16 December 2021
EMA/36625/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tepmetko

International non-proprietary name: tepotinib

Procedure No. EMEA/H/C/005524/0000

Note

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

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Administrative information

Name of the medicinal product:	Tepmetko
Applicant:	Merck Europe B.V. Gustav Mahlerplein 102 Ito Toren 1082 MA Amsterdam NETHERLANDS
Active substance:	Tepotinib hydrochloride monohydrate
International Non-proprietary Name/Common Name:	tepotinib
Pharmaco-therapeutic group (ATC Code):	protein kinase inhibitors, other protein kinase inhibitors (L01EX21)
Therapeutic indication(s):	Tepmetko as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	225 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/PE/PVDC/PE/PVC/alu)
Package size(s):	60 tablets

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
BOR	Best overall response
CF1/2/3	Capsule formulation 1/2/3
CL	clearance
C_{max}	maximum plasma concentration
COVID-19	Coronavirus Disease 2019
CR	Complete response
CrCl	Creatinine clearance
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
ctDNA	Circulating tumour DNA
CV	coefficient of variation
CYP	cytochrome P450
DCR	Disease control rate
DDI	drug-drug interaction
DOR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13
EQ VAS	EuroQol visual analog scale
EQ-5D-5L	EuroQol Five Dimension Five Level Scale
F	bioavailability
FIH	first-in-human
GCN	Gene copy number
GCP	Good Clinical Practice
HGF	Hepatocyte growth factor
IAP	Integrated analysis plan
IC_{50}	concentration exerting 50% inhibition
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRC	Independent Review Committee

ITT	Intention-to-Treat
ITT-02 Apr 2019	The ITT analysis set restricted to subjects who received a first dose of tepotinib before 02 April 2019
ITT-02 Oct 2019	The ITT analysis set restricted to subjects who received a first dose of tepotinib before 02 October 2019
L−	Liquid biopsy negative
L+	Liquid biopsy positive
LBx	Liquid biopsy
LC-SCRUM	Lung Cancer Genomic Screening Project for Individualized Medicine
LS	Least square
MATE	Multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal-epithelial transition factor
METex14	MET exon 14
MMRM	Mixed-effect model repeated measures
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
OCT	Organic cation transporter
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PE	Polyethylene
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	Permeability glycoprotein
PGx	Pharmacogenetics
PK	Pharmacokinetic
popPK	Population pharmacokinetic
PPI	Proton pump inhibitor
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QbD	Quality by design
QTcF	Fridericia's corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SD	Stable disease
SmPC	Summary of Product Characteristics
SOC	System organ class
T−	Tumour tissue biopsy negative
T+	Tumour tissue biopsy positive
TBx	Tumour tissue biopsy
TEAE	Treatment-emergent adverse event
TF1/2/3	Tablet Formulation 1/2/3
t_{max}	time to reach the maximum plasma concentration

UGT	uridine glucuronosyltransferase
ULN	Upper limit of normal
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Europe B.V. submitted on 5 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Tepmetko, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 December 2019.

The applicant applied for the following indication:

"Tepmetko is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations."

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 P/0279/2018 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.

1.5. Applicant's requests for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. New active Substance status

The applicant requested the active substance tepotinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. 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**
17 December 2015	EMEA/H/SA/3200/1/2015/III	David Brown; Armin Koch
21 April 2017	EMEA/H/SA/3200/2/2017/I	Dieter Deforce; Sheila Killalea
22 June 2017	EMEA/H/SA/3200/1/FU/1/2017/II	Carin Bergquist; Paolo Foggi
18 October 2018	EMEA/H/SA/3200/3/2018/HTA/II	Pierre Demolis; Martin Mengel
27 February 2020	EMEA/H/SA/3200/3/FU/1/2020/II	Armin Koch; Serena Marchetti

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

The applicant received Scientific Advice on the development of Tepotinib for treatment of patients with advanced or metastatic (stage IIIB/IV) non-small cell lung cancer (NSCLC) whose tumours harbour MET exon 14 skipping alterations from the CHMP on several occasions as follows

EMEA/H/SA/3200/1/2015/III - Scientific advice was sought on

- pre-clinical development, including metabolites, drug interactions, and dose
- clinical development strategy including conditional MA, phase 2 historical control in the proposed open-label, multicenter, single-arm Phase 2 study and population.

EMEA/H/SA/3200/2/2017/I Scientific advice was sought on

- quality development including proposed drug substance starting materials for the intended commercial synthesis process

EMEA/H/SA/3200/1/FU/1/2017/II Scientific advice was sought on

- clinical development including the proposed clinical pharmacology package, DDI, patients with renal impairment only, assessment of cardiac safety

EMEA/H/SA/3200/3/2018/HTA/II Scientific advice was sought on

- clinical development including conditions to support CMA, historical control strategy including relevant available therapies in 1st -3rd Line NSCLC, confirmatory data collection, population definition, adequacy of safety database size for CMA

EMEA/H/SA/3200/3/FU/1/2020/II Scientific advice was sought on

Acceptability of clinical data and supportive real-world, published literature, intra-study data in the 1st line, 2nd line, and 3rd line treatment settings to support registration of tepotinib, via a conditional marketing authorization (CMA), for treatment of patients with advanced NSCLC with METex14 skipping alterations. Introduction of a new product formulation (TF3) during generation of confirmatory evidence and for MAA. Proposal of a single dose reduction level of 250 mg for the management of

Adverse Events following the administration of the recommended clinical dose of 500 mg, and Safety data pooling strategy.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Karin Janssen van Doorn

The application was received by the EMA on	5 November 2020
The procedure started on	26 November 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 February 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 February 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 March 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 July 2021
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	30 August 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 September 2021
The CHMP agreed on a list of outstanding issues in writing and in an oral explanation to be sent to the applicant on	16 September 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 October 2021
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	28 October 2021
SAG experts were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	03 November 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	09 November 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	16 December 2021

a marketing authorisation to Tepmetko on	
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	16 December 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The sought indication is: Tepmetko is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations.

2.1.2. Epidemiology

Lung cancer remains the leading cause of cancer death in men and the second leading cause of cancer death in women worldwide, with 2.1 million new cases and 1.8 million deaths estimated globally for 2018 (Ferlay 2018).

NSCLC accounts for 85% of all lung cancer cases (Navada 2006, Sher 2008) and the proportion of NSCLC patients with Stage IV disease (metastatic) at diagnosis has been reported in the range of 47% to 55%. Approximately 3% of NSCLCs harbour MET exon 14 (METex14) skipping alterations.

2.1.3. Biologic features

MET exon 14 (METex14) skipping alterations leads to a truncated MET receptor lacking the exon 14 encoded sequences. Deletion (i.e., skipping of exon 14) results in oncogenic activation of MET by expression of a truncated receptor with increased stability, as well as augmented and prolonged signalling capability, seemingly turning MET into an oncogenic driver (Cortot 2017).

2.1.4. Clinical presentation

Early and locally advanced non-small cell lung cancer (NSCLC) is potentially curable with surgery or curative radiotherapy for early disease (stage I and II), and adjuvant systemic therapy (mainly stage II-III, cisplatin doublets for three-four cycles resulting overall in 4%–5% absolute survival improvement at 5 years). Locally advanced disease (stage III) is frequently treated with concurrent definitive chemoradiotherapy (CRT), also when deemed unresectable.

2.1.5. Management

For advanced disease (typically nonresectable stage IIIB and stage IV), cure is not expected due to the extension of disease, and systemic treatments are administered with the aims of mitigating symptoms and extending lifespan. The recent non-biomarker selected standard for patients without major comorbidities was chemotherapy with a platinum doublet. Benefit in survival (versus best supportive care) has been observed for such chemotherapy (HR 0.77, a 1-year survival gain of 9% and an increase from 4.5 months to 6 months in median survival; NSCLC Meta-Analysis Collaborative group, 2008). For combinations of cisplatin/carboplatin and paclitaxel/docetaxel/gemcitabine response rate (ORR 19%) and survival (OS median 8 months) did not differ significantly between regimens in patients who had not received prior chemotherapy (Shiller 2002). In a more recent RCT, higher activity was observed for chemotherapy (carboplatin/nab-P vs. carboplatin/paclitaxel; ORR 33% vs 25%) with longer OS medians (12 vs 11 months).

The advent of immune therapy has reshaped the first-line advanced treatment landscape. Combinations of PD-1/PD-L1/CTLA-4 directed therapies and platinum doublets have achieved ORR:s in the 40%-55% range, DoRs of 8-13 months, and notably OS medians of frequently 20+ months (14-30). For patients with ≥ 50% PD-L1 expression, pembrolizumab monotherapy is an option, with similar outcomes.

Second line options include checkpoint inhibitors and docetaxel/ramicirumab-docetaxel with ORRs of 14% -23%, DORs of 16-19 months (longer for pembrolizumab in PD-L1 ≥ 1%; KEYNOTE-010), and OS medians of about 12 months, and platinum doublets for patients who received checkpoint-inhibitor monotherapy first line.

Currently there is no available treatment option that specifically targets advanced NSCLC harbouring METex14 skipping alterations in EU. The median OS of METex14 NSCLC patients who never received a MET inhibitor was reported to be in the range of 8 to 11 months (Awad 2019, Wolf 2018). Furthermore, METex14 skipping alterations have been found to be most frequently reported in elderly patients (Schrock 2016, Awad 2019).

2.2. About the product

Tepotinib is a reversible Type I adenosine triphosphate (ATP)-competitive small molecule inhibitor of MET. Tepotinib blocked MET phosphorylation and MET-dependent downstream signalling such as the phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular-signal regulated kinase (MAPK/ERK) pathways in a dose-dependent manner. Tepotinib demonstrated pronounced anti-tumour activity in tumours with oncogenic activation of MET, such as METex14 skipping alterations.

The CHMP adopted a positive opinion for the following indication:

Tepmetko as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

Treatment must be initiated and supervised by a physician experienced in the use of anticancer therapies.

Prior to initiation of treatment with Tepmetko the presence of *MET*ex14 skipping alterations should be confirmed by a validated test method.

- Posology

The recommended dose is 450 mg tepotinib (2 tablets) taken once daily. Treatment should continue as long as clinical benefit is observed.

If a daily dose is missed, it can be taken as soon as remembered on the same day, unless the next dose is due within 8 hours.

- *Dose modification for adverse reactions*

The recommended dose reduction level for the management of adverse reactions is 225 mg (1 tablet) daily. Detailed recommendations for dose modification are provided in the table hereafter.

Adverse reaction	Severity	Dose modification
Interstitial lung disease (ILD) (see section 4.4)	Any grade	Withhold Tepmetko if ILD is suspected. Permanently discontinue Tepmetko if ILD is confirmed.
Increased ALT and/or AST without increased total bilirubin (see section 4.4)	ALT and/or AST greater than 5 times up to 20 times ULN	Withhold Tepmetko until recovery to baseline ALT/AST. If recovered to baseline within 7 days, then resume Tepmetko at the same dose; otherwise resume Tepmetko at a reduced dose.
	ALT and/or AST greater than 20 times ULN	Permanently discontinue Tepmetko.
Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or haemolysis (see section 4.4)	ALT and/or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN	Permanently discontinue Tepmetko.
Other adverse reactions (see section 4.8)	Grade 3 or higher	Reduce Tepmetko to 225 mg until the adverse reaction recovers to ≤ grade 2. A temporary interruption of Tepmetko treatment for no more than 21 days can also be considered.

ULN=upper limit of normal

2.3. Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

The applicant claims a positive benefit-risk arguing that tepotinib is a highly selective, targeted therapy, with substantial and sustainable efficacy, tolerable and manageable safety profile, and an uncomplicated mode of administration.

- It is likely that the applicant will be able to provide comprehensive data. The applicant proposed that comprehensive data would come from:

-efficacy and safety from confirmatory cohort C of the VISION study; results from the interim analysis are expected in March 2021

-extended follow-up (up to 2 years) of patients included in cohort A from the VISION;

-additional data from a pan-European disease registry to overcome the limitations of the 3 NISs presented in the dossier. According to the applicant, it should be reasonable and feasible to plan to

include around 150 patients on either tepotinib or standard of care per year into the registry (over a minimum 4.5-year recruitment period). The total number of patients in the registry expected to be approximately 700.

- Unmet medical needs will be addressed, as the applicant considers the absence of approved therapies in EU specifically in patients with MET exon 14 skipping alterations.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. The applicant considers that the benefit-risk profile of tepotinib in patients with advanced NSCLC harboring METex14 skipping alterations supports the request to make this medicinal product available as early as possible to this population with high unmet medical need. Available nontargeted therapies do not satisfactorily address the medical need of this severely diseased and elderly population.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 225 mg of tepotinib. The product contains the hydrochloride hydrate form of the active substance.

Other ingredients of the tablet core are: mannitol, colloidal anhydrous silica, crospovidone, magnesium stearate and microcrystalline cellulose. Ingredients of the film-coating are: hypromellose, lactose monohydrate, macrogol, triacetin, red iron oxide (E172) and titanium dioxide (E171).

The product is available in aluminium/polyvinyl chloride-polyethylene-polyvinylidene chloride-polyethylene-polyvinyl chloride (Al/PVC-PE-PVDC-PE-PVC) blister as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of the active substance is 3-{1-[(3-{5-[(1-*m*ethylpiperidin-4-yl)methoxy]pyrimidin-2-yl}phenyl)methyl]-6-oxo-1,6-dihydropyridazin-3-yl}benzonitrile hydrochloride hydrate corresponding to the molecular formula $C_{29}H_{28}N_6O_2 \cdot HCl \cdot H_2O$. It has a molecular mass of 547.05 g/mol and the following structure:

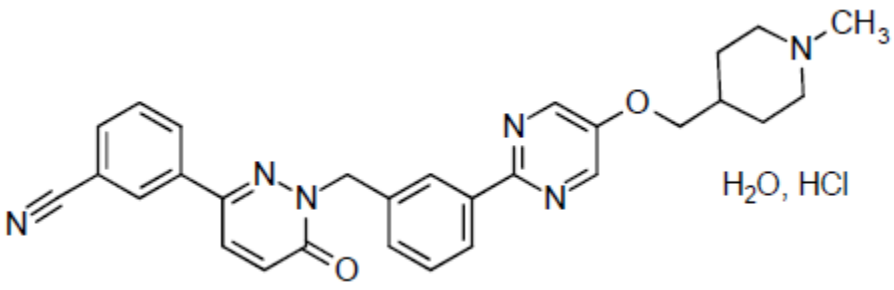


Figure 1: active substance structure

The chemical structure of tepotinib was elucidated by a combination of nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry, infrared (IR) spectroscopy, ultraviolet-visible (UV-Vis)

spectroscopy, ion-exchange chromatography, Karl Fischer titration and elemental analysis. The solid state properties of the active substance were measured by X-ray diffraction.

