysponoea (common) and hypotension (uncommon) were finally included in SmPC part 4.8, which is supported.

DB WD part 3

Similar proportions of subjects reported at least one AE in both treatment groups, however it is questionable what proportion of AEs recorded soon after re-randomisation could be attributed to previous administration of aprocitentan 25 mg during the 32 weeks of the SB part 2 of the study.

Overall, most common (reported for ≥2% of subjects) TEAEs were **COVID 19** (similarly reported in both groups), **atrial fibrillation** (8/9 cases in aprocitentan group), and **hypertension** (reported in 4 and 6 subjects, respectively)).

Deaths

11 deaths were treatment-emergent and all occurred in the aprocitentan groups, again, the vast majority during the SB part 2 (9/11). The remaining two patients died during the DB part 1 and the DB WD part 3, respectively, both due to COVID-19. Main causes of deaths were COVID-19 (5 cases) and MACE (5 cases). Of 9 patients who died during SB part 2, 5 died due to MACE adjudicated events, 3 of which were described as sudden cardiac deaths, although the review of provided narratives suggests that probably 4/5 cases were sudden cardiac deaths.

None of these treatment-emergent deaths was considered related to study treatment by the investigator. It is understood that a rather sick population with RHTN and pre-existing comorbidities was included in Study 301. However, with a limited duration of 48 weeks and a limited number of 730 patients included in Study 301 and without a control arm, the treatment-emergent 11 death cases observed during Study 301 are difficult to interpret and a numerical imbalance and/or safety signal for deaths cases in subjects treated with aprocitentan can not be excluded with certainty. A comparison with historical data from literature and RWE data is not considered adequate to resolve this safety concern.

Serious Adverse Events (SAEs)

In Study 301, 14.6% of subjects in the aprocitentan 25 mg group had at least 1 SAE up to 48 weeks of treatment. The most frequently reported SAEs were COVID-19 pneumonia (2.7%), followed by angina unstable (0.8%), atrial fibrillation and pneumonia (both 0.7%) and cardiac failure congestive, cerebrovascular accident and myocardial infarction (all 0.4%). The majority of reported SAEs were assessed as not related by the investigators.

Overall, the proportion of SAEs during controlled parts of the study was higher in the aprocitentan groups:

During the 4-week DB part 1 of Study 301, SAEs were reported for 3.3% of subjects in each aprocitentan group (12.5 mg and 25 mg) compared to 1.2% of subjects in the placebo group.

During the 12-week DB-WD part 3 of Study 301 and the 30-day safety FU period, the overall incidence of SAEs was numerically higher in the aprocitentan 25 mg group (18 subjects; 5.8%) than in the placebo group (9 subjects, 3.0%), but most SAEs were reported for single subjects. Slight numerical differences between

the aprocitentan 25 mg group and placebo group were observed for: COVID-19 pneumonia (4 subjects vs 2 subjects), atrial fibrillation (3 subjects vs 0 subjects), and pneumonia (2 subjects vs 0 subjects) without clear evidence of a causal association with aprocitentan treatment.

Discontinuations

Overall, 41 subjects (5.8%) discontinued due to AEs during up to 48 weeks of treatment with aprocitentan 25 mg – about half of them (2.8%) during the first 12 weeks of treatment. Each PT was reported in only 1 or 2 subjects, except for PT COVID-19 pneumonia (4 subjects) and PT oedema peripheral (3 subjects).

20 subjects (2.7%) discontinued due to study-specific criteria. 18 of them were receiving aprocitentan 25 mg and most commonly discontinued due to renal failure criteria (11 subjects), followed by haemoglobin abnormalities (4 subjects), liver transaminase abnormalities (2 subjects) and persistent fluid retention (1 subject).

Oedema / fluid retention

Consistent with other ERAs, edema / fluid retention is an expected adverse drug reaction to aprocitentan: overall, 26.3% of subjects reported dose dependent TEAE edema / fluid retention. Edema / fluid retention was overall well tolerated, with the vast majority of events of mild or moderate intensity (96.4%). Seven subjects discontinued due to edema / fluid retention.

Appropriate warning statements and precautionary measures are included in SmPC (section 4.4) regarding the risk of fluid retention in subjects with renal impairment and congestive heart failure.

Anaemia

Consistent with experience with other ERAs, TEAEs denoting anaemia during aprocitentan treatment were reversible, and were most likely secondary to plasma volume expansion and haemodilution.
After 4 weeks of treatment, a similar reduction in mean haemoglobin from baseline was observed in the 2 aprocitentan treatment groups, –8.0 g/L (12.5 mg) and –8.5 g/L (25 mg), vs almost no change in the placebo group, - 0.4 g/L. During the DB part 1, clear dominance in the lower aprocitentan dose regarding reported TEAE denoting anaemia/haemoglobin decreased (Hgb<100 g/L) was noted (3.7%, 1.2%, 0%, respectively), however it is considered to be an chance finding. A smaller difference was seen during the DB WD part 3 (1.9% vs 1.3%). During the SB part 2, TEAEs denoting anaemia were reported for 63 subjects (8.9%), with haemoglobin decreased being the most frequently reported PT (28 subjects, 4.0%), followed by PT anaemia reported for 17 (2.4%) subjects. The lowest haemoglobin values during aprocitentan treatment were all above 80 g/L.
The Applicant has carefully reviewed the 4 cases of bleeding events. The review of these 4 cases of bleeding does not suggest a causal relationship to aprocitentan treatment – in 3 of 4 cases, convincing alternative causative factors were reported, including arterial aneurism, peptic and duodenal ulcers. The exact origin of bleeding in the first patient with COVID-19 pneumonia remains unclear, however reported concomitant GI disorders could be the source of bleeding (gastritis or diverticulosis) and a causal relationship with aprocitentan use is unlikely in this case also. The Applicant additionally reviewed all other cases of bleeding reported during the study, which is acknowledged. No clear pattern could be established, i.e. no difference between the aprocitentan and the placebo groups were identified and no dose response could be observed. Overall, the Applicant's assessment of reported cases of bleeding during the study is agreed.
Furthermore, a warning has been added to section 4.4 of the SmPC that *"Initiation of JERAYGO is not recommended in patients with severe anaemia (< 8 g/dL). If clinically indicated, haemoglobin concentrations should be measured prior to initiation of treatment and during treatment."*

Heart failure (non-serious)
Overall, 8 subjects (1.1%) had non-serious TEAEs denoting heart failure, in the majority of cases of moderate severity. Only 1 patient discontinued treatment due to dyspnoea. All patients received aprocitentan, almost all aprocitentan 25 mg (7/8).

Due the fact that the vast majority of subjects developed non-serious HF during uncontrolled SB part 2 (6/8), an assessment of causality is difficult.

MACE-plus
28 MACE-plus events were reported for 27 subjects:

• 'MACE' in 16 subjects: cardiovascular death (5 subjects, all during SB part 2), non-fatal myocardial infarction (5 subjects, of whom 1 subject had 2 events), and non-fatal stroke (6 subjects).

• 'Hospitalization for heart failure' in 11 subjects.

23 of the 27 subjects who experienced MACE-plus received aprocitentan, including 13/16 subjects with MACE and 10/11 subjects with hospitalization for heart failure. 14 of these 23 cases occurred during the uncontrolled SB part 2.

A significant difference between aprocitentan and placebo was noted during the DB part 1: 6/7 cases of MACE-plus were recorded in the aprocitentan groups (3 in each dose group). Additional 14 subjects (2.0%) had adjudication-confirmed MACE-plus with onset during the SB part 2 – 5 CV deaths, 3 non-fatal MI, 6 hospitalizations due to HF. No clear difference in MACE incidence was noted during the DB-WD part 3 – there were 2 non-fatal MI in aprocitentan 25 mg group (vs 0 in placebo) and 2 non-fatal strokes in placebo (vs 0 in aprocitentan group).