The active substance (AS) is a white to off-white non-hygroscopic powder. The active substance is classified as soluble in dimethyl sulfoxide and slightly soluble in ethanol and methanol. In contrast, it is either only very slightly soluble or practically insoluble in 2-propanol, acetonitrile, acetone, and tetrahydrofuran. The active substance is freely soluble in aqueous hydrochloric acid 25% v/v (enhanced solubility due to 2nd protonation) and very slightly soluble in pure water. According to the solubility classification of Ph. Eur., the active substance is very slightly soluble in the presence of emulsifying agents such as sodium taurocholate and lecithin as contained in fed state simulated intestinal fluid. In other biorelevant dissolution media, e.g., simulated gastric fluid without pepsin, simulated intestinal fluid without pancreatin and fasted-state simulated intestinal fluid, the active substance is practically insoluble.

Tepotinib has a non - chiral molecular structure.

Polymorphism has been observed for tepotinib.

2.4.2.2. Manufacture, characterisation and process controls

Full information on the manufacturing of the active substance has been provided in the dossier. A single manufacturer of the active substance is used.

The active substance is synthesized in five chemical transformation steps followed by a salt-forming step, using well defined starting materials with acceptable specifications.

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 new active substances.
Potential and actual impurities were well discussed with regards to their origin and characterised.

QbD elements have been used in the process development, however no regulatory flexibility is claimed.

The active substance is packaged in double low-density polyethylene (LDPE) bags (primary packaging), sealed with a plastic binder. The LDPE bags are stored in high-density polyethylene (HDPE) drums (secondary packaging). Primary packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

2.4.2.3. Specification

The active substance specification includes tests for: description, identity (FT-IR, HPLC), identification of chloride (chemical precipitation test), assay (HPLC), impurities (HPLC), residual solvents (HS-GC), water content (KF), heavy metals (ICP-MS), microbial limits (Ph. Eur.), residue on ignition (Ph. Eur.), polymorphic form (XRPD) and particle size distribution (laser diffraction).

The active substance specifications are based on the active substance critical quality attributes (CQA).

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. Fate and purge experiments have been agreed based on the questions raised on the control strategy of the active substance, and these points are proposed as quality recommendations.

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 and impurities testing has been presented.

Batch analysis data on 21 commercial scale batches and other supportive batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from six commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 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.

The following parameters were tested: description, identification, assay, impurities, water content, microbial limits, polymorphic form and particle size distribution. The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications and no trends have been observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions (dry heat, humid heat, oxidative and hydrolysis were also provided on one batches. The test results obtained from the stress stability studies confirm that the active substance is sensitive to harsh oxidative conditions and slightly sensitive to basic hydrolytic conditions, but is not sensitive to dry heat, humid heat, or light. Its polymorphic form and water content did not change during stress stability studies.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months with no special storage conditions in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is available as white-pink, oval, biconvex film-coated tablets, with embossment "M" on one side and plain on the other side. The film-coated tablets have a length of approximately 18 mm, a width of approximately 9 mm, and a thickness of approximately 7 mm.

Pharmaceutical development of the finished product contains QbD elements.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Compatibility between the active substance and excipients has been validated in stability studies.

The active substance is classified as a BCS Class IV substance (low solubility and low permeability). The development of the dissolution method supports the selection of the proposed dissolution test conditions for robust QC testing of the finished product. The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is aluminium/polyvinyl chloride-polyethylene-polyvinylidene chloride-polyethylene-polyvinyl chloride (Al/PVC-PE-PVDC-PE-PVC) blister. The material complies with Ph.Eur.

and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of five main steps: dry granulation (weighing, sieving, blending, roller compaction), outerphasing (weighing, sieving, blending), tableting, film-coating and packaging. The process is considered to be a standard manufacturing process.

The manufacturing process of the finished product was successfully validated on four consecutive production-scale batches. 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 include appropriate tests for this kind of dosage form: description, dimensions, identification (HPLC, UV), assay (HPLC), degradation products (HPLC), resistance to crushing (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur) and microbial limits.

The active substance is classified as non-hygroscopic in accordance with Ph. Eur. Furthermore, the active substance is not sensitive to humid heat (70°C/75% RH) – results of stress studies show no significant changes. The water content of the film-coated tablets remains constant even after storage under stress conditions with humid heat (70°C/75% RH) in open containers for four weeks. The water content may impact the hardness of the film-coated tablets, which is adequately controlled by the parameter resistance to crushing. Based on the above scientific rationale, water content needs not be specified for the finished product.

The potential presence of elemental impurities in the finished product has been assessed 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 polymorphic form of the active substance is controlled by the specification of the active substance. For the DP, the desired polymorphic form was confirmed during development as a parameter during release and stability testing under long-term and accelerated storage conditions. Also, during stress studies with light (photostability), dry heat, humid heat and freeze-thaw cycles, no change of the polymorphic form was observed. Therefore, polymorphic form needs not be specified for the finished product.

Residual solvents in the active substance are controlled either by the specification of intermediate and active substance with acceptance criteria at or below the limits recommended by ICH Q3C. Furthermore, organic solvents are not used during manufacture of the finished product nor are they expected to form during storage of the finished product. Therefore, residual solvents do not need to be specified for the finished product.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed 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 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 and impurities testing has been presented.

Batch analysis results are provided for 16 commercial scale batches as well as a number of supportive batches confirming used during the development. The consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from 3 commercial scale batches (except for one batch which was manufactured at half-commercial scale) of finished product stored for up to 24 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, degradation products, resistance to crushing dissolution and microbial limits. The analytical procedures used are stability indicating.

All results available so far met the acceptance criteria and were well within specification. With the exception of a slight decrease regarding resistance to crushing at accelerated conditions, no trend or influence of the applied storage conditions on the stability-indicating parameters was observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Stress stability studies were performed to deliver insights into the chemical and physical stability of the finished product. The studies included testing on sensitivity to light (photostability), oxidative stress, dry heat, humid heat, and freeze-thaw cycles.

The test results obtained from the stress stability studies confirm that the finished product is sensitive to harsh oxidative conditions and humid heat (dissolution only), but not sensitive to dry heat, light or freeze and thaw cycles. Polymorphic form did not change during stress stability studies.

Based on available stability data, the proposed shelf-life of 36 months and no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Adventitious agents

It is confirmed that 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 and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces with regulatory flexibility in mind were claimed for the manufacturing process of the active substance, nor for the finished product.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to purge studies of active substance impurities. These points are put forward and agreed as three recommendations relating to impurity purge experiments and impact on active substance specification for future quality development.

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 TSE safety.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Fate and purge experiments have been agreed based on the questions raised on the control strategy of the active substance.

2.5. Non-clinical aspects

2.5.1. Introduction

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Primary pharmacodynamics *in vitro*

The binding interaction of tepotinib free base to the MET kinase domain was investigated by X-ray structure analysis that indicated that tepotinib is a Type I, ATP competitive, reversible inhibitor of MET. In ATP competition studies it was shown that increasing concentrations of ATP suppressed inhibition of MET activation induced by tepotinib, indicating that tepotinib acts via an ATP competitive mechanism (Bladt 2013). Surface plasmon resonance measurements performed with the MET kinase domain (amino acids 1048-1348) also demonstrated reversible binding of tepotinib to MET. Furthermore, since truncated MET receptors lacking exon 14 encoded sequences still express a wild-type kinase domain, the performed X-ray crystal structure analyses are considered to reflect binding of tepotinib to full-length MET as well as MET with exon 14 skipping. However, the biochemical binding of tepotinib to METex14 skipping alterations was not tested, which is considered acceptable.
In a biochemical assay, tepotinib and its free base showed similar and dose-dependent MET kinase inhibitory activity with IC50 values around 1.8 and 3.7 nM, respectively. In kinase screens tepotinib at 1 µM showed inhibiting activity, by more than 50%, for 5 out of >400 kinases tested: Axl, IRAK1, IRAK4, TrkA and TrkC. Out of these 5, only IRAK4 and TrkC were inhibited by more than 75%, in one

out of two kinase screens. 1 µM corresponds to approximately 19-fold of the average maximal free tepotinib concentration achieved at steady state in patients with the daily dose of 500 mg. At 0.1 µM, tepotinib did not inhibit any kinase unrelated to MET within a panel of 298 kinases. From the kinase profiling data tepotinib appears as a selective MET inhibitor. This indicates that the observed antitumour activity of tepotinib in preclinical models and in patients likely can be attributed to the inhibition of MET.

Tepotinib showed dose dependent inhibition of MET kinase activity at the tumour cellular level as well as affecting the tumour cell proliferation, anchorage independent growth and migration at a single-digit nanomolar range. The presence of serum proteins had a moderate impact on the inhibitory activity of tepotinib. The inhibitory activity of tepotinib was observed irrespective of the mode of MET activation in cell lines with ligand-dependent and -independent MET activation (including *MET*ex14 skipping and high-level *MET* gene amplification).

In addition to inhibition of MET phosphorylation, tepotinib was shown to also inhibit the MET downstream signal transduction as phosphorylation of the adaptor/scaffold protein Gab1, activation of anti-apoptotic Akt signalling, and ERK phosphorylation. All at single-digit or sub- nanomolar IC50 level.

Primary pharmacodynamics *in vivo*

Tepotinib was tested in a variety of different murine models with human tumour cell line xenografts derived from various cancer indications (including NSCLC, gastric cancer and HCC). Tumours were inoculated subcutaneously (if not otherwise indicated) into immunocompromised mice (NOD-SCID, CD1-nude, Balb/c nude, humanized HGF SCID). No treatment-related body weight loss was observed in the described studies with tepotinib (up to 200 mg/kg, QD, po), indicating that tepotinib was well tolerated.

Tepotinib was tested in tumours with different mechanism of MET activation: Studies were carried out on tumours with oncogenic alterations of the MET gene such as *MET*ex14 skipping alterations, high-level *MET* gene amplification (here defined as a MET GCN > 10), and *MET* fusion (anecdotally reported in patients from various cancer indications including NSCLC); on tumours with co-expression of MET/HGF (autocrine MET activation); and on tumours with MET overexpression without underlying oncogenic alterations. About 15-21% of NSCLC tumours harbouring METex14 skipping alterations also have a concomitant MET gene amplification.

The tumour reducing effect by tepotinib was most pronounced in treated mice inoculated with tumours harbouring oncogenic MET alterations. Only two models with *MET*ex14 skipping alteration were included, assumingly due to a limited availability of such tumour models. The observed efficacy level in these two models ranged from complete tumour regression in Hs746T (gastric cancer origin with *MET*ex14 skipping & high-level *MET* gene amplification) in 10/10 mice at 6 mg/kg/qd, T/C 3% with regressions in 5/10 mice at 3 mg/kg/qd; to tumour growth inhibition with a T/C of 30% at highest tested dose, 100 mg/kg/qd, without tumour regression, in H596 (NSLC origin with *MET*ex14 skipping). However, the presence of two additional oncogenic alterations that are not known to be targeted by tepotinib, a phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) mutation and expression of high-levels of EGFR, likely affected the outcome in the H596 model. Three tumours with high-level *MET* gene amplification were tested. In two models , complete tumour regression was observed: in the EBC-1 (NSCLC) in 10/10 mice at 25 mg/kg/qd, in 7/10 at 15 mg/kg/qd and in 5/10 at 6 mg/kg/qd, with similar T/C of 48% or 43% for tepotinib or its free base, respectively; and in the MHCC97H (HCC) in 9/10 mice at 100 mg/kg/qd, with no tumour recurrence in a 3-mo follow-up. In addition, in an orthotopic intrahepatic tumour model with the MHCC97H cell line, tumour regression was achieved in 9/9 mice of which 2/9 showed complete regression. In addition, serum AFP levels and number of lung metastasis foci were significantly reduced. In the third model with high-level *MET* gene

amplification, tepotinib at 25 and 200 mg/kg/qd led to tumour growth inhibition with T/C values of -46% and -52% at Day 11, respectively, and partial tumour regressions (defined as a reduction of tumour volume of ≥ 50% at the end of treatment relative to the start of treatment) in 4/8 mice at both doses. Thus, in addition to achieving only partial tumour regression, no dose response was observed. This is in contrast to the complete tumour regressions observed in the EBC-1 and MHCC97H, as well as the Hs746T models. In a syngeneic (murine tumour) mouse model carrying a MET gene fusion, complete tumour regression was observed in 4/8 mice at 25 mg/kg/qd, including regression also in larger tumours.

In tumours with upregulated expression levels of HGF or strong overexpression of MET not caused by underlying oncogenic alterations of the *MET* gene, the antitumour activity was weaker without complete tumour regressions at doses up to 200 mg/kg/qd.

In studies in PDX tumour models derived from brain metastasis, which were not preselected based on molecular markers or profile but only retrospectively analysed for cancer-specific mutations, it was found that only the two explants retrospectively shown to carry oncogenic MET alterations responded to the tepotinib treatment, confirming the results from the xenograft tumour cell line model studies. In follow-up studies, tepotinib resulted in complete subcutaneous tumour regression and 63 and 84% median intra cranial tumour volume change at 125 mg/kg/qd for the two explants respectively.

Tepotinib was also tested in models without oncogenic MET alterations but with HGF/MET autocrine loops or MET overexpression (derived from NSCLC, glioblastoma, pancreatic carcinoma). In these models, tumour growth inhibition was also observed but at a modest level (T/C 17, 30, 60 and 22% at 200 mg/kg/qd for the models H441, U-87 MG, KP-4 and KP-4 (PK/PD)) with a somewhat unclear dose dependency and without or only partial tumour regressions.

Tepotinib treatment was not able to inhibit the tumour growth in NSCLC derived models with high MET expression levels and basal MET activation coexisting with oncogenic EGFR kinase domain mutations, despite the high MET expression levels and basal MET activation. The applicant conclude the in vivo PD data indicate that MET or HGF expression levels do not reliably predict MET dependency and may therefore not be ideal predictive biomarkers for selecting patients to tepotinib monotherapy. This is agreed.

For PK/PD purposes, tepotinib treatments were tested in two xenograft models, one more and one less sensitive to tepotinib treatment. The latter was employed to achieve a more conservative estimate of the tepotinib dose-efficacy relationship. In the tepotinib sensitive Hs746T model, a tepotinib dose at 10 mg/kg or above resulted in more than 90% inhibition of MET phosphorylation for a period of at least 72 h. The inhibition of the proangiogenic production of human IL-8 showed a similar pattern, but the plasma levels of tumour- derived IL-8 returned to baseline values earlier than MET phosphorylation. A single dose of tepotinib transiently also inhibited histone H3 phosphorylation and cyclin D1 expression as well as caused a transient increase in p27. At the highest dose some of the effects were more persistent over the 96 hours studied. In the more modestly tepotinib sensitive KP-4 model, the dose dependent antitumour activity by tepotinib corresponded to the inhibition of MET phosphorylation. A persistent inhibition of MET phosphorylation of >95% for at least 24 hours was only observed at the highest dose, 200 mg/kg. In both models, higher tepotinib concentrations were found in the tumour than in the plasma.