Due to study design, and considering high background risk of CV morbidity and mortality of the population included, perspective causality assessment of MACE is difficult, in particular for the 5 cases of CV deaths observed during the uncontrolled SB part 2 of the study. It should be noted that in 4/5 death cases, the narratives provided do not allow clear conclusions on the cause of death – 3 cases seem to be sudden cardiac deaths, and 1 patient with concomitant invasive breast carcinoma had a cerebral edema and subdural haemorrhage discovered at autopsy, however the primary cause of death is not clear as patient deteriorated sharply at home and died on the same day. The narrative suggests an increased potassium levels of mild intensity, however in the laboratory listing it was actually severe hyperkalaemia with potassium 7.1 mmol/L 10 days before death, unresolved at EOS. Baseline potassium levels were normal (4.5 mmol/L). In another death which also presented as sudden cardiac death, potassium levels were also moderately elevated, 6.9 mmol/L, however the patient had somewhat elevated potassium also at baseline (5.8 mmol/L). It cannot be concluded or excluded that some rhytmogenic incident was the cause of those deaths. Only 1 death was clearly due to a massive cerebrovascular accident, probably not related to treatment.

None of provided supplementary data (IQVIA RWE study and literature review) is considered robust enough to enable firm and reliable conclusion that aprocitentan does not increase risk of major cardiovascular events and death in an already high risk population with resistant hypertension. In the context of the ICH1 guideline, exposure to aprocitentan is considered limited as only 50 patients with resistant hypertension received aprocitentan 25 mg for 48 weeks and no long-term safety data beyond 48 weeks is available. The assessment is further hindered by the fact that all CV deaths occurred under aprocitentan treatment during

the uncontrolled SB part 2 and available narratives do not allow reliable conclusion on the cause of death in 4 out of 5 fatal cases.

During the study, 11 patients were hospitalized for HF, 10 of which under aprocitentan treatment (all received 25 mg dose), 6 of them during SB part 2. Only one patient from the placebo group (during the DB WD part 3) was hospitalized for HF.

In total, 3 of the 8 non-serious AEs of heart failure and 5 of the 10 SAEs of hospitalization for heart failure under aprocitentan treatment (i.e., almost half of them) were preceded by signs of fluid retention reported as AEs. In the context of high frequency of AEs denoting fluid retention overall, the cardiovascular safety profile needs thorough evaluation.

Cardiovascular safety

In the specific Guidelines on clinical investigation of medicinal products in the treatment of hypertension (EMA/CHMP/29947/2013/Rev. 4) and Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015), it is requested that development programmes should include data that enable an adequate characterisation of the cardiovascular safety profile of new medicinal products. Those data could be collected either by meta-analytic approach or a dedicated CV outcome study. The presented dossier did not include such data as only one, largely uncontrolled study with overall limited exposure is representative of the target population. The only true placebo controlled part of the study lasted 4 weeks which is deemed too short to enable reasonable conclusions on CV safety of long-term aprocitentan use.

Additionally, 11 TE deaths occurred during the aprocitentan development program, all in the aprocitentan groups during study 301. 5 of those cases were MACE adjudicated deaths including 3 (possibly 4) sudden cardiac deaths, and all occurred during the uncontrolled part of the study. The remaining patients died due to COVID-19 (5 events) and procedural bowel perforation (1 event).

To account for the absence of a placebo control during the 32-week SB part of study 301, a systematic literature review and a real-world evidence study were performed to compare the incidence rates of hospitalization for heart failure and MACE in study 301 to external data in the target population. Although such data are supportive and can contextualize the safety evaluation, the approach cannot serve as a substitute for controlled long term data to characterize CV safety.

Overall, the presented data from clinical development program for aprocitentan in patients with resistant hypertension do not allow a straightforward comparison of the safety of aprocitentan as compared to placebo or to another treatment strategy during long term treatment. Dose related fluid retention and oedema may aggravate MACE events. Overall, information on long term safety, especially cardiovascular safety in this vulnerable population, is insufficient and long term controlled data are needed to investigate specifically CV safety in patients at high and very high risk for CV events.

Laboratory findings and vital signs

Liver toxicity

There was no clear hepatotoxicity signal from the aprocitentan development program. Nevertheless, hepatotoxicity is a well-known AE associated with ERAs and considering that overall safety data for aprocitentan in resistant hypertension are scarce in both, the number of exposed patients and duration of exposure, a potential association between aprocitentan and risk of liver toxicity cannot be definitively ruled

out. This remark is further corroborated by the fact that significant alterations, i.e. ALT and/or AST > 10 × ULN were recorded in one patient during SB part 2 and in one patient at the very beginning of DB WD part 3 indicating that clinically relevant serum aminotransferase abnormalities were recorded only in patients who received aprocitentan.

For precautionary reasons, a contraindication for patients with severe hepatic impairment (Child-Pugh class C; with or without cirrhosis) was added in section 4.3 of the SmPC and instructions for appropriate monitoring of liver enzymes during treatment with aprocitentan were included in section 4.4 of the SmPC. Severe liver injury is also mentioned in the RMP as important potential risk.

Although there is no clear hepatotoxicity signal from aprocitentan development program, considering hepatotoxicity is a well-known AE associated with ERAs and the fact that overall safety data for aprocitentan in resistant hypertension are somewhat scarce in both the number of exposed patients and duration of exposure, a potential risk of liver toxicity with longer exposure cannot be definitively ruled out. A warning statement has been included for patients with elevated transaminases (>3xULN).

Kidney function
During the DB part 1, a dose-dependent decrease in mean eGFR was observed: from −1.2 (12.5 mg) to −2.4 (25 mg) mL/min/1.73m2. During the SB part 2, the mean decrease in eGFR in the whole group stabilized at −3.3 at Week 12, reaching –2.3 at Week 36. During the DB-WD part 3, when compared to mean eGFR values at Week 36, eGFR values at Week 48 remained basically unchanged in the placebo group (−0.1), while a further small decrease was observed in the aprocitentan group (−1.7). Considering that after week 12 in the SB part 2, eGFR was stabilised at about -3.3 mL/min/1.73m2 compared to baseline, the reason for a further decline of eGFR in the DB WD part 3 in subjects who continued on aprocitentan 25 mg is not understood. Also, data in the placebo arm in the DB WD part 3, raise doubts that the decline in eGFR is entirely be reversible in all patients..

Additionally, proportions of subjects who had new onset of eGFR values < 30 mL/min/1.73 m2 were significantly higher (and dose dependent) in the aprocitentan groups during the controlled parts of the study – during the DB part 1 for 1.7% in the aprocitentan 12.5 mg group, 2.6% in the aprocitentan 25 mg group, and 0.9% in the placebo group, and during the DB WD part 3, 4.7% and 0.7% of subjects, respectively, had newly reported eGFR values < 30 mL/min/1.73 m2. Overall, 6.4% of subjects exposed to aprocitentan 25 mg for up to 48 weeks had newly reported eGFR values < 30 mL/min/1.73 m2. The Applicant argues that almost all these patients had a lower eGFR at baseline, however this does not preclude additional detrimental effects of aprocitentan treatment on kidney function and its consequences, regardless of the effect being PD effect on renal haemodynamics due to vasodilatation or true AKI.
Following D120 LoQ, the Applicant provided a more detailed discussion regarding kidney function under aprocitentan treatment. Overall, there is no indication of acute renal injury; however, a clear and dose-dependent decline of eGFR is observed throughout the study, and in some patients with lower baseline eGFR it decreased below 30 mL/min/1.73 m2. Reasurringly, stopping the treatment lead to complete reverse of eGFR in the majority of patients who discontinued due to kidney-related reasons.
Nevertheless, the significance of the findings remain unclear in the context of long term use of aprocitentan considering that patients with renal impairment who received aprocitentan at any dose had a higher reported rate of anaemia and fluid retention. The Applicant added a warning in section 4.4, referring to CKD patients, advising close monitoring of Hb concentration, signs of fluid overload, and incipient HF, which is supported.