PK/PD modelling revealed that tepotinib plasma concentrations of 215 and 454 ng/mL were predicted to achieve 90 and 95% maximum tumour growth inhibition, corresponding to tumour regression in the KP-4 model. The preclinical PK/PD model established that a continuous >95% target inhibition is required for achieving tumour regression. Taking into account differences in plasma protein binding between mice and man these PK/PD modelling results corresponds to tepotinib plasma concentrations of 390 and 823 ng/mL in humans. In consecutive simulations based on human population PK/PD

model, it was indicated that ≥90% of patients achieve ≥95% target inhibition at the suggested clinical dose of 500 mg.

From PK/PD studies it could be concluded that the contribution of major human metabolite MSC2571109A to the anti-tumour activity of tepotinib can be considered to be negligible. This was based on that although MSC2571109A had almost the same potency as tepotinib in the in vitro assay, MSC2571109A did not show anti-tumour activity in vivo, despite achieving relevant exposure levels in plasma. The difference of anti-tumour activity could possibly be explained by that concentrations of MSC2571109A were lower in tumour tissue than in plasma, while tepotinib is enriched in tumour tissue. Moreover, the levels of MSC2571109A dropped substantially 24 hours after dosing, indicating fast elimination.

The pharmacological activity of MET in the species used in the toxicological testing, rat, rabbit and dog, was not investigated in any of the pharmacological studies. In the toxicological section, the applicant is requested to discuss the lack of information on pharmacological relevance of the selected species.

In summary, dose-dependent tumour suppressing efficacy of tepotinib was observed in various tumours, and for all tested mechanisms of MET activation. The PD data provide non-clinical support for targeting oncogenic MET alterations for achieving anti-tumour effects in the clinic, in tumours "oncogenically addicted" to MET.

2.5.2.2. Secondary pharmacodynamic studies

Tepotinib was evaluated in vitro for potential off target effects on a broad class of pharmacologically active cell receptors, ion channels, transporters, and enzymes. Only two receptors (melatonin receptor ML2 (MT3=Melatonin binding site 3) and imidazoline receptor I1 were identified with a ratio of binding IC_{50} off-target/binding IC_{50} MET kinase below 50. However, ML2 (MT3) is poorly characterized, and the downstream effects of its modulation remain unclear. The clinical relevance of a possible interaction with receptor I1, known to be involved in blood pressure regulation, was addressed in cardiovascular studies in rats and dogs.

In a cutaneous wound healing model in mouse tepotinib at 25 or 50 mg/kg/qd for 3 or 10 days (n=10/group) had no effect on the wound healing parameters studied in comparison to vehicle.

2.5.2.3. Safety pharmacology programme

Safety pharmacology in vitro assays addressing the cardiovascular system showed that tepotinib inhibited Kv11.1 (hERG) channel current with an IC_{50} of 1.2 µM. This concentration is 24-fold higher than the steady state mean human free C_{max} of 0.05 µM. In addition, tepotinib inhibited cardiac ion channel hNav1.5 (up to 26%) at the tested concentration of 10 µM. Moreover, a slight increase in the refractory period of guinea pig papillary muscles was recorded up to 11% at 10 and 30 µM tepotinib. These effects were observed at concentrations more than 100-fold higher than the steady state mean free C_{max} of 0.05 µM in patients.

No effects were observed up to a concentration of 2.7 µM of the main human metabolite MSC2571109A in a hERG assay. This concentration is approximately 385-fold higher than the measured free C_{max} of 0.007 µM MSC2571109A at steady-state at tepotinib dose of 500 mg,

In an oral cardiovascular study in rats by telemetry no effects on heart rate and arterial blood pressure were seen following a once daily oral administration of tepotinib of up to 50 mg/kg/day for 8 days. Total and free C_{max} were respectively 325 ng/mL and 13 ng/mL i.e., approximately half of the steady state mean free C_{max} of 25.8 ng/mL determined in humans. No effect on heart rate, arterial blood

pressure, and electrocardiogram (ECG) parameters were seen in dogs following a single oral administration of tepotinib at 70 mg/kg. Exposure to tepotinib in the dog was relatively low (i.e. total and free C_{max} were respectively 67 ng/mL and 4 ng/mL).

No significant effects were seen in a respiratory study in male rats following a single oral administration of tepotinib up to 200 mg/kg. No effects on the central nervous system were seen in a functional observation battery study in rats following a single oral administration of tepotinib up to 200 mg/kg. Exposure data are not available from these studies. However, a C_{max} of approximately 560 ng/mL for males and 936 ng/mL for females can be calculated (assuming PK dose proportionality) using mean exposure data from an oral 4-week repeat-dose toxicity study in rats conducted under similar experimental conditions.

2.5.2.4. Pharmacodynamic drug interactions

No Pharmacodynamic drug interactions relevant to the applied indication have been submitted.

2.5.3. Pharmacokinetics

Methods of analysis

Liquid chromatography methods with tandem mass spectrometric detection (LC-MS/MS) for the quantification of tepotinib (free base) were validated in rat, dog, and rabbit plasma to support safety/toxicity studies in those species.

Absorption

In nonclinical species, peak plasma concentrations were observed at ≤ 1 hour in mice and up to 12 hours in female monkeys (mean t_{max}). The data generally indicate a rather slow absorption. The oral bioavailability ranged from slightly more than 20% in male rats, female monkeys and dogs, to about 55% in female rats

Distribution

The in vitro plasma protein binding of tepotinib was moderate to high across species, with unbound fractions (f_u) ranging from 3% in mouse to 7% in dog and between 1.6 and 3.4% in human. The mean f_u of the major circulating metabolite (MSC2571109A) in human plasma (1.2%) was even lower compared to tepotinib and ranged between 1.0% and 2.5% in the investigated animals (mouse, rat, and dog)

Tepotinib demonstrated a very high binding to rat brain tissue in a concentration-independent manner. The unbound fraction in brain tissue ($f_{u,br}$) in equilibrium was 0.35% (i.e., 11-fold lower than the 4% f_u value in rat plasma.

Distribution studies with tepotinib in rats (whole-body autoradiography and dissection) revealed that total radioactivity was mainly present in the gastrointestinal tract after oral dosing. In the remaining body, highest concentrations of radioactivity were detected in the liver, lungs, and kidneys and, 24 hours after administration, in the lymph nodes. In pigmented animals, medium levels of radioactivity were found in the eyes and skin throughout the investigational period of 96 hours, leading to the assumption that the drug and/or its metabolites may bind to melanin containing structures. The investigation of the brain penetration potential of tepotinib in rats resulted in an average brain-to-plasma ratio of 2.87 at steady-state (following 24 hours infusion). However, due to its considerably higher brain tissue binding than plasma protein binding, the partition coefficient of unbound drug in plasma and brain ($K_{pu,u}$) was 0.25.

Metabolism

The in vitro interspecies comparison of hepatic metabolism suggested a rather simple metabolic pathway of tepotinib. In humans, only 2 diastereomeric N-oxides and a direct (probably human specific) glucuronide appeared to be relevant. In rat hepatocytes, the N-oxides also represented the major portion of the sample radioactivity. Besides this, only a demethylated metabolite was found. A similar metabolite pattern was observed in dogs.

A human mass balance trial indicated that tepotinib was moderately metabolized resulting in 10 different Phase 1 and Phase 2 metabolites in plasma, faeces, and urine. The chiral metabolite M506 was identified as the only major plasma metabolite and is an oxidative metabolite, later identified as a mixture of MSC2571109A and MSC2571107A. Ratios of geometric mean values of AUC for M506 to total radiolabeled material and to parent tepotinib were 40.4% and 74.9% respectively.

Although racemic metabolite M506 was not detected in vivo in early rat studies conducted at doses up to 50 mg/kg, it was detected in one rat toxicity study performed later using tepotinib doses up to 2000 mg/kg. Racemic metabolite M506 was detected at low levels in dog toxicokinetic samples.

Excretion

In all species tested, the major route of excretion is faecal, with a high fraction of tepotinib being eliminated unchanged.

2.5.4. Toxicology

Tepotinib has been evaluated non-clinically according to and exceeding the requirements set up in ICH S9. A comprehensive set of non-clinical toxicity studies with tepotinib administered by the oral route (clinical route) in rats, dogs and rabbits have been performed. All pivotal studies were conducted in accordance with GLP.

The toxicology program is comprised of general toxicology studies in rats and dogs up to 26- and 39-weeks, respectively, preliminary embryo-foetal development studies in rabbits indicating teratogenicity and studies of genotoxicity, phototoxicity and immunotoxicity. In addition, studies on metabolites and impurities have also been performed. Different batches of tepotinib drug substance were used throughout the non-clinical development program. None of non-clinical studies were performed with clinical or commercial batches of the drug substance. T drug substance produced with the commercial synthesis process has been qualified in the 14 days bridging study in dogs, the 39-week study in dogs, the last 4-week repeat-dose toxicity study in rats, the phototoxicity study in rats and the embryo-foetal toxicity studies in rabbits.

The systemic exposure in the toxicology studies were, overall, considerably lower than observed in humans at clinical dose. However, in the 4-week rat study an MTD of 450 mg/kg/day was determined, corresponding to exposure levels comparable to exposure levels in humans.

2.5.4.1. Single dose toxicity

Two GLP compliant single-dose toxicity studies have been performed, one in rats and one in mice. Information on acute toxicity in dogs was obtained from an oral short-term dose escalation study.

Mouse, Single Dose Oral (Study Report T17194)

In this GLP-compliant study six (3 per sex) Crl:NMRI BR mice were treated orally with a single administration of 2000 mg/kg and observed during a 15-day post-treatment period. Directly before

administration, the test material was prepared with 0.25% aqueous hydroxypropyl methylcellulose (Methocel® K4M Premium) as the vehicle.

There were no deaths during the study and no signs of toxicity were observed after treatment with 2000 mg/kg. No relevant effects were observed on body weight. The gross pathological examination revealed no organ alterations.

Overall, tepotinib did not show any toxicity and the approximate lethal dose was higher than 2000 mg/kg after single oral administration in mice.

Rat, Single Dose Oral (Study Report T17193)

In this GLP-compliant study six (3 per sex) Wistar HsdCpb: WU rats were treated orally with a single dose of 2000 mg/kg and observed during a 15-day post-treatment period. Directly before administration, the test material was prepared with 0.25% aqueous hydroxypropyl methylcellulose (Methocel® K4M Premium) as the vehicle.

There were no deaths during the study and no signs of toxicity were seen after treatment with 2000 mg/kg. No relevant effects were seen on body weight. The gross pathological examination revealed no organ alterations. The gross pathological examination did not reveal any organ alterations.

Overall, tepotinib did not show any toxicity and the approximate lethal dose was higher than 2000 mg/kg after single oral administration in rats.

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicity studies of tepotinib have been performed in Wistar rats up to 26-weeks and Beagle dogs up to 39-weeks.

Mortalities

Treatment related mortalities/sacrifices were evident in rats and rabbits (EFD studies) at exposure levels below clinical exposure levels. No mortalities were observed in dogs.

Body-weight and food consumption

In rats, effects on body-weight and food consumption were generally mild and non-adverse.

In dogs, decreased body weight and food consumption was observed at exposure levels below human exposure. There were also cases of repeated refusal of diet.

Lower food consumption and mean body weight gain was also seen at sub-clinical exposure levels in rabbit mothers in a preliminary embryo-foetal study.

Effects on liver/hepatobiliary system

The liver/hepatobiliary system was a target organ of toxicity in both rats and dogs.

In rats, mild increases in liver enzymes were seen from 15 mg/kg/day. This was coupled to mild increase in liver weights from 30 mg/kg/day. Liver cell hypertrophy was seen in female rats from 135 mg/kg/day in the 26-week study. These effects are probably adaptation effects. In the 4-week study with tepotinib, hepatocellular necrosis and mononuclear infiltrates were present from 450 mg/kg/day and vacuolation was seen at 2000 mg/kg/day. Liver changes were reversible, but it can be noted that last 4-week rat study did not include a recovery period, and therefore it is unclear if the effects seen at close to clinical exposure are reversible.

In dogs, increased hepatic-biliary parameters (GLDH, ALAT, ASAT, AP, bilirubin) were seen in all repeat-dose toxicity studies. In the 4- and 39-week dog studies the increased hepatic-biliary parameters observed respectively at doses of 40 mg/kg/day and 30 mg/kg/day, correlated histologically with a pronounced cholangitis and pericholangitis, inflammatory infiltrates in the liver and bile duct. Moreover, bile duct hypersplasia associated with fibrosis was seen as well as gross pathalogy effects on liver and bile ducts. In dogs, most effects showed recovery, however mild bile duct effects were still observed after the 12-week recovery period in the 39-week study.

Effects on the gastro-intestinal system

In dogs, dose dependent gastrointestinal effects (vomiting and diarrhoea) were frequently seen in all studies at all doses. Effects showed signs of reversibility, but soft stool was still observed after the recovery period. Also, in the 13-week study, non-reversible lymphoid infiltrates in the large intestine was seen.

In rats, mild effects (soft faeces) were reported in a 4-week study in rats at the highest administered dose of 2000 mg/kg/day. Upon sacrifice of the high dose animals, signs of disturbed gastro-intestinal passage were observed.

Gastrointestinal disorders, including diarrhoea, nausea and vomiting were also reported under the most frequent adverse events observed in patients receiving tepotinib.

Effects on the respiratory system

Mild lung effects were observed in rats but not in dogs.

In rats, reversible alveolar macrophage aggregates (foam cells), not associated with any inflammatory reaction, were seen in the lungs in some females at the high dose of the first 4-week studies, (90 and 270 mg/kg/day) and at the mid and high dose of the 26-week study (45 and 135 mg/kg/day). Alveolar macrophage aggregates with minimal mixed cell infiltrates were also observed in the more recent 4-week study in rat performed at high doses (i.e., 450 mg/kg/day). which was considered a sequela of metabolic overload following administration of a high dose.

Although there was no evidence of test item related respiratory distress in any repeat-dose toxicity study in rats, the alveolar macrophage aggregates observed in rat could be of clinical relevance since interstitial lung diseases (ILDs) has been defined as an important identified risk for tepotinib.

Effects on the renal system

Although no kidney toxicity was observed in repeat-dose studies in rats and dogs, there were signs of kidney toxicity in the first preliminary EFD study in female rabbits dosed once daily orally between day 6 and day 18 after pregnancy. Dose dependent treatment related changes of the kidney were seen in pregnant and non-pregnant rabbits from 50mg/kg/day at exposure levels seven orders of magnitude lower than human exposure levels. An increased frequency and degree (from minimal up to moderate) compared to the control animals of otherwise background findings (parenchymal mineralization, tubular basophilia or tubular dilation mainly in the cortical area) was observed. There were also single cases of tubular proteinuria. No kidney effects were seen in the second preliminary EFD study in rabbits up to 25 mg/kg/day. The kidney findings are known background findings in NZW rabbits and most likely not relevant to humans.

Toxicokinetics in the repeat-dose toxicity studies

Toxicokinetic investigations conducted within the repeat-dose toxicity studies indicated that overall, exposure levels were significantly below human exposure. Higher exposure in female animals (up to approximately 3-fold) than in males was generally observed and exposure increased with increasing

tepotinib doses, although less than dose proportional. Minimal accumulation of tepotinib was observed after multiple doses.

2.5.4.3. Genotoxicity

A full program of genotoxicity studies has been performed by the applicant. The Bacterial Reverse Mutation Assay (Ames test) was negative. The in vitro mouse Lymphoma Thymidine Kinase (TK) Gene Mutation Assay is considered overall negative although there was a slight increase in mutagenic frequency at 1,58 µg/mL, but not at 5 µg/mL in one of the two assays. The micronucleus test was negative, although it should be noted that the exposure levels in the rat is estimated to be 3-fold lower than clinical exposure, resulting in an uncertainty.

2.5.4.4. Carcinogenicity

Carcinogenicity studies have not been performed based on the current indication in subjects suffering from advanced cancer.

2.5.4.5. Reproductive and developmental toxicity

Fertility and early embryonic development/Pre-and Postnatal development studies/Juvenile toxicity studies

No studies on fertility and early embryonic development and pre- and postnatal development were conducted based on the therapeutic indication of tepotinib for treatment of patients with advanced cancer. No toxicity studies in juvenile animals were conducted as tepotinib is not intended to be used in paediatric patients.

No morphological changes in male or female reproductive organs were seen in the repeat-dose toxicity studies in rats and dogs, except for reduced secretion in seminal vesicles of male rats in a 4-week repeat-dose toxicity study at 450 mg per kg per day (comparable to human exposure at the 450 mg clinical dose). In addition, sperm analysis (morphology and motility) conducted at the end of the dosing period in the 26-week repeat-dose toxicity study in rats did not show any treatment-related change.

Embryo-foetal studies

In a first oral embryo-foetal development study, pregnant rabbits received doses of 50, 150, and 450 mg tepotinib hydrochloride hydrate per kg per day during organogenesis. The dose of 450 mg per kg (approximately 61% of the human exposure at the recommended dose of tepotinib 450 mg once daily based on AUC) was discontinued due to severe maternal toxic effects. In the 150 mg per kg group (approximately 40% of the human exposure at the 450 mg clinical dose), two animals aborted and one animal died prematurely. Mean foetal body weight was decreased at doses of ≥ 150 mg per kg per day. A dose-dependent increase of skeletal malformations, including malrotations of fore and/or hind paws with concomitant misshapen scapula and/or malpositioned clavicle and/or calcaneous and/or talus, were observed at 50 mg per kg (approximately 14% of the human exposure at the 450 mg clinical dose) and 150 mg per kg per day.

In the second embryo-foetal development study, pregnant rabbits received oral doses of 0.5, 5, and 25 mg tepotinib hydrochloride hydrate per kg per day during organogenesis. Two malformed foetuses with malrotated hind limbs were observed: one in the 5 mg per kg group (approximately 0.21% of the human exposure at the recommended dose of tepotinib 450 mg once daily based on AUC) and one in the 25 mg per kg group (approximately 1.3% of the human exposure at the 450 mg clinical dose),

together with a generally increased incidence of foetuses with hind limb hyperextension (see section 5.3 of the SmPC).

2.5.4.6. Toxicokinetic data

Toxicokinetics investigations conducted within the repeat-dose toxicity studies indicated that all animals were exposed throughout the treatment period, with higher exposure in female animals (up to approximately 3-fold) than in males. Overall, exposure increased with increasing tepotinib doses, although less than dose proportional. Minimal accumulation of tepotinib was observed after multiple doses.

2.5.4.7. Local Tolerance

No dedicated local tolerance studies have been conducted since the compound is developed as a tablet administered via the oral route. Histological evaluations of the gastric and intestinal tract have been included in repeat-dose studies and showed adverse effects in the GI tract of dogs.

2.5.4.8. Other toxicity studies

Immunotoxicity

Data collected from repeat-dose toxicity studies in rats and dogs, including haematology and clinical chemistry investigations, absolute and relative weights and histopathology of lymphoid organs were not indicative for an immunotoxic potential of tepotinib. In addition, flow cytometry of blood immune cells performed in the repeat-dose toxicity studies in rats did not show any clear toxicologically meaningful findings.

Metabolites

The human major metabolite MSC2571109A was found to be present in both rats and dogs. The exposure in both rats and dogs to MSC2571109A was comparatively low indicating that it represents a disproportionate metabolite. Given that the current indication falls under ICH S9, no further non-clinical qualification of metabolites is required.

MSC2571109A was found to be negative in a Bacterial Reverse Mutation Assay (Ames test) up to 1580 µg MSC2571109A per plate and in an in vitro mouse Lymphoma Thymidine Kinase (TK) Gene Mutation Assay.

Impurities

Potential impurities which may be present in the drug substance were assessed for their mutagenic potential through in silico structure-activity-relationship (SAR) evaluations which classified them in Class 4 or 5 and thus considered non-mutagenic.

Seven organic impurities i.e., MSC2209428A, MSC2270983A, MSC2157042B, MSC2200552B, MSC2200106A, MSC2489308A , and triphenylphosphine oxide (TPPO) have been identified and specified in tepotinib drug substance.

The specified identified impurities MSC2209428A, MSC2270983A MSC2157042B, MSC2200552B and MSC2200106A were synthetized and tested in in vitro GLP compliant genotoxicity studies for point mutation and chromosomal aberration. For impurity MSC2270983A an in vivo Comet assay in rats was also conducted. For impurities MSC2489308A and TPPO clinical data or experimental genotoxicity data and structure-activity-relationship (SAR) evaluations for mutagenicity/DNA reactivity are available. All

impurities were negative for genotoxic potential. Moreover, the specified impurities were also qualified in at least one pivotal repeat-dose toxicity study in rat or dog.

Other studies

Phototoxicity

Tepotinib showed phototoxic potential in in vitro experiments but gave negative results in an in vivo phototoxicity study in rats. In the rat in vivo phototoxicity study the exposure levels were only around 66% of human exposure. Moreover, a small portion of the second absorption peak showed some overlap with lower wavelengths of natural sunlight (UVB, 290-320 nm) and the emission spectrum of the UV lamp did not fully cover wavelengths where tepotinib absorbs light resulting in an uncertainty. A whole-body autoradiography study shows retention in eyes and skin suggesting melanin binding. However, given that tepotinib absorbs light mainly in the high UV-C region, the phototoxic potential should be significantly reduced. Although the above uncertainties have been identified, the in vivo study is considered to be negative and indicative of low risk for phototoxicity in humans.

2.5.5. Ecotoxicity/environmental risk assessment

Substance (INN/Invented Name): Tepotinib			
CAS-number (if available): #1100598-32-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential log D_{ow}	OECD TG117	pH 4: 2.53 pH 7: 5.99 pH 9: 6.04	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	5.99	B
	BCF	NA?	Not determined
Persistence	DT90	825d	P
Toxicity	NOEC	<0.01mg/L (FELS)	T
PBT-statement :	The compound is considered a <u>possible</u> vPvB The compound is considered a <u>possible</u> PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surface water, refined prevalence	0.002	µg/L	> 0.01 threshold (N)
Other concerns (e.g., chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD TG106	*Soil adsorption* K_d =1411 L/kg K_d =1463 L/kg K_d =8916 L/kg K_{oc} = 95 982 L/kg K_{oc} = 355 202 L/kg K_{oc} = 512 435 L/kg *Sludge adsorption* K_d = 1981 L/kg K_d = 3646 L/kg K_{oc} = 4954 L/kg K_{oc} = 9348 L/kg	Based on 3 soils and 2 sludges.

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	20C $DT_{50,\ water}$ = 2.1-4.2d $DT_{50,\ whole\ system}$ = 1.6-4.9d $DT_{90,\ water}$ = 7-13.8d $DT_{90,\ whole\ system}$ = 639-825d 12C $DT_{50,\ water}$ = 4.5-8.9d $DT_{50,\ whole\ system}$ = 3.4-10.4d $DT_{90,\ water}$ = 14.9-29.4d $DT_{90,\ whole\ system}$ = 1360-1755d % shifting to sediment > 10%			Classified as persistent based on the DT90 values (20C).
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD TG201	*Growth rate* NOEC LOEC ErC10 ErC50 *Yield* NOEC LOEC EyC10 EyC50	 0.032 0.100 0.063 0.099 <0.010 0.010 0.030 0.058	 mg/ L mg/ L	*P. subcapitata* 72h exposure. The NOEC/LOEC and ECx values are nominal values. The lowest concentration is a LOEC (**OC**).
Daphnia sp. Reproduction Test	OECD TG211	*Survival* NOEC LOEC EC50 *Reproduction* NOEC LOEC EC50	 2.69 >2.69 1.83 0.53 1.50 1.66	 mg/ L mg/ L	*Daphnia magna* 21d exposure.
Fish Early Life Stage Toxicity Test/ *Zebrafish*	OECD TG210	*Mortality* NOEC LOEC EC50 *Size* NOEC LOEC EC50	 <10 10 72.1 31.6 100 139	 µg/L µg/L	*Danio rerio* The lowest concentration is a LOEC (**OC**).
Phase IIb Studies					
Sediment-dwelling organism	OECD TG219	*Emergence rate* NOEC LOEC EC50 *Developmental rate* NOEC LOEC	 0.00682 0.01920 0.01810 ≥0.0938 ≥0.0938	 mg/ L	*Chironomus riparius* No emergence of midges at highest concentration

Bioconcentration in fish	OECD TG305				Recommendation to submit by Dec 2022.

2.5.6. Discussion on non-clinical aspects

Pharmacology

In the kinase screen studies at 1 µM Tepotinib, more than 50% inhibition was observed for IRAK1, IRAK4 and TrkC in two in vitro studies and for Axl and TrkA in 1 out the 2 in vitro studies. The dose of 1 µM Tepotinib is approximately 19-fold of the average maximal free tepotinib concentration achieved at steady state in patients with the daily dose of 500 mg. The applicant stated that "these off-target activities may not result in relevant (patho)physiological effects". However, in the same studies, equivalent percentage of inhibition were observed with several MET variants at 1 µM Tepotinib (e.g. D1246H, Y1248D, F1200I, M1250T, P991S, T992I, T1173I, V1092I, Y1235D). If relevant in vivo activity was demonstrated with these MET variants, the off-target effects on IRAK1, IRAK4, TrkC, Axl and TrkA could potentially therefore be considered clinically relevant. However, the applicant clarified that all the tumour cells used in the in vivo xenograft studies, except for EBC-1, do not harbour the point mutations in MET receptor (D1246H, Y1248D, F1200I, M1250T, P991S, T992I, T1173I, V1092I, Y1235D) and therefore the in vivo activity has not been evaluated for these MET variants. Furthermore, according to the available literature, the tumour cell line EBC-1 neither harbour such point mutations in MET receptor. The applicant did also provide additional preclinical data and further discussed that the off-target activity of tepotinib is not considered clinically relevant, which was accepted. The residual inhibitory activities observed for MET-unrelated kinases at 100 nM, was further investigated by testing if tepotinib could promote growth inhibition in the TrkA (NTRK1)-driven KM12 cell line (carrying a TPM3-NTRK1 fusion). TrkA was chosen as a target because the most potent inhibition of a MET-unrelated kinase at 100 nM was observed for TrkA (35% inhibition). Treatment of KM12 cells with approved NTRK inhibitors as references led to a marked decrease in cellular viability with IC50 values in the low nanomolar range. In contrast, tepotinib did not show signs of activity up to the maximal concentration of 1 µM. In addition, in an independent external study using a chemical kinome screen (kinobeads) in tumour cell lysates and quantitative mass spectrometry, Tepotinib showed no interaction with any other kinase except MET up to 1 µM (Klaeger, 2017).

A tepotinib tumour reducing dose-response was indicated in several studies on tumours with high-level MET amplification, however when treating established MKN-45 tumours, no dose response was observed. In the MKN-45 model, tepotinib at 25 and 200 mg/kg/qd led to tumour growth inhibition with T/C values of -46% and -52% at Day 11, respectively, and partial tumour regressions (defined as a reduction of tumour volume of $\geq$ 50% at the end of treatment relative to the start of treatment) in 4/8 mice at both doses. This is in contrast to the results in the presented treatment studies with the Hs746T gastric cancer as well as the EBC-1 NSCLC murine models. The applicant suggests that the dose of 25 mg/kg/qd was likely sufficient to provoke maximal anti-tumour activity in MKN-45 tumours, which would explain why no increase in tumour reduction response was observed with the higher dose of 200 mg/kg/qd. This explanation is considered plausible.

The reason why tepotinib treatment did not result in complete tumour regression in MKN-45 tumours is not known. However, the applicant describes two mechanisms that potentially could explain the discrepancy to tumour models where complete tumour regression occurred. First, it is possible that the maximal anti-tumour activity was not yet achieved at Day 11. An anti-tumour response delayed beyond day 11 has been observed in some sc tumour models with oncogenic MET alterations such as EBC-1 or LU5349 (PDX), where maximal tepotinib effects were seen after 14 days or later. Another

possibility would be the appearance of a de novo resistance in a minor fraction of tumour cells, although the applicant also acknowledge that no such concomitant genetic alterations that could explain resistance of at least a fraction of tumour cells to tepotinib treatment have been reported for MKN-45. In addition, the applicant proposes that other mechanisms such as epithelial-mesenchymal transition that could render at least a fraction of MKN-45 resistant to tepotinib treatment may exist. The applicant summarizes that both possibilities, the short treatment duration and potential resistance mechanisms, are speculative and would warrant further investigations. Moreover, the applicant summarizes that the observed in vivo anti-tumour activity in MKN-45, nevertheless, was considerable and that this is in line with the sensitivity of the MKN-45 cell line to tepotinib treatment in vitro. This reasoning was accepted.

In vitro and in vivo safety pharmacology studies with tepotinib or its free base did not show any relevant off target, cardiovascular, respiratory or CNS effects. In the in vivo studies in rats (CNS, respiratory) exposure levels (C_{max}) were comparable or above the steady state mean free C_{max} in patients at the therapeutic dose of 500 mg. However, in the cardiovascular studies in dogs, exposure was substantially below the clinical exposure.