Patients receiving aprocitentan had an overall higher incidence of TEAEs denoting renal impairment, dose dependent decline in eGFR and accompanying increase in creatinine levels, however there was no clear

association with increase in potassium levels - no clear pattern could be established regarding potassium values > 5.5 mmol/L, and the majority of potassium values > 6.0 mmol/L were reported during the uncontrolled SB part 2 (9/12 cases). The relevance of hyperkalaemia in two reported cases of sudden deaths remains unknown.

Overall, 18 subjects discontinued study treatment due to impairment of kidney function; 12 subjects met the study-specific study treatment discontinuation criteria, 4 subjects discontinued due to renal AEs and 2 subjects were withdrawn by the investigator due to their eGFR levels. Again, majority of subjects discontinued during SB part 2.

Weight
After an initial dose-dependent mean increase in the aprocitentan treatment groups during the DB part 1 (Week 4: +0.43 kg [12.5 mg] and +0.63 kg [25 mg]; vs −0.21 kg for placebo), mean values returned to baseline by Week 12 during the SB part 2. Significant weight gains of more than 2 kg occurred most often in the aprocitentan 25 mg groups.

Pulse rate
No clinically relevant changes were observed. Similar mean reductions were observed in all 3 treatment groups at week 4: −3.3 bpm in the aprocitentan 12.5 mg group, −2.6 bpm in the aprocitentan 25 mg group, and −2.7 bpm in the placebo group. No case of orthostatic hypotension was reported.

ECG
Overall, 8 subjects had significant prolongation of QTcF > 500 ms, 6 of them during uncontrolled SB part 2. Other 2 events were reported, one in the placebo group (DB part 1) and one on aprocitentan 25 mg (DB WD part 3). During the SB part 2, 1.1% of subjects had clinically significant increase of > 60 ms in QTcF interval from baseline. No causality assessment could be made based on those data.

Elderly
There were about 10% of patients older than 75 years of age included in the study. The Applicant presented data on AESI in aprocitentan 25 mg set and during DB part 1 according to age groups indicating increased incidences of all AESI – hepatic disorders, anemia, edema / fluid retention and heart failure - in elderly subjects. For edema / fluid retention, the increased incidence with age is more noticeable with 25 mg than with 12.5 mg, while for other AESIs the number of events was too small for any meaningful comparison between doses. Similarly, patients 75 years of age or older, had higher incidences of MACE and hospitalizations for heart failure (aprocitentan 25 mg set). Considering that majority of those events occurred during SB part 2, no comparisons between doses could be made.

Warning statements and recommendations for the management of elderly patients were included in the SmPC.

Rebound effect
No signal of rebound in BP was observed following discontinuation of aprocitentan after 32 weeks of SB treatment in study 301 or after 8 weeks of DB treatment in study 201.

2.6.10. Conclusions on the clinical safety

The safety data are limited in terms of controlled exposure and follow up to enable reliable conclusions on long term safety of aprocitentan in the treatment of resistant hypertension.

Most frequent TEAEs were oedema peripheral, fluid retention, and haemoglobin decreased / anaemia. Those effects were expected as class-effects.

Although there is no clear hepatotoxicity signal from the aprocitentan development program, hepatotoxicity is a well-known AE associated with ERAs. Since the controlled safety data for aprocitentan in resistant hypertension are limited in both the number of exposed patients and duration of exposure, a potential risk of liver toxicity with longer exposure cannot be definitively ruled out. For precautionary reasons, it is not recommended to administer aprocitentan in patients with elevated transaminases (>3xULN).

In the one pivotal Study 301, the only true placebo-controlled data come from the DB part 1 of the study which lasted only 4 weeks. The second placebo-controlled period was the DB-WD part 3 which lasted 12 weeks. However, only patients having tolerated aprocitentan treatment over at least 32 weeks and were not dropped out were re-randomised. Therefore this selected group does not entirely represent the target group of patients.

In the absence of a longer-term control group in the pivotal Study 301, it is not possible to exclude a negative impact of aprocitentan on cardiovascular outcome and prognosis.

Most concerning issues represent multiple death cases which all occurred in the aprocitentan groups, the majority during the uncontrolled part of the study. Almost half of deaths were of CV origin most of the remaining deaths were related to COVID-19. All CV deaths occurred during the uncontrolled part of the study which makes a causality assessment difficult.

The data do not indicate a prolongation of QT in the therapeutic range. At supratherapeutic doses of 100 mg a small increase in QTc was observed which may have to be taken into consideration in case of overdose.

Glomerular filtration rate decreased and Body weight increase (fluid retention) are listed in section 4.8 of the SmPC. Since the data available do not allow to reliably conclude on a causal association of the treatment with Heart failure/ aggravation of existing heart failure, these events are currently not listed in section 4.8.

The safety profile for JERAYGO (aprocitentan) 12.5 mg and 25 mg film-coated tablets once daily in adult subjects with difficult-to-control HTN on a background of other antihypertensive medications is limited.

No information is available on long-term dose related safety when comparing the 12.5 and the 25 mg dose.

The duration of exposure to the target group of patients in a controlled setting within the Phase 2/3 programme is limited with regards to an assessment of safety, esp. CV safety.

There are no controlled data above >12 weeks in the target population. Fluid retention has been discussed as a potential aggravating factor contributing to a negative numerical imbalance in the rate of major CV events with another ERA in patients with RHT (Lancet 2009; 374: 1423–31). In the absence of a control group it is neither possible to reliably evaluate the cardiovascular events as observed in study 301 and to characterize the cardiovascular safety profile as requested by the Guideline on clinical investigation of medicinal products in the treatment of hypertension (EMA/CHMP/29947/2013/Rev. 4) and the Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015), nor is it possible to exclude a negative impact of aprocitentan on cardiovascular outcome and prognosis. Eleven deaths occurred in the pivotal study 301, all in the aprocitentan groups. Five of those cases were MACE adjudicated deaths and all

occurred during the uncontrolled part of the study. Although an analysis of the individual cases did not raise concerns of a causal link to the treatment with aprocitentan, a final assessment is hampered by the absence of controlled long-term safety data.

Information coming from external controls or from patients with PAH cannot serve as a substitute and the comparison with literature and RWE data is considered insufficient to provide sufficient reassurance. Long term safety data allowing to evaluate whether dose related differences in fluid retention and other AEs between the 25 mg and the 12.5 mg are of relevance for cardiovascular events are neither available.

Notably, the applicant did not follow the recommendations given in the 2015 and 2017 EMA scientific advices with respect to the need to generate evidence to exclude a detrimental effect in CV safety with aprocitentan.

The request for long-term controlled safety data is maintained. The Applicant has provided a proposal of a PASS Cat. 3. It is a multicenter, international, prospective, randomized, controlled, open-label, pragmatic study in patients with RHT in need of additional BP lowering therapy despite treatment with at least 3 antihypertensives. Patients are randomized in a 1:1 ratio to the following groups:

- aprocitentan added to the existing antihypertensives (henceforth, aprocitentan group), or
- any other antihypertensive therapy added to the existing antihypertensives, according to physician's choice (henceforth, control group).