The systemic exposure in the toxicology studies were, generally, considerably lower than observed in humans, although a 4-week rat study which determined an MTD, resulted in exposure levels comparable to human exposure.

The repeat-dose toxicology studies indicate that the main target organs of toxicity is the liver/hepatobiliary system (rats and dogs), the gastro-intestinal system (rats and dogs) the lungs (rats) and the kidney (rabbit). The non-clinical findings are in line with adverse effects observed in the clinical program. It is however noted that the non-clinical toxicology data failed to identify oedema, which appears to be a common adverse event in humans receiving tepotinib or other MET inhibitors.

No mutagenic or genotoxic effects of tepotinib were observed in in vitro and in vivo studies. However, the maximally feasible dose used in the in vivo micronucleus test in rats provided an estimated systemic exposure close to 3 fold lower than the clinical plasma exposure. The major circulating metabolite was shown to be non-mutagenic.

In line with the ICH S9 guideline, no studies have been performed to evaluate the carcinogenic potential of tepotinib (see section 5.3 of the SmPC).

Two preliminary embryo-foetal toxicity studies in rabbits indicate that tepotinib has teratogenic effects at exposure levels several magnitudes below human exposure levels.

Starting at a dose level of 5 mg/kg/day corresponding to exposure levels less than 1% of the human exposure, skeletal malformations (hind limb malrotation, hyperextension of hind limb) were observed.

Tepotinib can cause foetal harm when administered to pregnant women. Pregnancy testing is recommended in women of childbearing potential prior to initiating treatment with tepotinib. Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during tepotinib treatment and for at least 1 week after the last dose (see sections 4.4, 4.5 and 4.6 of the SmPC).

In accordance with ICH S9, no studies on fertility and early embryonic development and pre- and postnatal development were conducted. No morphological changes in male or female reproductive organs were seen in the repeat-dose toxicity studies in rats and dogs, except for reduced secretion in seminal vesicles of male rats in a 4-week repeat-dose toxicity study at 450 mg per kg per day (comparable to human exposure at the 450 mg clinical dose).

Tepotinib has no influence on the ability to drive and use machines (see section 4.7 of the SmPC).

Environmental risk assessment

Based on Log D > 4.5, tepotinib is a PBT candidate. It furthermore fulfils the criteria for persistence (P, in sediment) and toxicity (T, in developing fish). With regard to the OECD TG308 and its DT-values, it can also be noted that in terms of the study on transformation in water/sediment systems the applicant calculated the half-lives for the total systems based on the FOMC kinetics and concluded "*…that DT50 values probably exceed 180 days, and it can be concluded that the compound is persistent*". This assumption is correct indeed and should be confirmed.

The B status of tepotinib has not been experimentally characterized or determined (based on that measurements in midges in an OECD TG219 test were <LoQ but without any further testing. This cannot be considered sufficient to declare that the PBT B-criterion is not fulfilled. Furthermore, exposure of fish cannot be excluded even at low concentrations in water. Furthermore, the considerations by the applicant in terms of possible bioaccumulation in sediment dwelling organisms based on observations in the toxicity test on sediment dwelling organisms is considered not appropriate for the use in the PBT assessment. The applicant is recommended to provide a bioaccumulation study (OECD TG305) before Q3 2023. Until more experimental observations have been provided, this leaves tepotinib as a possible PBT candidate.

2.5.7. Conclusion on the non-clinical aspects

Overall, the pharmacological studies provide evidence that support efficacy in humans. The repeat-dose toxicological data indicates that the main target organs of toxicity is the liver/hepatobiliary system, the gastro-intestinal system, the lungs and the kidney. The non-clinical findings are in line with adverse effects observed in the clinical program. It can however be noted that the non-clinical toxicology data failed to identify oedema, which appears to be a common adverse event in humans receiving tepotinib or other MET inhibitors. In addition, preliminary embryo-foetal toxicity studies in rabbits have shown foetal malformations (teratogenicity). Environmental risk assessment studies have shown that tepotinib has the potential to be very persistent and toxic to the environment.

From a non-clinical perspective, the MAA for tepotinib can be approvable.

2.6. Clinical aspects

2.6.1. Introduction

In the SmPC, the strength is expressed as tepotinib (free base form). In this report, the strength representation corresponds to tepotinib hydrochloride hydrate. As a consequence "500 mg tepotinib" corresponds to 500 mg tepotinib hydrochloride hydrate and is equivalent to 450 mg tepotinib (free base form), and "250 mg tepotinib" corresponds to 250 mg tepotinib hydrochloride hydrate and is equivalent to 225 mg tepotinib (free base form).

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**

Study (Country/ Regions)	Study Design	Indication / Study Population	Objectives (Primary objectives are indicated in bold)	Dose Regimen	No. of Participants Treated		Study Status (as of submission)
					Tepotinib	Active Control / RW systemic therapy	
Pivotal Study							
MS200095-0022 - VISION (Europe/US/Asia)	Phase II, multicenter, open-label, single-arm	Patients with advanced or metastatic NSCLC with *MET*ex14 skipping alterations or *MET*amp	**Efficacy**, Safety, Tolerability, PK, and Pd	500 mg QD	Cohort A (*MET*ex14): 152 Cohort B (*MET*amp): 24 Cohort C (*MET*ex14): 139	-	Ongoing
Other Studies in Cancer Patients							
EMR200095-001 (Multicenter: US/Germany)	Phase I, open-label, nonrandomized, dose escalation, first in human study	Patients with solid tumours, refractory to standard therapy or for which no effective standard therapy is available	**MTD/RP2D**, Safety, Tolerability, Efficacy, PK, and Pd	R1: 30-400 mg [a] R2: 30-315 mg [a] R3: 300-1,400 mg [a]	149	-	Completed
EMR200095-003 (Multicenter: Japan)	Phase I, open-label study	Japanese patients with solid tumours	**MTD/RP2D**, Safety, Tolerability, Efficacy, PK, and Pd	215, 300, and 500 mg QD	12	-	Completed
EMR200095-004 (Multicenter: Asia)	Phase Ib/II, randomized study	Asian patients with advanced HCC, 1L (sorafenib-naïve) MET+ tumours only	**RP2D** (Ib), **Efficacy** (II), Safety, Tolerability, PK, and Pd	300, 500, and 1,000 mg QD	27 (Ib) 45 (II)	- 44 (II)	Completed [b]

Study (Country/ Regions)	Study Design	Indication / Study Population	Objectives (Primary objectives are indicated in bold)	Dose Regimen	No. of Participants Treated		Study Status (as of submission)
					Tepotinib	Active Control / RW systemic therapy	
EMR200095-005 (Multicenter: EU/US)	Phase Ib/II, single arm study	Patients with advanced HCC, 2L (after failure of sorafenib treatment), MET+ tumours only	**RP2D** (Ib), **Efficacy** (II), Safety, Tolerability, PK, and Pd	300 and 500 mg QD	17 (Ib) 49 (II)	- -	Completed
EMR200095-006 (Multicenter: Worldwide)	Phase Ib/II, randomized, open-label study comparing tepotinib + gefitinib vs chemotherapy: Phase Ib part	Patients with advanced NSCLC after failure of EGFR-TKI treatment, MET+ tumours only	**RP2D**, Safety, Tolerability, PK, and Pd	300-500 mg + 250 mg gefitinib QD	18	-	Completed [b]
	Phase II randomized part	Patients with advanced EGFRm+ NSCLC, 2L (after failure of 1L EGFR-TKI treatment), MET+ and EGFR T790M- tumours only	**Efficacy**, Safety, Tolerability, PK, and Pd	500 mg + 250 mg gefitinib QD	31	23	Completed [b]
	Phase II non-randomized part	Patients with advanced EGFRm+ NSCLC, 2L (after failure of 1L EGFR-TKI treatment), MET+ and EGFR T790M+ tumours only	Safety, Tolerability, Efficacy, PK, and Pd	500 mg + 250 mg gefitinib QD	15	-	Completed [b]

Study (Country/ Regions)	Study Design	Indication / Study Population	Objectives (Primary objectives are indicated in bold)	Dose Regimen	No. of Participants Treated		Study Status (as of submission)
					Tepotinib	Active Control / RW systemic therapy	
MS200095-0031 Multicenter: Europe, Asia, and North America	Phase II randomized part	Participants with advanced or metastatic NSCLC harboring activating EGFR mutations and having relapsed on prior first-, second-, or third-generation EGFR-TKI therapy due to *MET* amplification (INSIGHT 2 Study)	**Efficacy**, Safety, Tolerability, and PK, Pd	500 mg + 80 mg osimertinib QD RP2D + 80 mg osimertinib QD	19	-	Ongoing
Studies in Noncancer Participants							
EMR200095-002 (Single center: France)	Phase I, open-label, randomized, crossover study	Healthy participants	**Relative BA (CF2/TF1), Food effect (TF1)**, Safety, Tolerability, PK, and Pd	30 mg single dose	28	-	Completed
EMR200095-007 (Single center: The Netherlands)	Phase I, open-label, 3-part study: Part A	Healthy participants	**Mass balance, metabolite profile**, Safety, Tolerability, PK	500 mg (498 mg spiked with 2.67 MBq ^{14}C-labeled tepotinib)	6	-	Completed
	Part B		**Absolute BA (TF1)**, Safety, Tolerability, PK	500 mg single dose followed by ~50 kBq ^{14}C-labeled tepotinib IV bolus injection at 4 h post oral dose	6	-	Completed
	Part C		**Relative BA (Oral solution/ TF1) and (TF1/TF1*)**, Safety, Tolerability, PK	A: 100 mg B: 100 mg C: 100 mg Each single dose per period in 3-way crossover	15	-	Completed

Study (Country/ Regions)	Study Design	Indication / Study Population	Objectives (Primary objectives are indicated in bold)	Dose Regimen	No. of Participants Treated		Study Status (as of submission)
					Tepotinib	Active Control / RW systemic therapy	
MS200095-0012 (Single center: UK)	Phase I, open-label, randomized, crossover study	Healthy participants	**Relative BA (TF1/TF2)**, Safety, Tolerability, PK	500 mg TF1 and 500 mg TF2 Each single dose In 2-way crossover	24	-	Completed
MS200095-0028 (2 Centers: US)	Phase I, open-label, parallel-group study	Healthy participants and patients with Child-Pugh A and B hepatic impairment	**Relative BA (healthy participants/ patients with hepatic impairment)**, **PK**, Safety, Tolerability	Part 1: 500 mg single dose Part 2 (optional): 500 mg to 1,000 mg	18	-	Completed
MS200095-0030 (Single center: Germany)	Phase I, open-label, single sequence, 2-period crossover study	Healthy participants	**DDI perpetrator potential toward CYP3A4**, PK, Safety, Tolerability	11 administrations of 500 mg	12	-	Completed
MS20z0095-0032 (Single center: Germany)	Phase I, open-label, single sequence, 2-period study	Healthy participants	**DDI perpetrator potential toward P-gp**, PK, Safety, Tolerability	8 administrations of 500 mg	20	-	Completed
MS200095-0038 (Single center: Germany)	Phase I, open-label, single-dose, randomized, 2-period, 2-sequence crossover study	Healthy participants	**BE (TF3: 5 x 100 mg and 2 x 250 mg)**, PK, Safety, Tolerability	2 administrations of 500 mg	18	-	Completed
MS200095-0039 (Single center: Germany)	Phase I, open-label, 3-period crossover study	Healthy participants	**DDI victim potential toward PPI**, PK, Safety, Tolerability	500 mg single dose in each period	12	-	Completed
MS200095-0044 (Single center: Germany)	Phase I, open-label, 3-part crossover study	Healthy participants	**BE Between TF3 and TF2, Food Effect**, PK, Safety, Tolerability	500 mg single dose	Part A: 40 Part B: 14 Part C: 12	-	Completed

Study (Country/ Regions)	Study Design	Indication / Study Population	Objectives (Primary objectives are indicated in bold)	Dose Regimen	No. of Participants Treated		Study Status (as of submission)
					Tepotinib	Active Control / RW systemic therapy	
Non-interventional Studies							
MS200095-0027	Retrospective cohort design, using individual patient-level data pooled from 3 real-world data sources (including MS200095-0015, MS200095-0035, and the COTA RWE database)	Advanced NSCLC patients with *MET*ex14 skipping alterations	**Effectiveness** (RW)	NA	-	201	Completed [c]
MS200095-0015 (US)	Non-interventional descriptive, dynamic cohort study using real-world patient data	Advanced or metastatic NSCLC, with documented *MET*ex14 alterations (Part A) or *MET*amp (Part B)	**Effectiveness** (RW)	NA	-	62 *MET*ex14 NSCLC patients	Ongoing [c]
MS200095-0035 (US, Israel, The Netherlands, Taiwan)	Non-interventional descriptive, cohort study using real-world patient data	Advanced or metastatic NSCLC, with documented *MET*ex14 alterations or *MET*amp	**Effectiveness** (RW)	NA	-	70 *MET*ex14 NSCLC patients	Completed [c]
Subtotal Monotherapy					839	44 [d]	
Subtotal Combination Therapy					83	23 [d]	
Total					922	67 [d]	

Source: Section 2.7.2, Table 1 and Section 2.7.4, Table 1.
1L=first line, 2L=second line, BA=bioavailability, BE=bioequivalence, CF=Capsule Formulation, CYP3A4=cytochrome P450 3A4, DDI=drug-drug interaction, EGFRm+=epidermal growth factor receptor mutation-positive, EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor, HCC=hepatocellular carcinoma, MET=mesenchymal-epithelial transition factor, *MET*amp=*MET* amplification, *MET*ex14=MET tyrosine kinase receptor exon 14, MTD=maximum tolerated dose, NA=not applicable, NSCLC=non-small cell lung cancer, Pd=pharmacodynamic, P-gp=p-glycoprotein, PK=pharmacokinetic, PPI=proton pump inhibitors, QD=once daily, RP2D=Recommended Phase II Dose, RW=real-world, RWE=real-world evidence, TF=Tablet Formulation, TF1*=tablet formulation 1.

a EMR200095-001 only: R1=Regimen 1: 14 days on, 7 days off QD dosing within a cycle of 3 weeks; R2=Regimen 2: 3 times per week dosing (Day 1, 3 and 5) within a cycle of 3 weeks; R3=Regimen 3: Continuous QD dosing within a cycle of 3 weeks (21 days).

b Studies EMR200095-004 and EMR200095-006 are considered as completed (CSR is available), although there is still a limited number of patients treated with tepotinib as of 01 July 2020.

c For non-interventional studies, "completed" means study report available at the time of submission. Study MS200095-0015 is based on a dynamic cohort

design, entailing multiple data updates. Data Update 1 is completed and reported for Part A and Part B. Data Update 2 is completed and reported for Part A and ongoing for Part B. Data Update 3 for Part A and B is planned.

d Not including non-interventional studies.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Throughout the development program, several different capsule and tablet formulations of tepotinib were used in clinical studies. Tepotinib was initially formulated as a capsule (Capsule Formulation [CF] 1), that was used in the first part of the FIH study (EMR200095-001). CF2 replaced CF1 in study EMR200095-001. Tablet Formulation (TF) 1 was introduced in the later part of study EMR200095-001. All Phase II studies, except for the pivotal VISION study, were conducted using TF1 under fed conditions. TF2 was administered in the ongoing VISION study and in several clinical pharmacology studies. TF3, the proposed commercial formulation, contains a different qualitative and quantitative composition compared with TF2. It is provided as 250 mg film-coated tablets. Patients in the VISION study were gradually switched from TF2 to TF3 upon implementation of Protocol Amendment 6 (dated 26 March 2019) until 10 March 2020.

Methods

Bioanalysis

Tepotinib and its metabolites MSC2571109A and MSC2571107A were analysed in plasma using validated LC-MS/MS methods.

Non-compartment data analysis

Standard non-compartmental analysis was performed in all studies where rich sampling was applied.

Physiologically-based pharmacokinetic model-based analysis

Two PBPK models have been submitted in order to investigate the drug-drug interaction potential. These models have not been assessed since they are not necessary or cannot be used in order to exclude clinically relevant interaction (see Discussion on clinical pharmacology).

PopPK analysis

The objectives of the population pharmacokinetic (PK) analysis were to evaluate the dose – exposure relationship of tepotinib and its metabolite MSC2571109A in the overall population, and to evaluate the intrinsic and extrinsic factors that are predictive of the variability in PK.

<u>PopPk dataset</u>

The population PK analysis was based on data collected from 12 studies: 11 completed studies and one ongoing study (MS200095-0022, data cut-off by February 18th 2019). Concentrations of MSC2571109A were only measured after its discovery, while the clinical development was ongoing, and hence less observation records are available for MSC2571109A than for tepotinib.

The summary of number of subjects and number of observations in the tepotinib and MSC2571109A analysis data sets is presented in Table 7. Table 23 shows the number of observations affected by reason for exclusion.

Methods

The analyses were performed using NONMEM version 7.3.0.

The covariate searches performed in this modelling project were performed using the SCM procedure. Summaries of baseline covariates for the subjects in the tepotinib analysis data set are presented in *Table 1* and *Table 2*.

Table 1. Descriptive statistics for baseline continuous covariates, for subjects in the tepotinib analysis data set

Covariate	N[a]	Mean	sd[b]	Median	Min	Max
Age (years)	613	55.8	15.7	58.0	18.0	89.0
AGP (mg/dL)	18	63.9	26.9	62.0	29.0	124
ALP (IU/L)	613	134	133	90.0	20.0	1310
BILI (µmol/L)	613	10.5	6.70	9.00	2.00	66.0
eGFR (mL/min/1.73m^2)	591	99.8	26.2	97.4	39.4	236
INR	578	1.09	0.172	1.05	0.870	2.90
Total protein (g/L)	535	71.7	6.16	71.0	50.0	93.0
S-Albumin (g/L)	511	39.3	5.36	40.0	23.0	72.0
Sum of longest diameters (mm)[c]	425	84.8	55.5	72.0	10.0	368
WT (kg)	613	72.9	15.8	72.0	35.5	136

[a]Number of subjects with non-missing values
[b]Standard deviation
[c]Sum of the longest diameters for target lesion at baseline, assessed by investigator
Values are rounded to 3 significant digits.
AGP: alpha-1 acid glycoprotein; ALP: alkaline phosphatase; BILI: total bilirubin; eGFR: estimated glomerular filtration rate; INR: international normalized ratio; WT: body weight

Table 2. Descriptive statistics for (baseline) categorical covariates, for subjects in the tepotinib analysis data set

Covariate		N	%
Sex	Male	439	71.6
	Female	174	28.4
Tumor type	Subject without cancer	175	28.5
	Hepatocellular carcinoma	144	23.5
	Non-small cell lung cancer	157	25.6
	Renal cell carcinoma	5	0.8
	Head and neck cancer	20	3.3
	Gastroesophageal cancer	31	5.1
	Colorectal cancer	29	4.7
	Breast cancer	10	1.6
	Prostate cancer	6	1.0
	Pancreatic cancer	3	0.5
	Other solid tumor	33	5.4
Food intake[a]	Fasted	93	15.2
	Fed standard breakfast	455	74.2
	Fed high fat breakfast	65	10.6
Formulation[a]	CF1	41	6.7
	CF2	111	18.1
	TF1	273	44.5
	TF1*	5	0.8
	TF2	151	24.6
	TF3	32	5.2
ECOG	ECOG 0	130	21.2
	ECOG 1	299	48.8
	ECOG 2	8	1.3
	ECOG 3	1	0.2
	(Missing)	175	28.5
Race	Caucasian	362	59.1
	African Origin	17	2.8
	Japanese	28	4.6
	Other East Asian	145	23.7
	Hispanic	25	4.1
	Other	14	2.3
	(Missing)	22	3.6
Cirrhosis	Grade0	560	91.4
	Grade1	33	5.4
	Grade2	18	2.9
	Grade3	1	0.2
	(Missing)	1	0.2
HBV/HCV	HBV/HCV-	445	72.6
	HBV/HCV+	55	9.0
	(Missing)	113	18.4
NCI ODG class	NCI 0	448	73.1
	NCI 1	146	23.8
	NCI 2	16	2.6
	NCI 3	3	0.5

[a] Covariate category at first dosing occasion for each subject
See List of Abbreviations and Definition of Terms for definitions.

Final Tepotinib model

The final population PK model for tepotinib is a 2-compartment model with sequential zero- and first-order absorption and first-order elimination from the central compartment. IIV terms are included on CLpar, ka, D1 and Fpar.

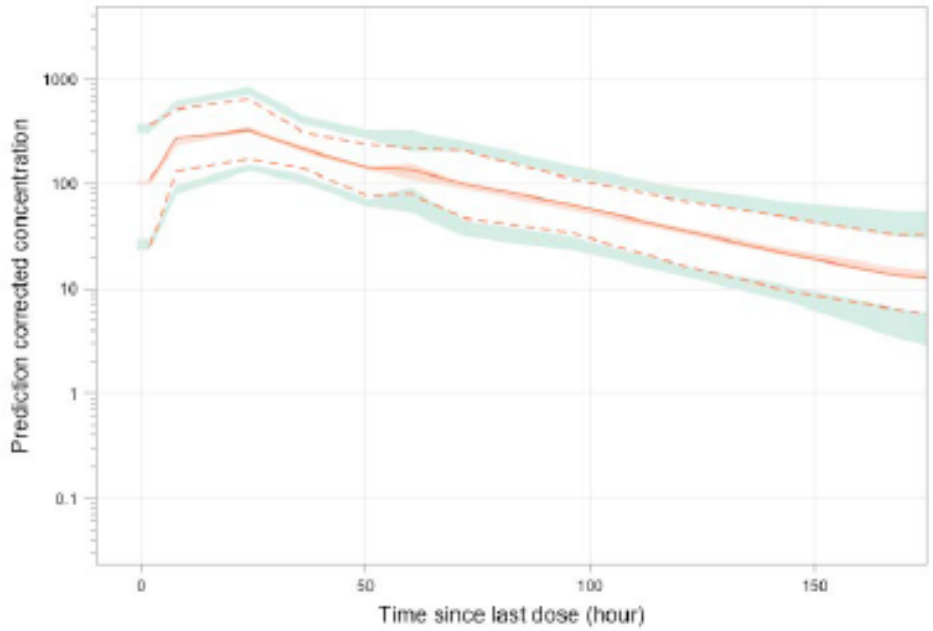
The population PK model parameter estimates of the final tepotinib population PK model are presented in *Table 3*. The pcVPC plots for the overall data and stratified by study and by formulation generally show a good agreement for the observed median concentrations (*Figure 2*). For the pcVPCs data were simulated 100 times using the doses and covariate data from the subjects that were used in the analysis data set with the same study design.

Table 3. Parameter estimates of the final tepotinib population PK model

	Final model for tepotinib
Run	80
OFV	-8891.44
Condition number	56.93

		Final model for tepotinib		
	Unit	Value	RSE (%)	SHR (%)
CL_{par}[a]	L/h	20.4	2.07	
$V_{c,par}$[a]	L	1020	2.00	
k_a	h^{-1}	0.278	6.16	
Q_{par}[a]	L/h	1.32	4.22	
$V_{p,par}$[a]	L	1180	16.6	
D1	h	4.09	5.34	
F_{par}	(CV)	1.00	(FIX)	
Fasting state covariate on D1		-0.370	5.19	
DOSE covariate on F_{par} (/100 mg)		-0.0412	9.71	
Fasting state covariate on F_{par}		-0.209	4.94	
High fat meal covariate on F_{par}		0.320	5.96	
CF1 covariate on F_{par}		-0.656	7.67	
TF3 covariate on F_{par}		0.154	7.08	
Fasting state covariate on k_a		-0.561	2.63	
CF1 covariate on k_a		-0.442	15.1	
TF1 covariate on k_a		0.305	6.35	
TF1* covariate on k_a		0.674	10.2	
eGFR at baseline covariate on CL_{par}		0.199	23.5	
Hepatocellular carcinoma covariate on CL_{par}		0.130	44.2	
Colorectal cancer covariate on CL_{par}		-0.281	16.4	
μ-opioids covariate on CL_{par}		-0.167	10.1	
NCI ODG class > 0 covariate on D1		-0.332	6.09	
Body weight at baseline covariate on F_{par}		-0.475	15.4	
NCI ODG class > 0 covariate on F_{par}		-0.0729	16.7	
INR at baseline covariate on Q_{par}		3.81	10.5	
Serum albumin at baseline covariate on Q_{par}		4.14	10.9	
Age covariate on $V_{c,par}$		0.219	14.7	
Non-small cell lung cancer covariate on $V_{c,par}$		-0.232	13.2	
Patient subject covariate on $V_{p,par}$		-0.810	4.52	
Study 0028 covariate on CL_{par}		-0.115	22.4	
IIV CL_{par}	(CV)	0.335	4.57	36.4
IIV k_a	(CV)	0.653	5.86	31.2
IIV D1	(CV)	0.652	4.98	26.1
IIV F_{par}	(CV)	0.283	5.78	44.0
IIV F_{par} for CF1	(CV)	0.713	10.8	75.7
IIV CL_{par} for healthy subject	(CV)	0.128	7.64	54.6
IIV F_{par} for healthy subject	(CV)	0.188	6.38	54.7
Prop. RUV	(CV)	0.337	0.351	6.39

[a] Multiplied by a conversion factor of 0.9.
The SEs were obtained from the $COV step in NONMEM using the MATRIX=S option. The RSE for IIV and RUV parameters are reported on the approximate SD scale. Values are rounded to three significant digits.
The equations for the covariate effects on each parameter are provided in Appendix 10.1.
See List of Abbreviations and Definition of Terms for definitions.



The data are presented on a log-linear scale. The solid and dashed red lines represent the observed median, 5th and 95th percentiles; the shaded red area represents the 95% confidence interval of the model predicted median and the shaded blue areas represent the 95% confidence interval of the model predicted 5th and 95th percentiles, based on 100 simulated data sets. The x-axis was cut at 175 hours.

Figure 2. pcVPC of tepotinib concentrations versus time since last dose using the final tepotinib population PK model

Final MSC2571109A model

The final model for MSC2571109A is a 2-compartment model with input from the central compartment in the tepotinib model, scaled by a parameter FM, fraction of tepotinib metabolized to MSC2571109A, and a first-order elimination from the central compartment.

Updated tepotinib model (from Adendum report)

The main objective of the analysis provided in the addendum was to update the popPK models with the new 01 January 2020 cut-off analysis data set and compare with previous model the 18 February 2019 cut-off analysis data set. This is an additional 101 subjects, 422 tepotinib samples, and 404 MSC2571109A samples compared to the 18 February 2019 cut-off data set.

Results

The parameter estimates of the tepotinib model based on the 18 February 2019 cut-off analysis data set were re-estimated with the 01 January 2020 cut-off analysis data set (run194), including the changed NCI ODG class covariate (*Table 4*).

Table 4. Parameter estimates of the final tepotinib population PK model based on the 18th of February 2019 cut-off analysis data set and the model re-estimated with the 1st of January 2020 cut-off analysis data set and changed NCI ODG class covariate

		Final tepotinib model		Re-estimated tepotinib model	
Run		80		194	
OFV		−8891.44		−8947.66	
Condition number		56.93		53.39	
		Final tepotinib model		**Re-estimated tepotinib model**	
	Unit	**Value**	**RSE (%)**	**Value**	**RSE (%)**
CL_{par}[a]	L/h	20.4	2.07	20.5	1.93
$V_{c,par}$[a]	L	1020	2.00	1030	1.89
k_a	h^{-1}	0.278	6.16	0.276	6.06
Q_{par}[a]	L/h	1.32	4.22	1.34	4.06
$V_{p,par}$[a]	L	1180	16.6	1260	15.3
D1	h	4.09	5.34	3.94	5.22
F_{par}		1.00	(FIX)	1.00	(FIX)
Fasting state covariate on D1		-0.370	5.19	-0.357	5.28
DOSE covariate on F_{par}		-0.0412	9.71	-0.0417	9.78
Fasting state covariate on F_{par}		-0.209	4.94	-0.207	5.06
High fat meal covariate on F_{par}		0.320	5.96	0.321	5.79
CF1 covariate on F_{par}		-0.656	7.67	-0.659	7.63
TF3 covariate on F_{par}		0.154	7.08	0.153	7.11
Fasting state covariate on k_a		-0.561	2.63	-0.561	2.65
CF1 covariate on k_a		-0.442	15.1	-0.443	16.0
TF1 covariate on k_a		0.305	6.35	0.280	6.70
TF1* covariate on k_a		0.674	10.2	0.695	10.2
eGFR at baseline covariate on CL_{par}		0.199	23.5	0.200	22.5
Hepatocellular carcinoma covariate on CL_{par}		0.130	44.2	0.175	32.9
Colorectal cancer covariate on CL_{par}		-0.281	16.4	-0.271	16.3
μ-opioids covariate on CL_{par}		-0.167	10.1	-0.169	9.74
NCI ODG class > 0 covariate on D1		-0.332	6.09	-0.270	12.7
Body weight at screening covariate on F_{par}		-0.475	15.4	-0.524	12.8
NCI ODG class > 0 covariate on F_{par}		-0.0729	16.7	0	(FIX)
INR at baseline covariate on Q_{par}		3.81	10.5	4.14	9.34
Serum albumin at baseline covariate on Q_{par}		4.14	10.9	4.10	10.6
Age covariate covariate on $V_{c,par}$		0.219	14.7	0.219	14.6
Non-small cell lung cancer covariate on $V_{c,par}$		-0.232	13.2	-0.250	11.4
Healthy subject covariate on $V_{p,par}$		-0.810	4.52	-0.819	3.97
Study 0028 covariate on CL_{par}		-0.115	22.4	-0.106	24.3
IIV CL_{par}	(CV)	0.335	4.57	0.325	4.17
IIV k_a	(CV)	0.653	5.86	0.692	5.35
IIV D1	(CV)	0.652	4.98	0.668	4.79
IIV F_{par}	(CV)	0.283	5.78	0.277	5.65
IIV F_{par} for CF1	(CV)	0.713	10.8	0.715	10.5
IIV CL_{par} for healthy subject	(CV)	0.128	7.64	0.128	7.65
IIV F_{par} for healthy subject	(CV)	0.188	6.38	0.190	6.18
Prop. RUV	(CV)	0.337	0.351	0.337	0.342

[a] Multiplied by a conversion factor of 0.9.
The RSE for IIV and RUV parameters are reported on the approximate SD scale. Values are rounded to three significant digits.
See List of Abbreviations and Definition of Terms for definitions.