5094 (later diminished in applicant's responses to 2830) patients randomized are proposed to be followed over 1.5 years with MACE plus heart failure as a proposed primary endpoint. Pending an assessment of the final protocol, the study design is expected to provide relevant data on long-term CV safety and on safety in patients at high risk. The results are considered important for an assessment of the benefit risk balance and has therefore to be classified as a PASS Cat 1. The SmPC section 4.4 has been updated to include warnings and precautions of use to mitigate the CV risk in light of the absence of long-term CV data. In addition, it is expected that the PASS will provide additional data and to further characterise the long-term cardiovascular safety of aprocitentan in patients with resistant hypertension and also information on whether the risk mitigation measures in place are sufficient. However, since the PASS is considered key to benefit-risk of the product, the categorisation of the PASS has been changed to category 1.

The CHMP considers the following measures necessary to address issues related to safety:

Description	**Due date**
Interventional post-authorisation safety study (PASS): In order to further characterise the long-term cardiovascular safety of aprocitentan in patients with resistant hypertension, the MAH should conduct and submit the results of a randomized, active-controlled study in adult patients with resistant hypertension, according to an agreed protocol.	Final report: 31 March 2031

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant identified the following safety concerns in the RMP version 0.7:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Teratogenicity
Important potential risks	• Heart failure due to fluid retention in predisposed patients • Severe liver injury • Male infertility
Missing information	• Long-term cardiovascular safety under controlled clinical setting

2.7.2. Pharmacovigilance plan

Table Part III.3: On-going and planned additional pharmacovigilance activities

Study; Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Study 401 PASS – Multicenter, randomized, open label, active-controlled, pragmatic trial in patients with RHT. (Planned)	Primary objective: • Compare MACE-plus rates between the aprocitentan group and the SoC group Secondary objective: • Characterize the long-term safety profile of aprocitentan in adult subjects with RHT including on: ▪ Heart failure due to fluid retention in predisposed patients ▪ Severe liver injury	Long-term CV safety profile of aprocitentan under controlled clinical setting Heart failure due to fluid retention in predisposed patients Severe liver injury	Protocol submission	30 Sep 2024
			Progress Reports	Annual Update
			Final study report	31 March 2031
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				

Study; Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
Not applicable				

CV = cardiovascular; MACE = major adverse cardiac event(s); PASS = post-authorisation safety study; PRAC = Pharmacovigilance Risk Assessment Committee; RHT = resistant hypertension.

2.7.3. Risk minimisation measures

3. Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Teratogenicity	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, 4,5,4.6, and 5.3 PL section 2. Medicinal product subject to medical prescription. **Additional risk minimisation measures:** Patient card.	No additional routine pharmacovigilance activities beyond adverse reaction reporting, signal detection and evaluation in aggregated PSUR are planned.
Important potential risk: Heart failure due to fluid retention in predisposed patients	**Routine risk minimisation measures:** SmPC section 4.4 PL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None	No routine pharmacovigilance activities beyond adverse reaction reporting, signal detection and evaluation in aggregated PSUR are planned. Additional pharmacovigilance activities: PASS (study 401); final study report due date: 31 March 203
Important potential risk: Severe liver injury	**Routine risk minimisation measures:** SmPC sections 4.3,4.4 and 4.8 PL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:**	Routine pharmacovigilance activities beyond adverse reaction reporting, signal detection and evaluation in aggregated PSUR.

3. Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Patient card	Hepatic AE questionnaire. Additional pharmacovigilance activities: PASS (study 401); final study report due date:31 March 2031
Important potential risk: Male infertility	**Routine risk minimisation measures:** SmPC section 4.6 and 5.3 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None	No additional routine pharmacovigilance activities beyond adverse reaction reporting, signal detection and evaluation in aggregated PSUR are planned.
Missing information: Long-term cardiovascular safety under controlled clinical setting	**Routine risk minimisation measures:** SmPC section 5.1 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None	Additional pharmacovigilance activities: PASS (study 401); final study report due date:31 March 2031

The Applicant proposed a patient card as additional risk minimisation measures (aRMM) to address the important identified risk "teratogenicity" and the important potential risk ""severe liver injury" which is agreed and considered necessary in order to assure the safe and effective use of aprocitentan in clinical practice.

3.1.1. Conclusion

The CHMP considers that the risk management plan version 0.7 is acceptable.

3.2. Pharmacovigilance

3.2.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the

requirements of Article 8(3) of Directive 2001/83/EC.

3.2.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 19 March 2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

3.3. Product information

3.3.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3.3.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, JERAYGO (Aprocitentan) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it has a PASS imposed at the time of authorisation.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

4. Benefit-Risk Balance

4.1. Therapeutic Context

4.1.1. Disease or condition

Aprocitentan is an orally active dual ETA/ETB endothelin receptor antagonist and is planned to be marketed as JERAYGO 12.5 mg and 25 mg film-coated tablets.

The therapeutic indication wording proposed by the applicant in section 4.1 of SmPC is as follows:

"JERAYGO is indicated for the treatment of resistant hypertension in adult patients in combination with at least three antihypertensive medicinal products (see section 5.1)."

HTN is a leading cause of CV disease and mortality worldwide [GBD 2017 Risk Factor Collaborators 2018]. An estimated 1.3 billion people have HTN [NCD-RisC 2021], of whom approximately 10% have difficult-to-control HTN [Noubiap 2019, Williams 2018]. HTN is generally defined as difficult to control, or "treatment-resistant", if BP is not controlled despite the administration of at least 3 antihypertensive medications at appropriate doses. For a subject to fulfill this definition, pseudo RHT linked to e.g. white coat effect, inappropriate BP measurement or medical inertia (insufficient efforts to optimize therapy) should have been excluded, as well as curable secondary causes of HTN [Carey 2018, Williams 2018]. These exclusions were ensured during the screening process of Study 301.

4.1.2. Available therapies and unmet medical need

Available therapies
Difficult-to-control HTN patients per definition fail to achieve BP control target on a triple therapy consisting of mechanistically complementary antihypertensive agents, commonly including a long-acting calcium channel blocker (CCB), a RAS blocker (ACE inhibitor or angiotensin receptor blocker), and a diuretic [Carey 2018, Williams 2018]. All 3 must be prescribed at maximum or maximally tolerated (i.e., optimal) doses and at the appropriate dosing interval. Of note, beta-blockers can be considered at any stage in patients with complicated HTN especially if associated with heart failure, angina pectoris, post-MI, or atrial fibrillation [Mancia 2022].

The guidelines, as well as HTN textbooks, consistently emphasize that the use of a diuretic is critically important in difficult-to-control HTN as it is considered from a physiology-pathology standpoint a volume-dependent HTN (i.e. inverse to the renin and/or sympathetic-dependent HTN) [Carey 2018, Unger 2020, Whelton 2018]. If BP remains uncontrolled on a thiazide diuretic, it is recommended to switch to a long-acting thiazide-like diuretic (i.e. chlorthalidone or indapamide) due to their effect on nocturnal BP and additional antihypertensive benefit. In patients with CKD grade 3b to 5, a loop diuretic is usually preferable since thiazide-like agents progressively lose their efficacy as renal function declines.

There is no consensus on the choice of a fourth agent for those patients who still have uncontrolled BP. Most guidelines recommend a steroidal MRA, spironolactone or eplerenone, as fourth-line therapy following the PATHWAY-2 study [Williams 2015].

Unmet medical need

Despite HTN awareness and considerable improvement in the treatment and control of HTN in high-income countries (North America and EU included) since the 1980s, the extent of BP control has plateaued in the past decade [NCD-RisC 2019]. Patients whose BP is not controlled on ≥ 3 agents have a higher risk for adverse long-term CV outcomes, proportional to the number of background medications, as shown in numerous epidemiological studies and subgroup analyses of clinical trials [Carey 2018]. Therefore, there is a major medical need for an additional pharmacological therapy acting on a pathway different from those currently used, targeting the pathophysiology of these types of HTN, and able to be combined with existing therapies without increasing their risks, while providing additional BP lowering potential.

4.1.3. Main clinical studies

The main evidence of efficacy submitted is a prospective, multi-center, randomized, parallel-group, blinded Phase 3 study with aprocitentan in subjects with RHT.

The study consisted of a screening period, placebo run-in period (single blind), randomized treatment period (double blind, aprocitentan 12.5 mg qd vs. 25 mg qd vs. placebo) over 4 weeks), followed by a single blind treatment with aprocitentan 25 mg over 32 weeks, followed by a double blind withdrawal over 12 weeks comparing after rerandomization aprocitentan 25 mg vs. placebo, and a safety follow-up period of 30 – 33 days. Adult patients on at least three antihypertensive drugs of different classes with refractory arterial hypertension, as defined by Mean SiSBP ≥ 140 mmHg recorded via unattended automated office blood pressure measurement (uAOBPM) were included. Out of 1965 screened subjects, 911 were included in the placebo RI period and 730 were randomized. 662 of 730 randomized subjects (90.7%) completed the study.

4.2. Favourable effects

The key favourable effects of aprocitentan are restricted to the blood pressure lowering efficacy in patients with resistant arterial hypertension as measured by two different devices, uAOBM and ABPM.

As compared to placebo, changes in blood pressure were as follows (mmHg) after 4 weeks of treatment:

SiSBP (uAOBM) (primary efficacy endpoint)

12.5 mg: LS Mean difference vs Placebo: -3.79, 97.5% confidence limit: - 6.76; -0.82, P-Value: 0.0042

25 mg: LS Mean difference: -3.73, 97.5% confidence limit: - 6.67; -0.78, P-Value: 0.0046

SiDBP (uAOBM)

12.5 mg: LS Mean difference vs Placebo: -3.94, 95% confidence limit: - 5.57; -2.31, P-Value: < 0.0001

25 mg: LS Mean difference: -4.47, 95% confidence limit: - 6.09; -2.85, P-Value: < 0.0001

24h mean SBP (ABPM):

12.5 mg: LS Mean difference vs Placebo: -4.18, 95% confidence limit: - 6.25; -2.12, P-Value: < 0.0001

25 mg: LS Mean difference: -5.90, 95% confidence limit: - 7.94; -3.85, P-Value: < 0.0001

24h mean DBP (ABPM):

12.5 mg: LS Mean difference vs Placebo: -4.32 95% confidence limit: -5.66; -2.98, P-Value: < 0.0001

25 mg: LS Mean difference: -5.81, 95% confidence limit: -7.14; -4.49, P-Value: < 0.0001

Maintenance of efficacy was demonstrated by a randomized withdrawal at week 36 to week 40. BP values increased in the placebo arm but not in the aprocitentan 25 mg arm:

SiSBP (uAOBM): 25 mg: LS Mean difference vs Placebo: - 5.87, 95% confidence limit: --7.98; -3.76, P-Value: < 0.0001

SiDBP (uAOBM): 25 mg: LS Mean difference vs Placebo: -5.29, 95% confidence limit: --6.72; -3.86, P-Value: < 0.0001

24h mean SBP: 25 mg: LS Mean difference vs Placebo: -6.53, 95% confidence limit: -8.50; -4.56, P-Value: < 0.0001

24h mean DBP: 25 mg: LS Mean difference vs Placebo: -6.75, 95% confidence limit: -7.98; -5.52, P-Value: < 0.0001

For the primary efficacy endpoint consistent results were observed over almost all predefined and post hoc defined subgroups by age, sex, BMI, Region, Urine Albumin-to-Creatinine Ratio (UACR), Diabetes mellitus, Betablocker use, and sleep apnoe (present/absent). Lack of efficacy, treatment by subgroup interactions or trends thereof for the primary efficacy endpoint by Race, CKD stage and weight could be sufficiently explained by variability or large placebo effects in small subgroups, measurements by ABPM and during the withdrawal showed consistent BP lowering effects over these groups.

UACR

At the end of DB part 1 (Week 4), a decrease in UACR was observed in both aprocitentan groups, while UACR remained close to baseline in the placebo group. The reduction in UACR compared to placebo was 30 and 34% for aprocitentan 12.5 mg and aprocitentan 25 mg, respectively. UACR ratio to baseline remained stable up to Week 36. After withdrawal of aprocitentan, UACR in the placebo group increased between Week 36 and Week 40 and thereafter remained stable. In the aprocitentan 25 mg group UACR reduction was sustained until Week 48. In subjects with microalbuminuria (> 30–300 mg/g), a 4-week treatment with aprocitentan was associated with decreases in UACR from baseline of 43% in the 12.5 mg group and 45% in the 25 mg group, compared to placebo. In subjects with baseline macroalbuminuria (> 300 mg/g), the treatment effect was more pronounced, with a UACR reduction of 48% with aprocitentan 12.5 mg and of 61% with aprocitentan 25 mg, compared to placebo. In subjects with UACR < 30 mg/g the effect of aprocitentan was less pronounced than with the higher doses.

4.3. Uncertainties and limitations about favourable effects

- The additional benefit of the 25 mg over the 12.5 mg dose is limited. There was no difference in efficacy between both doses for systolic and diastolic BP when measured with uAOBM. Analyses based on 24h ABPM indicated a small additional effect on systolic and diastolic blood pressure (< 2 mmHg) in the overall population. Larger effects are postulated by the Applicant in patients > 75 years of age, with CKD3-4, and in Black/African American patients, but these results are not considered robust. The possible impact of the higher rate of additional diuretics administered in the 25 mg Aprocitentan group and the relevance for subgroups of interest (in particular CKD3-4 and patiens aged > 75 years) has been analysed by sensitivity analyses. Addition of diuretics decreased the BP but had no relevant effect on the difference in efficacy

between the 25 and the 12.5 mg dose. Sensitivity analyses did not indicate a relevant impact of missing data on the result.

- Representativeness and characterization of the study population

Upon request the Applicant amended the wording of the indication – ie. specified that aprocitentan is indicated for the treatment of resistant hypertension in combination with at least three antihypertensive medicinal products (see section 5.1).

The patients were sufficiently representative for a study population with RHT with risk factors as expected.

A large placebo effect was observed, 40.6% of patients on placebo reached combined BP target values within 4 weeks and were according to the 2018 ESC/ESH guideline not to receive additional antihypertensive medication. Although mean SBP at baseline (measured via uAOBPM) was approximately 157 mmHg across treatment arms, mean 24-hour baseline SBP values were below 140mmHg across treatment arms. This is expected and not considered an issue. As the baseline 24 h mean SBP in study 301 (137 mmHg) corresponded to the 24 h mean SBP defined in the a.m. guideline (≥ 130 mmHg), and it can therefore be concluded that RHT in study 301 was confirmed by ABPM.

- Hydrochlorotiazide was chosen in all participants as part of the SBAT despite stronger diuretics available and needed in some patients.

- Comparative data on efficacy vs. treatment options as recommended by current guidelines are not available. Meaningful controlled data on cardiovascular outcome were not generated. Although this was discussed within this procedure mainly from safety perspective it is considered as well relevant issue for efficacy and will be studied within PASS cat 1 in the post-authorisation phase.