Conclusion

Overall, the 01 January 2020 cut-off data from study MS200095-0022 had only a minor impact on the previously reported PK models for tepotinib (and for MSC2571109A, not shown).

Absorption

A slow absorption of tepotinib is observed. The median (range) for t_{max} were 8.0 h (6.0 h to 12.0 h) for single-dose administration of 500 mg of the commercial formulation TF3 under fed conditions (high-fat, high-calorie breakfast) (study MS200095-0044).

An absolute bioavailability of 71.6% was observed following administration of the clinical dose (500 mg) as formulation TF1 (given as 5x100 mg tablets) in the fed state (Study EMR200095-007 part B).

Tepotinib is a low-solubility drug and has pH-dependent solubility (slightly soluble at a pH 4.5 and practically insoluble at pH 1.2 and 7.4). Tepotinib has moderate *in vitro*-permeability and it has not

been demonstrated that the fraction absorbed was above 85% (according to the applicant's calculations it is approximately 85%). Thus tepotinib can be classified as a BCS class IV substance.

Tepotinib is a substrate of P-gp.

In the FIH study EMR200095-001, exposure following multiple-administration of tepotinib (CF2 or TF1) is summarised in Table 5. In Figure 3, concentration-time profiles after single dose and multiple dose treatment with 500 mg tepotinib is demonstrated.

Table 5: EMR200095-001: Overview of PK Parameters of Tepotinib Following Multiple Dose Administration of CF2 or TF1 - Regimen 3, Cycle 1, Day 14 (PK Analysis Set)

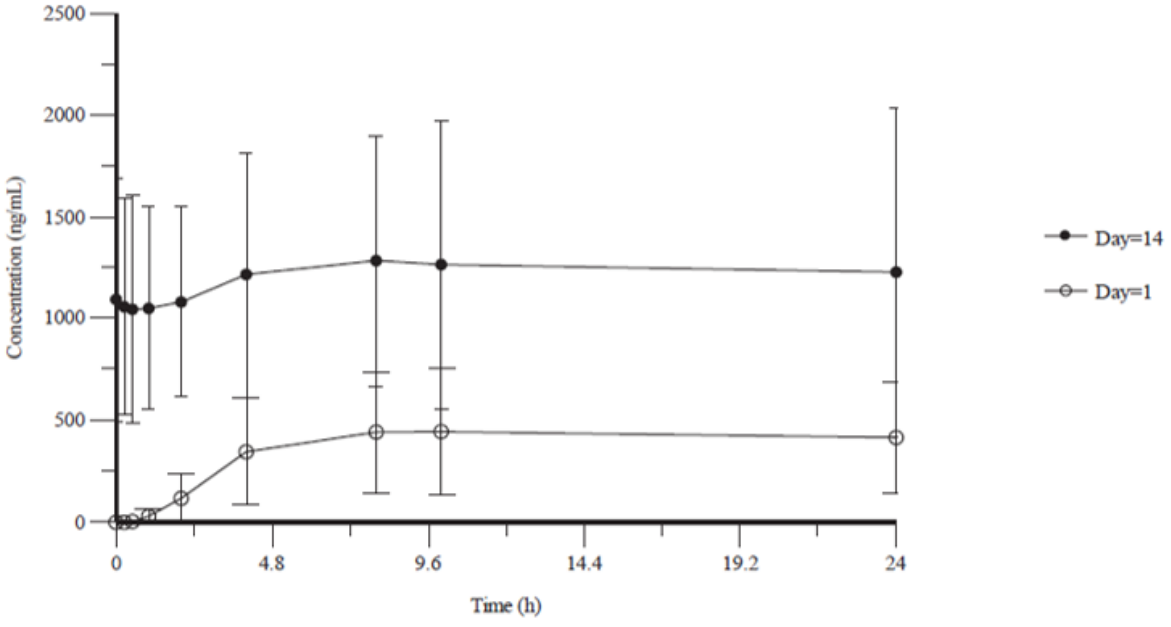
Daily Dose (mg) / Formulation	N	Geometric Mean (Geometric CV%) Median (Min – Max)				
		C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng × h/mL)	CL_{ss}/F (L/h)	C_{av} (ng/mL)
300 / CF2	3	741.6 (45.7) 923.0 (449 – 984)	- 10.0 (0.5 – 10.0)	15,597.6 (50.0) 18,929.2 (9,104 – 22,019)	17.2 (50.8) 14.26 (12.0 – 29.7)	649.8 (50.0) 788.7 (379.3 – 916.9)
500 / CF2	17	943.1 (34.6) 1,040 (497 – 1,570)	- 8.0 (0.0 – 24.0)	20,169.3 (33.5) 20,827.9 (11,038 – 33,507)	22.3 (33.5) 21.16 (13.4 – 40.8)	840.39 (33.5) 868.5 (459.9 – 1,396.1)
500 / TF1	18	1,291 (48.1) 1,205 (599 – 2,960)	- 8.0 (2.0 – 24.0)	27,437.7 (51.7) [a] 27,208.7 (13,741 – 68,365)	23.8 (87.5) 22.53 (6.58 – 83.3)	1,097.9 (47.1) 1,131.5 (540.0 – 2,848.5)
700 / CF2	3	1,006 (39.4) 815.0 (801 – 1,560)	- 3.2 (0.3 – 8.0)	21,972.2 (42.9) 17,456.7 (17,210 – 35,309)	36.8 (3.2) 36.61 (35.8 – 38.1)	916.9 (43.2) 727.4 (717.1 – 1,477.9)
1,000 / CF2	6	1,219 (59.2) 1,116 (653 – 2,940)	- 8.8 (0.0 – 24.0)	27,214.4 (59.4) 24,590.0 (14,662 – 67,062)	32.5 (58.6) 37.08 (13.2 – 61.4)	1,133.4 (59.4) 1,024.8 (610.9 – 2,793.4)
1,400 / CF2	4	1,805 (31.2) 2,040 (1,150 – 2,220)	- 9.1 (2.8 – 24.0)	39,283.7 (28.0) 42,306.7 (26,696 – 50,040)	31.7 (29.5) 29.90 (24.1 – 47.2)	1,638.91 (28.1) 1,762.8 (1,112.3 – 2,095.6)

Source: Study EMR200095-001 CSR, Table 15.4.1.5; for CL_{ss}/F values refer to the Integrated PK Data Analysis Report, March 2020, Table 4.40, Table 4.42, Table 4.43, Table 4.44, Table 4.45, and Table 4.46.

CF2=Capsule Formulation 2, CL_{ss}/F=apparent clearance at steady state, CSR=clinical study report, CV=coefficient of variation, max=maximum, min=minimum, PK=pharmacokinetic, TF1=Tablet Formulation 1.

a n = 13.

Figure 3: EMR200095-001: Concentration-Time Profiles after Single Dose and Once Daily Administration (Day 14 at Steady State) of 500 mg Tepotinib (TF1) (PK Analysis Set)



Source: Study EMR200095-001 CSR, Figure 15.4.2.9, Figure 48.
StD=standard deviation, TF1=Tablet Formulation 1.

Bioequivalence/relative bioavailability

A number of biopharmaceutical studies have been performed, intended to investigate the relative BA/BE of the different formulations used during the clinical development program.

At a dose of 30 mg in the fed state, AUC and C_{max} were slightly higher for TF1 (used in all phase II studies except VISION and also in the study of absolute bioavailability) compared to CF2 (used in the dose escalation studies EMR200095-001 and EMR200095-003), but the 90% CIs were within or almost within acceptance criteria for bioequivalence (upper limit for C_{max} 125.2) (Study EMR200095-002). Comparable bioavailability between TF1 and CF2 can be concluded, although formal bioequivalence has not been demonstrated.

The relative bioavailability of tepotinib (and also of metabolites MSC2571109A and MSC2571107A) for TF2 (used in the VISION study as well as in several clin pharm studies) compared to TF1 in the fed state following a single 500 mg dose was in agreement with the criteria for bioequivalence (Study MS200095-0012).

A pivotal bioequivalence study in the fasted state (Study MS200095-0044) was performed between TF3 (the proposed commercial formulation, introduced in the later parts of the VISION study) and TF2 (the formulation used in the pivotal VISION study) at a dose of 500 mg. A two-stage design was applied. If the PK variability in Stage 1 turned out to be larger than initially assumed, the sample size was to be re-calculated (with alpha-correction) and additional subjects were to be randomized in Stage 2. As the power (estimated based on the measured variability) was 99.89%, the final bioequivalence analysis for Part A was performed after Stage 1 with an alpha level equal to 0.05 as planned. Thus, stage 2 was not performed.

The primary parameters AUC_{0-t} and C_{max} were slightly higher for TF3 compared to TF2 (ratio 115.35 and 113.57% respectively) but the 90% CIs were within conventional acceptance criteria. Results for tepotinib are summarised in *Table 6*.

Table 6: Study MS200095-0044: Summary and Statistical Comparison of Single Dose PK Parameters of 500 mg Tepotinib Administered as TF3 and TF2 (Fasted State)

Parameter	Part A	
	TF3 (Fasted) (n = 38)[a]	TF2 (Fasted) (n = 38)[a]
C_{max} (ng/mL), GeoMean (GeoCV%); 95% CI	288 (22.5) 267; 309	253 (20.6) 237; 271
Ratio TF3/TF2, % (90% CI)[b] Intraindividual CV (%)	**113.57** (107.62, 119.85) 13.94	
AUC_{0-t} (h×ng/mL), GeoMean (GeoCV%); 95% CI	18,645 (21.0) 17,417; 19,960	16,146 (23.4) 14,968; 17,417
Ratio TF3/TF2, % (90% CI)[b] Intraindividual CV (%)	**115.35** (108.55, 122.58) 15.77	
$AUC_{0-\infty}$ (h×ng/mL), GeoMean (GeoCV%); 95% CI	19,316 (21.3) 18,026; 20,699	16,728 (23.9) 15,481; 18,076
Ratio TF3/TF2, % (90% CI)[b] Intraindividual CV (%)	**115.34** (108.51, 122.60) 15.83	
t_{max} (h), median (range)	12.0 (8.00 – 36.0)	14.1 (6.00 – 48.0)
t_{last} (h), GeoMean (GeoCV%); 95% CI	167 (5.5) 164; 170	167 (2.5) 166; 169
$t_{1/2}$ (h), GeoMean (GeoCV%); 95% CI	30.9 (15.3) 29.4; 32.5	31.8 (17.8) 30.0; 33.7
λ_z (h^{-1}), GeoMean (GeoCV%); 95% CI	0.0224 (15.3) 0.0213; 0.0236	0.0218 (17.8) 0.0206; 0.0231
CL/F (L/h), GeoMean (GeoCV%); 95% CI	23.3 (21.3) 21.7; 25.0	26.9 (23.9) 24.9; 29.1
V_z/F (L), GeoMean (GeoCV%); 95% CI	1,038 (24.3) 959; 1,123	1,232 (28.5) 1,124; 1,351
$\%AUC_{extra}$ (%), GeoMean (GeoCV%); 95% CI	2.99 (59.7) 2.50; 3.59	3.05 (54.9) 2.58; 3.61

Source: CSR MS200095-0044, Table 15.4.4.1, Table 15.4.4.2, Table 15.4.4.6.
CV=coefficient of variation; Geo=geometric; PK=pharmacokinetic; TF=tablet formulation.
a n = 38, excluding 2 participants, who discontinued treatment after Period 1.
b Ratio of geometric mean least squares.
Notes: TF2 administered as 1 × 500 mg, TF3 administered as 2 × 250 mg.

A bioequivalence study in the fasted state was also performed between two strengths of TF3 formulation: 100 mg (not included in current application) and 250 mg at a dose of 500 mg ((Study MS200095-0038). Results were within accentance criteria for bioequivalence.

Influence of food

Based on initial assessments of food effect from the FIH study (EMR200095-001), it was decided to administer the product in the fed stated in the further clinical development.

A slight food effect was observed for TF1, with a 17-18% increase in AUC and a 29% increase in C_{max} following a high-fat, high-calorie meal (Study EMR200095-002).

A marked food effect was observed for the proposed commercial formulation TF3 following a high-fat high-calorie meal (1.6-fold increase in AUC and 2-fold increase in C_{max}) and also for the previous formulation TF2 used in the pivotal VISION study (1.9-fold increase in AUC and 2.4-fold increase in C_{max}) (study MS200095-0044). Results for tepotinib are summarised in *Table 7*.