- As patients with cardiovascular instability for several predefined reasons, including heart failure NYHA III and IV or patients after recent stroke or myocardial infarction, were not included, handling of patients with such an event on treatment is unclear and therefore a warning was included in section 4.4 of the SmPC that aprocitentan is not recommended in these patients. Fluid retention by aprocitentan is an aggravating factor in such instances. For these instances the SmPC proposes an individual assessment as to whether treatment with aprocitentan should be continued.

- In the single-blind part 2 of the pivotal study, presumably only participants were blinded to the study treatment, while the investigators, trial management, sponsor and other interested parties were not blinded. The applicant described in detail the changes that were made to the protocol based on the study data or the IDMC suggestion. Taking into account all the amendments made to the protocol during the study, it can be concluded that the study population was narrowed down, especially for safety reasons which was reflected in the SmPC.

The application is essentially based on one pivotal trial with high expectations on compellingness, quality of data and internal and external consistency. Regarding external consistency one study with another ET-1RA in a similar patient group showed consistent results regarding BP lowering efficacy but raised some concerns regarding MACE-+ effects that might have been aggravated by fluid retention (see below, safety).

4.4. Unfavourable effects

• Edema/ fluid retention (class effect with endothelin receptor antagonists) were observed as AE in 23.8% of subjects on aprocitentan 25 mg for 48 weeks during Study 301 with a lower incidence of this AE in subjects

on aprocitentan 12.5 mg vs 25 mg (9% vs 18%) and 2.1% in the placebo group during the 4-week DB part 1 of Study 301. In most of the subjects experiencing edema/ fluid retention, the AEs were mild (62.4%) or moderate (33.5%) in intensity. Severe AEs of edema/ fluid retention were reported in 7 of 170 subjects (4.1%). Six subjects discontinued study treatment prematurely due to edema/ fluid retention. Higher risk of edema/ fluid retention were reported for subjects with high BMI, age > 75 years, CKD stage 3–4, diabetes and, only during the first 4 weeks and especially with 25 mg, subjects with a history of heart failure. A considerable part of subjects (24.7%) did not completely recover at end of study despite strong loop diuretic treatment.

• Mean hemoglobin decrease of approx. 0,8 g/dL (i.e. ~6% decrease as the baseline was ~14 g/dL) was observed in almost all subjects (class effect with endothelin receptor antagonists due to hemodilution). This effect was seen within the first 4 weeks of treatment and stabilized thereafter, without further decrease. Effect was similar at the two doses, and reversible when treatment was stopped. Estimated plasma volume (ePV) increased by 10–11% at the two doses. Effect on hemoglobin concentration was slightly more pronounced in elderly subjects (> 75 years) and subjects with a medical history of cardiac failure or diabetes, and particularly subjects with CKD stage 3–4 (15 – < 60 mL/min/1.73 m2). Six subjects exposed to aprocitentan 25 mg for up to 48 weeks received a blood transfusion (1 during DB part 1 and 5 during SB part 2 of the study). All cases were assessed by the investigator as not related to aprocitentan.

• Heart failure: 19 of 730 subjects (2.6%) had at least 1 treatment-emergent heart failure event across all study parts and treatment groups in Study 301. Following CAC adjudication, 11 of the 19 subjects had heart failure requiring hospitalisation (10 subjects on aprocitentan 25 mg, 1 subject on placebo). Most of the 11 subjects had multiple risk factors, including pre-existing edema (36%), heart failure (45%), baseline eGFR 15 – < 60 mL/min/1.73 m2 (55%), BMI > 35 kg/m2 (55%), age > 65 years (64%) and diabetes (100%). At screening, 91% of the 11 subjects with SAEs of heart failure were receiving beta-blockers and 55% of the subjects were receiving loop diuretics or more than 1 diuretic before switching to standardized background antihypertensive therapy (SBAT). Analysis of the serious hospitalisation for heart failure events over time showed that 50% of the subjects had the event during the first 12 weeks of treatment with no increase in incidence over time. No event of heart failure had a fatal outcome. Two subjects prematurely discontinued study treatment due to serious heart failure.

• MACE: 4 subjects experienced a MACE prior to randomization. 12 of 713 subjects (1.7%) in the aprocitentan 25 mg set had MACE up to 48 weeks of treatment. The proportion of subjects with MACE for different time intervals during treatment with aprocitentan 25 mg was low and no notable trend was observed over time. Furthermore, no imbalance to placebo in the number of MACE was observed for aprocitentan 25 mg in the placebo-controlled parts (DB part 1 and DB-WD part 3) of Study 301.

• Low incidence of liver abnormalities, limited to isolated cases of asymptomatic liver enzyme elevations. No evidence of drug-induced hepatotoxicity.

• Kidney function: Aprocitentan induced a small, dose-dependent initial decline in eGFR, followed by stabilization. A few cases of more pronounced decreases in eGFR occurred, none of them evoking an acute kidney injury. The effect is possibly due to renal hemodynamic effects.

• Some cases of hyperkalemia were reported, posibly due to valsartan administered in subjects with a combination of CKD, diabetes, and beta-blockers.

• There was a serious adverse event of hypersensitivity (allergic dermatitis) requiring hospitalization and medical treatment. The investigator assessed allergic dermatitis as related to aprocitentan.

4.5. Uncertainties and limitations about unfavourable effects

• Overall safety data are deemed insufficient in terms of both, duration and exposure, as only one pivotal study of limited duration is presented, where only 50 patients with rHTN were exposed to aprocitentan 25 mg dose and again, only to a maximum of 11 months. The longest part of the study was uncontrolled, and some of the most important events considered potential safety concerns occurred during this uncontrolled part which makes a safety assessments difficult. The presented development program is deemed limited considering lack of long term safety data, and uncertainties regarding CV mortality and morbidity under aprocitentan treatment. Hence a category 1 PASS was agreed to be conducted post-authorisation with main objective to further characterise the long-term cardiovascular safety of aprocitentan in patients with resistant hypertension.

• There are no placebo- or actively controlled data on safety above >12 weeks within the Phase 2/3 development programme in the target population and no information is available on long term dose related safety when comparing the 12.5 and the 25 mg dose. In this regard, the Applicant has not followed the CHMP advice in 2017. The CHMP strongly recommended to generate comparative data against an active control like spironolactone in patients with preserved renal function or alpha blockers like doxacosin over at least 6 months. At that time the CHMP proposed to integrate an active control arm in study 301 as it was stated:" *an active comparator arm might be the only way in which interpretable long term safety data can be generated*."

• 11 deaths occurred during the development program, all during the pivotal study 301 and all in the aprocitentan groups. 5 of those 11 deaths were adjudicated as MACE, however except of one case where a clear cause of death was described (massive CVI), all other narratives do not allow firm conclusions on the underlying cause of death and it cannot be excluded that all 4 subjects died due to sudden cardiac death. Additionally, all 5 subjects died during the uncontrolled part of the study, and considering a high background risk of CV mortality and morbidity of the population included, establishing causality is difficult. Uncertainty also remains for cardiovascular adverse events (including cases of heart failure and MACE) and the 6 subjects who needed a blood transfusion (1 during DB part 1 and 5 during SB part 2 of Study 301, all exposed to aprocitentan 25 mg). The issue is highlighted by data coming from the literature revealing a negative imbalance for cardiovascular events. In a controlled study with Darusentan, another ET-1 receptor antagonist, when investigated in a similar population (Weber et al., Lancet 2009; 374: 1423–31), 5 cardiac events requiring admission were observed on active treatment (n = 247 at three different dose levels), one sudden death in the placebo arm but no other major cardiac events (n= 132). Two patients on Darusentan with underlying CAD had NSTEMI, associated with fluid retention and heart failure, one patient had atrial fibrillation associated with heart failure. Two patients had fluid retention and heart failure and the authors concluded on aggravation by fluid retention for such events.

• Almost all (10/11) hospitalization for heart failure events occurred in patients being treated with aprocitentan, 6 of them again during the uncontrolled part of the study. Aprocitentan clearly caused dose dependent retention of fluids, and although this side effect may be controlled with diuretics in most cases, it can pose a potentially serious additional risk in patients with heart failure.

• Aprocitentan has not been studied in patients with congestive heart failure NYHA stage III–IV, unstable cardiac function, or with NT-proBNP plasma concentration ≥ 500 pg/mL and should not be used in these patients.

• Results of the TQT study (ID-080-108) showed that administration of aprocitentan was associated with a dose related increase in QTcF that exceeded the threshold of regulatory concern (upper bound of the 90% CI

for ΔΔQTcF > 10 ms) at supratherapeutic doses of aprocitentan (100 mg) and at an aprocitentan concentration of 16.1 µg/mL. Outlier analyses did not reveal a signal of concern.

• An increase in heart rate by about 3 – 4 bpm over the whole day as observed in the TQT study could be relevant in the target population at increased CV risk. It has been estimated that an increase in HR by 10 bpm translates into an increase in CV mortality by 20%, indicating that a potential CV benefit associated with BP reduction might be counterbalanced by this effect. However, an increase in heart rate was not observed in Study 301, where a high percentage of the RHT patients received beta-blockers (median changes at Week 4 during DB part 1 for aprocitentan 12.5 mg, aprocitentan 25 mg and placebo were −3 bpm, −2 bpm, and −2 bpm, respectively).

• Edema/ fluid retention: It is unclear, how to manage AEs of edema/ fluid retention under aprocitentan treatment in subjects, who develop tolerance to chronic therapy with loop diuretics, which is a well-known problem for e.g. furosemide or when thiazide-like diuretics lose their efficacy in subjects with declining kidney function.

• Aprocitentan showed a dose-dependent decrease in eGFR and kidney function; the significance of those findings remains unclear in the context of long term use of aprocitentan and consequently, CV safety considering that patients with renal impairment who received aprocitentan at any dose had a higher reported rate of anaemia, fluid retention and heart failure.

• Other endothelin receptor antagonists have been reported to be teratogenic in animal experiments, clinical experience with pregnancy is very limited.

• There were no effects on fertility or spermatogenesis in male rats and dogs after treatment with aprocitentan in nonclinical toxicology studies and/or adequate safety margins to the maximum recommended human dose (see section 5.3 of SmPC). However, other ERAs have shown an adverse effect on spermatogenesis in humans and/or animals.

4.6. Effects Table

Table X. Effects Table for Aprocitentan

Effect	Short Description	Aprocitentan 12.5 mg	Aprocitentan 25 mg	Control
Favourable Effects				
Change from baseline to Week 4 of double-blind treatment				
Mean trough sitting BP, recorded via unattended automated office blood pressure measurement				
SiSBP at Week 4 (mmHg) FAS **primary endpoint**	mean trough SiSBP	-15.5	-14.9	-11.5
	LS Mean diff vs PBO 97.5% CI P-value	-3.79 - 6.76; -0.82 0.0042	-3.73 - 6.67; -0.78 0.0046	
SiDBP at Week 4 (mmHg) FAS	mean trough SiSBP	-10.8	-10.8	-6.3
	LS Mean diff vs PBO 97.5% CI P-value	-3.94 - 5.57; -2.31 < 0.0001	-4.47 - 6.09; -2.85 < 0.0001	
24 h mean BP recorded via ambulatory blood pressure monitoring				
	24 h mean SBP	-6.74	-8.54	-2.43

Effect	Short Description	Aprocitentan 12.5 mg	Aprocitentan 25 mg	Control
24h mean SBP at Week 4 (mmHg) aFAS	LS Mean diff vs PBO 95% CI P-value	-4.18 - 6.25; -2.12 < 0.0001	-5.90 - 7.94; -3.85 < 0.0001	
24h mean DBP at Week 4 (mmHg) aFAS	24 h mean DBP	-6.50	-7.61	-1.80
	LS Mean diff vs PBO 95% CI P-value	-4.32 -5.66; -2.98 < 0.0001	-5.81 -7.14; -4.49 < 0.0001	
Change from double-blind withdrawal baseline (Week 36) to Week 40				
Mean trough sitting BP, recorded via unattended automated office blood pressure measurement				
SiSBP at Week 40 (mmHg) mFAS **key secondary endpoint**	mean trough SiSBP		-1.2	4.0
	LS Mean diff vs PBO 95% CI P-value		- 5.87 -7.98; -3.76 < 0.0001	
SiDBP at Week 40 (mmHg) mFAS	mean trough SiSBP		-0.5	4.7
	LS Mean diff vs PBO 95% CI P-value		-5.29 -6.72; -3.86 < 0.0001	
24 h mean BP recorded via ambulatory blood pressure monitoring				
24h mean SBP at Week 40 (mmHg) maFAS	24 h mean SBP		-0.10	6.56
	LS Mean diff vs PBO 95% CI P-value		-6.53 -8.50; -4.56 < 0.0001	
24h mean DBP at Week 40 (mmHg) maFAS	24 h mean DBP		-0.5	4.7
	LS Mean diff vs PBO 95% CI P-value		-6.75 -7.98; -5.52 < 0.0001	

Effect	Aprocitentan 12.5 mg	Aprocitentan 25 mg	Control	Aprocitentan 25 mg
Unfavourable Effects				
Number and proportion of patients n [%]	4-week DB part 1 of Study 301			up to 48 weeks of Study 301
N	**243**	**245**	**242**	
TEAEs	67 [27.6%]	90 [36.7%]	47 [19.4%]	504 [70.7%]
SAEs	8 [3.3%]	8 [3.3%]	3 [1.2%]	104 [14.6%]
Discontinuations from study drug due to AE	7 [2.9%]	5 [2.0%]	2[0.8%]	51 [5.8%]
Oedema/ fluid retention	22 [9.1%]	45 [18.4%]	5 [2.1%]	170 [23.8%]
Haemoglobin decreased	6 [2.5%]	0 [0%]	0 [0%]	33 [4.6%]
Anaemia	9 [3.7%]	3 [1.2%]	0 [0%]	73 [10.2%]
Headache	0 [0%]	5 [2.0%]	3 [1.2%]	34 [4.8%]
Upper Respiratory Tract Infection	0 [0%]	6 [2.4%]	4 [1.7%]	31 [4.3%]
MACE	3 [1.2%]	1 [0.4%]	1 [0.4%]	12 [1.7%]
Heart failure	1 [0.4%]	2 [0.8%]	0 [0%]	19 [2.6%]
eGFR < 30 mL/min/1.73m^2	4 [1.7%]	6 [2.6%]	2 [0.9%]	44 [6.4%]
Hepatic disorders	0 [0%]	1 [0.4%]	2 [0.8%]	20 [2.8%]

Effect	Aprocitentan 12.5 mg	Aprocitentan 25 mg	Control	Aprocitentan 25 mg
Treatment-emergent deaths	1 [0.4%]	0 [0%]	0 [0%]	11 [1.5%]

Strengths of evidence
- The safety profile of aprocitentan was characterized at doses of 12.5 mg and 25 mg in Study 301 and at doses of 5 mg, 10 mg, 25 mg, and 50 mg in Study 201.
- Overall, 1220 subjects with HTN were included in the combined safety analyses of Study 301 (N=730) and Study 201 (N=490), of which 1051 subjects were exposed to aprocitentan: 81 subjects to aprocitentan 50 mg, 795 subjects to aprocitentan 25 mg, 325 subjects to aprocitentan 10/12.5 mg, and 82 subjects to aprocitentan 5 mg
- Safety profile of aprocitentan was consistent with the known safety profiles of other endothelin receptor antagonists (ERAs).

Limitations and uncertainties related to risks
- No placebo-controlled long-term safety data during Study 301. The only true placebo-controlled data come from the DB part 1 of the study which lasted only 4 weeks. Second placebo-controlled period was DB-WD part 3 which lasted 12 weeks, however all patients re-randomised to placebo received aprocitentan 25 mg during previous 32 weeks (in the uncontrolled SB part 2) and therefore this group is not suitable for a true placebo comparison.
- The use of aprocitentan is accompanied by one main adverse reaction: the development of edema and/or signs of fluid retention in about one-quarter of the subjects, mostly during the first few weeks of treatment. It is unclear, how to manage AEs of edema/ fluid retention under aprocitentan treatment in subjects, who develop tolerance to chronic therapy with loop diuretics, which is a well-known problem for e.g. furosemide or when thiazide-like diuretics lose their efficacy in subjects with declining kidney function.
- With a limited duration of 48 weeks and a limited number of 730 patients included in Study 301 and without placebo-controlled data across the whole study duration, the treatment-emergent 11 death cases observed during Study 301 are difficult to interpret and a numerical imbalance and/or safety signal for deaths cases in subjects treated with aprocitentan can not be excluded with certainty. The same is true for CV adverse events (including cases of heart failure and MACE) and other AEs following treatment with aprocitentan.
- Aprocitentan has not been studied in patients with congestive heart failure NYHA stage III–IV, unstable cardiac function, or with NT-proBNP plasma concentration ≥ 500 pg/mL. Aprocitentan should not be used in these patients.

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

There is a need for new medicinal products for the treatment of patients with RHT. This is particularly the case for patients with renal failure where alternative options like MRAs, currently not approved for this indication, cannot be used. It is a major advantage of aprocitentan that patients with renal failure down to CKD stage 3–4 (15 – < 60 mL/min/1.73 m2) were included, showed relevant efficacy and an overall favourable renal safety profile.

The magnitude of the effect on systolic and diastolic blood pressure as shown in the pivotal trial per se would be sufficient to assume a clinical benefit on CV outcomes. According to the Applicant's assumptions, the effect is expected to mediate a reduction by 2 CV events per 100 patients over the next 5 years, which would translate into a reduction in the cumulative event rate from 25% to 23% within 5 years. These assumptions are well in line with Canoy D., et al. (Curr Cardiol Rep. 2022; 24(7): 851–860) calculating a 10% decrease in CV events for each 5-mmHg reduction in systolic blood pressure. However, such an assumed benefit has to be weighed against potential adverse events and the uncertainties related to the lack of controlled long-term data. Fluid retention may aggravate heart failure and MACE events.

Importance of unfavourable effects.

Most important unfavourable effects of aprocitentan are the development of edema and/or signs of fluid retention in about one-quarter of subjects with the majority of edema/ fluid retention events starting during the first few weeks of treatment. This may aggravate heart failure and MACE events and is therefore relevant

for the assessment of the benefit risk balance. Although an analysis of individual cases did not specifically raise concerns, the absence of comparative long-term data was an obstacle to clearly assess whether CV events were due to the patient characeristics or whether aprocitentan had an impact on the occurrence of such events. It remains unclear, how to manage AEs of edema/ fluid retention under aprocitentan treatment in subjects, who develop tolerance to chronic therapy with loop diuretics, which is a well-known problem for e.g. furosemide or when thiazide-like diuretics lose their efficacy in subjects with declining kidney function. In about 25% of patients, fluid retention/oedema was resistant to therapy including administration of loop diuretics which may in part but not entirely be attributable to concomitant administration of amlodipine.

Aprocitentan also caused a dose-dependent decrease in eGFR, and both fluid retention and decline in eGFR are known to increase cardiovascular risk in hypertensive patients. Aggravation of heart failure and 5 cases of CV deaths occurred during the treatment with aprocitentan, however, causality and CV safety are difficult to assess due to a lack of controlled data for most of the study duration.

There are other adverse events where the relevance depends on the individual patient characteristics. Among these are the decrease in hemoglobin, the effect on QTcF interval in the TQT study at supratherapeutic doses which may be of relevance in case of overdose.

No signal for major concerns regarding liver toxicity was identified during the study. Hypotension also did not present a significant AE or reason for discontinuations.

4.7.2. Balance of benefits and risks

For the clinical part, a clinically relevant effect of aprocitentan on systolic, diastolic and mean arterial blood pressure has been demonstrated over 24 hours in the target group of patients with RHT. Maintenance of this effect was demonstrated in a 4-week randomized withdrawal setting. A small but relevant additional effect on arterial blood pressure of the 25 mg over the 12.5 mg dose has been demonstrated by 24 h ABPM. The observed blood-pressure lowering effect is considered clinically meaningful and expected to reduce the cardiovascular risk in the target population.

The safety concerns associated with the dose-dependent development of fluid retention/oedema are considered manageable by a number of risk minimisation measures in the SmPC, especially by labelling the 12.5 mg dose as the regular target dose that is only to be increased after cautious evaluation of the individual CV risk and the risk of developing oedema. The potential safety events (heart failure, potential aggravation of MACE) have been identified. Additional information is needed post marketing to further characterise these risks and whether the risk minimisation measures in place can be considered sufficient or may have to be amended. Such data have to be generated in a controlled trial in line with the Applicant´s proposal for a PASS comparing Aprocitentan as approved vs. best standard of care open label. Since the results of the study are key to the benefit-risk profile of the product, Study 401 has been classified as a category 1 study.

The benefit risk balance is considered positive.

4.7.3. Additional considerations on the benefit-risk balance

N/A

4.8. Conclusions

The overall benefit/risk balance of JERAYGO is positive, subject to the conditions stated in section 'Recommendations'.

5. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of JERAYGO is favourable in the following indication(s):

JERAYGO is indicated for the treatment of resistant hypertension in adult patients in combination with at least three antihypertensive medicinal products (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where JERAYGO is marketed, all patients who are expected to use JERAYGO have access to/are provided with the following educational material:

- Patient card

The Patient Card, which is addressed to patients prescribed JERAYGO, should include the following key elements/instructions:

Teratogenicity:

- JERAYGO may harm the development of the unborn child.
- Pregnant women must not take JERAYGO.
- Women of childbearing potential must use a reliable form of birth control (contraception).
- The recommendation for a pregnancy test before initiation of JERAYGO, monthly during treatment, and one month after treatment discontinuation.
- The need to report immediately to the treating physician any pregnancy that may occur.

Liver injury:

- Regular monitoring of liver function is recommended because, like other medicines of the same class, JERAYGO might cause liver injury.
- Description of the signs that can occur in case of liver problems.

The need to report any of the signs that could be due to liver problems to the treating physician

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Interventional post-authorisation safety study (PASS): In order to further characterise the long-term cardiovascular safety of aprocitentan in patients with resistant hypertension, the MAH should conduct and submit the results of a randomized, active-controlled study in adult patients with resistant hypertension, according to an agreed protocol.	Final report: 31 March 2031

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that aprocitentan in comparison to the known derivative macitentan approved previously authorised as a medicinal product in the European Union is to be qualified as a new active substance as it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substance.