Table 7: Study MS200095-0044: Summary and Statistical Comparison of Single Dose PK Parameters of 500 mg Tepotinib Administered as TF3 (Fed versus Fasted State) and TF2 (Fed versus Fasted State)

Parameter	Part C		Part B	
	TF3 (Fasted) (n = 12)	TF3 (Fed) (n = 12)	TF2 (Fasted) (n = 12)[a]	TF2 (Fed) (n = 14)
C_{max} (ng/mL), GeoMean (GeoCV%);	280 (15.3)	559 (17.0)	199 (29.5)	476 (19.6)
95% CI	254; 309	503; 623	165; 239	426; 533
Ratio Fed/Fasted, % (90% CI)[b]	**199.61** (176.44, 225.82)		**236.51** (215.69, 259.34)	
Intraindividual CV (%)	16.79		12.67	
AUC_{0-t} (h×ng/mL), GeoMean (GeoCV%);	17,964 (19.8)	29,307 (25.0)	12,609 (38.1)	23,457 (25.1)
95% CI	15,859; 20,348	25,056; 34,279	9,978; 15,932	20,333; 27,062
Ratio Fed/Fasted, % (90% CI)[b]	**163.15** (146.17, 182.10)		**186.37** (163.61, 212.28)	
Intraindividual CV (%)	14.93		17.96	
$AUC_{0-\infty}$ (h×ng/mL), GeoMean (GeoCV%);	18,447 (20.0)	30,118 (25.5)	13,037 (38.2)	24,443 (25.9)[c]
95% CI	16,262; 20,927	25,674; 35,331	10,314; 16,479	20,956; 28,510
Ratio Fed/Fasted, % (90% CI)[b]	**163.26** (146.09, 182.46)		**186.67** (163.78, 212.77)	
Intraindividual CV (%)	15.10		17.95	
t_{max} (h), median (range)	12.0 (3.00 – 36.0)	8.0 (6.00 – 12.0)	24.0 (6.00 – 48.0)	12.0 (4.00 – 12.0)
t_{last} (h), GeoMean (GeoCV%);	166 (4.5)	168 (0.2)	162 (7.0)	158 (22.9)
95% CI	161; 171	168; 168	155; 169	139; 180
$t_{1/2}$ (h), GeoMean (GeoCV%);	29.2 (14.7)	29.9 (14.5)	30.8 (11.6)	30.0 (12.9)[c]
95% CI	26.6; 32.0	27.3; 32.7	28.6; 33.1	27.8; 32.4
λ_z (h^{-1}), GeoMean (GeoCV%);	0.0237 (14.7)	0.0232 (14.5)	0.0225 (11.6)	0.0231 (12.9)[c]
95% CI	0.0216; 0.0261	0.0212; 0.0254	0.0209; 0.0243	0.0214; 0.0249
CL/F (L/h), GeoMean (GeoCV%);	24.4 (20.0)	14.9 (25.5)	34.5 (38.2)	18.4 (25.9)[c]
95% CI	21.5; 27.7	12.7; 17.5	27.3; 43.6	15.8; 21.5
V_z/F (L), GeoMean (GeoCV%);	1,027 (24.9)	644 (26.3)	1,531 (40.8)	797 (27.0)[c]
95% CI	879; 1,201	546; 759	1,193; 1,966	679; 936
$\%AUC_{extra}$ (%), GeoMean (GeoCV%);	2.44 (38.9)	2.43 (50.6)	3.13 (35.4)	2.35 (49.6)[c]
95% CI	1.92; 3.10	1.79; 3.29	2.51; 3.89	1.77; 3.12
$F_{rel,fed/fasted}$ (%), GeoMean (GeoCV%);	—	163 (20.6)	—	187 (24.6)[c]
95% CI		143; 186		161; 219

Source: CSR MS200095-0044, Table 15.4.4.1, Table 15.4.4.2, Table 15.4.4.8, Table 15.4.4.9.
CV=coefficient of variation; Geo=geometric; PK=pharmacokinetic; TF=tablet formulation.
$F_{rel,fed/fasted}$: Relative bioavailability (fasted versus fed), defined as $AUC_{0-\infty,fed}$ / $AUC_{0-\infty,fasted}$.
a n = 12, participants with available data for summary statistics (excluding 2 participants).
b Ratio of geometric mean least squares.
c For the calculation of statistics, unreliable PK parameters were set to missing (refer to CSR MS200095-0044 Listing 16.2.5.13).
Notes: TF2 administered as 1 × 500 mg, TF3 administered as 2 × 250 mg.

In the DDI study MS200095-0039, the effect of a standardised continental breakfast on TF2 formulation, when taken with omeprazole, was assessed. Fed (standardised continental breakfast) as compared to fasted conditions increased tepotinib exposure (AUC by about 1.5-fold and C_{max} by about 2-fold) in the presence of omeprazole.

Distribution

Following a single intravenous dose of ^{14}C-labeled tepotinib, the geometric mean (Geo-CV%) volume of the central compartment (Vc) was 34.6 L (44.3%) and the volume of distribution in the terminal phase (V_Z) was shown to be large with a geometric mean (Geo-CV%) of 573.6 L (14.4%) (Study EMR200095-007 part B).

The *in vitro* protein binding of tepotinib was investigated using equilibrium dialysis. The fraction unbound of tepotinib increased with increasing concentration and was 2% at the concentration 1 µM, closest to the steady state C_{max} of 2.6 µM. In the mass balance study (EMR200095-007 part A), the unbound fraction ranged from 1.8 to 2.5% on average and in the HI study (study MS200095-0028), unbound fractions of tepotinib ranged from 1.5% to 2.3% in healthy volunteers with normal hepatic function.

The *in vitro* protein binding in plasma of the major metabolite MSC2571109 was investigated using equilibrium dialysis. Protein binding was not dependant on concentration and was also high, with a fraction unbound of 1.2%.

Human serum albumin and α1-acid glycoprotein were identified as the main binding proteins for tepotinib and MSC2571109 in human plasma.

The mean *in vitro* blood-to-plasma ratio was 0.8 for both tepotinib and main metabolite MSC2571109. For parent drug a slight concentration dependency was observed, and the blood-to-plasma ratio determined at 1.0 µM (closest to the steady state Cmax) was 1.0. Blood/plasma ratio from the mass balance study was around 0.8.

Elimination

Following a single intravenous dose of tepotinib the geometric mean (geometric CV%) clearance was estimated to be 12.8 L/h (7.8%). A geometric mean elimination half-life of 31 hours was observed after administration of a ^{14}C-tepotinib tracer intravenous dose (Study EMR200095-007 part B).

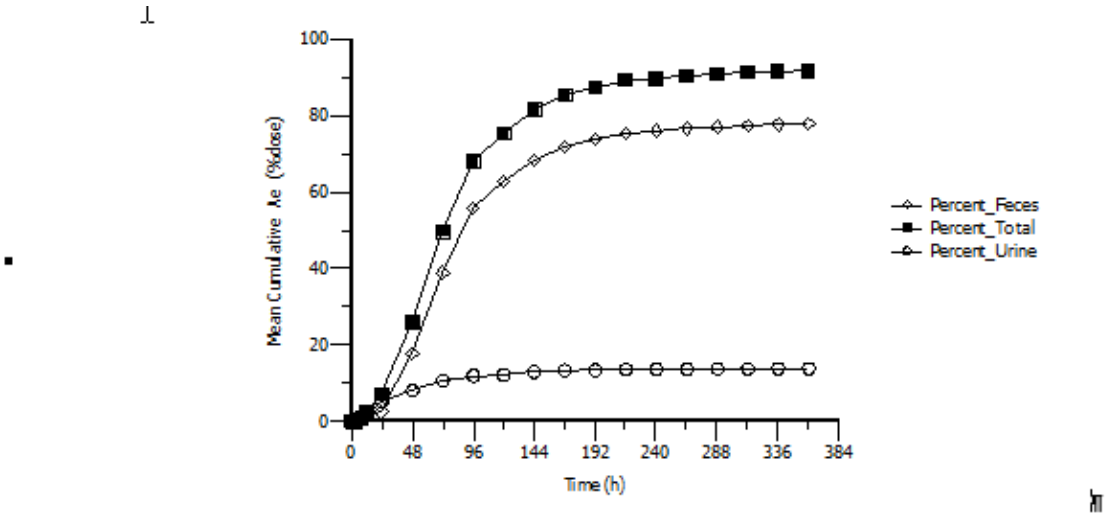
Following a single oral administration of tepotinib 500 mg (TF3) in healthy participants, the geometric mean elimination $t_{1/2}$ was 30.9 h (geometric CV% 15.3%; Study MS200095-0044).

Based on a population PK analysis, tepotinib has a CL/F of 20.4 L/h (relative standard error [RSE] 2.07%) and the effective half-life is 32.1 h (standard error: 0.5 h).

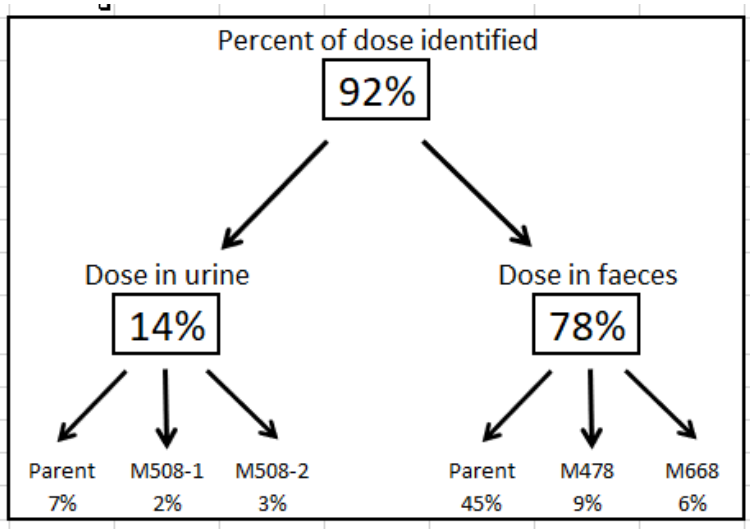
Mass balance

Part A of study EMR200095-007 was a single-dose mass balance study conducted in 6 healthy male volunteers in the fed state (tepotinib administered 30 min after the start of a high-fat breakfast). Subjects received a single oral nominal dose of 500 mg tepotinib (498 mg spiked with 2.67 MBq ^{14}C-labeled tepotinib) as Capsule Formulation 3 (CF3, prepared from crushed TF1 tablets). A total of 91.9% (geometric mean; range 87.1% to 96.9%) of the ^{14}C-labeled dose could be recovered in excreta collected daily up to Day 16 after dosing. Radioactivity was mainly excreted via feces (geometric mean of 77.9%; range 69.4% to 82.5%). Urinary excretion accounted for only 13.6% (geometric mean; range 8.8% to 17.7%) of the total radioactive material. In urine, the parent compound accounted for 7% of the total radioactive material administered. In faeces, the parent compound tepotinib accounted for 45% of the total radioactive material administered.

Figure 4: Study EMR200095-007: Cumulative Recovery of Total ^{14}C Radioactivity in Urine and Feces as Well as Total Recovery



Source: Study EMR200095-007 CSR, Table 15.4.1.32, Table 15.4.1.34, and Table 15.4.1.36.



In faeces, the racemic metabolite M506 (R-enantiomer MSC2571109A of M506 being a major metabolite in plasma that is assessed for interaction potential) accounted for about 3% of the administered dose.

Metabolism

In vitro metabolism data indicate that CYP3A4 and CYP2C8 are involved in the metabolism of tepotinib, although this could not be confirmed in the study in hepatocytes. The formation of the major metabolite was also investigated in a separate study, indicating that this occurred in two steps with involvement of several CYPs (mainly CYP3A4, 2C8 and 1A2) and also cytosolic enzymes and non-enzymatic reactions.

10 different Phase I and Phase II metabolites were found in plasma, feces, and urine in the mass balance study.

Parent drug accounted for 54% of the radioactivity in plasma. The chiral metabolite M506 (MSC2569775) was identified as the only major circulating metabolite in plasma with AUC geometric mean ratios of 40.4% and 74.9% in relation to total radioactive material and parent compound tepotinib, respectively. This metabolite had previously not been detected using human hepatocytes. No other metabolites had an extent of exposure more than 10% of parent drug or total radioactive material (M668 had AUC ratios of 3.4% and 6.3% in relation to total radioactivity and parent compound, respectively). M506 is a chiral mixture; using an enantio-selective UPLC-MS/MS method it was later clarified that the R-enantiomer MSC2571109A accounted for 64.6% and the S-enantiomer MSC2571107A for only about 4.5% of the exposure of the parent drug in the mass balance study.

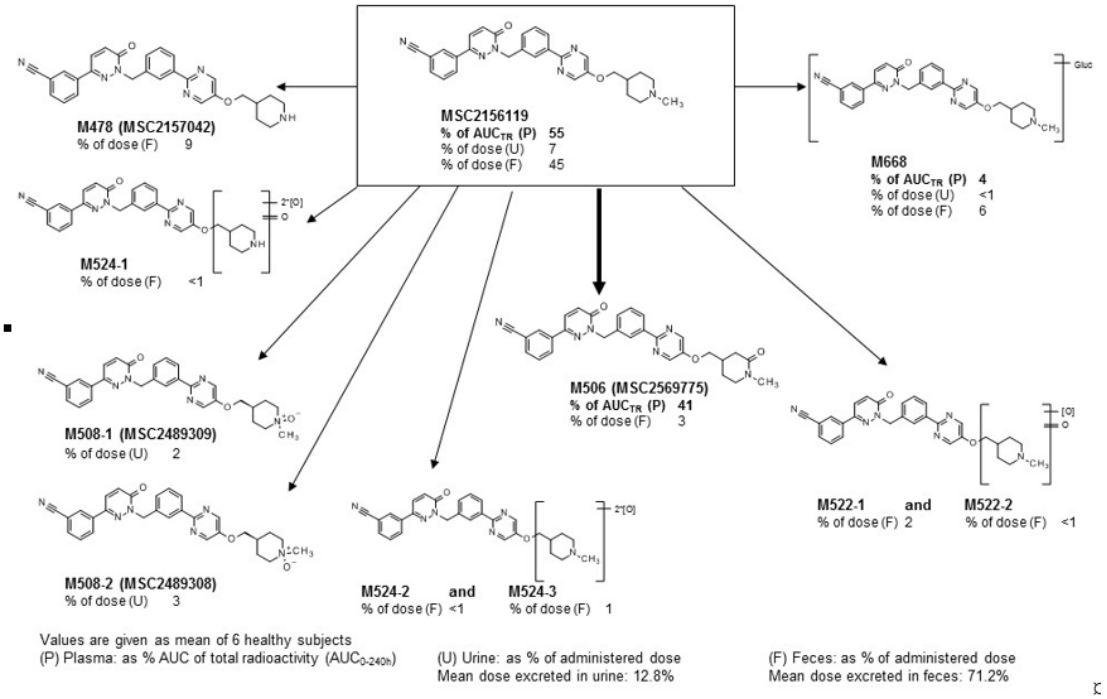
In urine, 91% of the recovered radioactivity could be identified. The parent compound tepotinib was the main renally eliminated constituent with 7% of the administered radioactive dose. N- oxide metabolites, i.e. M508-1 (MSC2489309) and M508-2 (MSC2489308) accounted in urine to about 2% and 3% of the administered dose, respectively.

In feces, 93% of the recovered radioactivity could be identified and allocated to metabolite structure proposals. The main radioactive constituent was parent compound tepotinib accounting for 45% of the administered radioactive dose. The des-methyl metabolite M478 (MSC2157042) accounted for 9% of administered dose and the direct N-glucuronide M668 for 6% of the administered dose. The racemic metabolite M506 (MSC2569775) accounted for about 3% of the administered dose and all further oxidized metabolites M524-1,-2 and-3 and M522-1 and -2 accounted for less than 2% of the administered dose each.

In total, metabolites accounted for 48% of recovered tepotinib-related radioactivity.

The metabolism scheme suggested by the applicant is presented in Figure 5 and a figure of the major routes of excretion is presented in Figure 6.

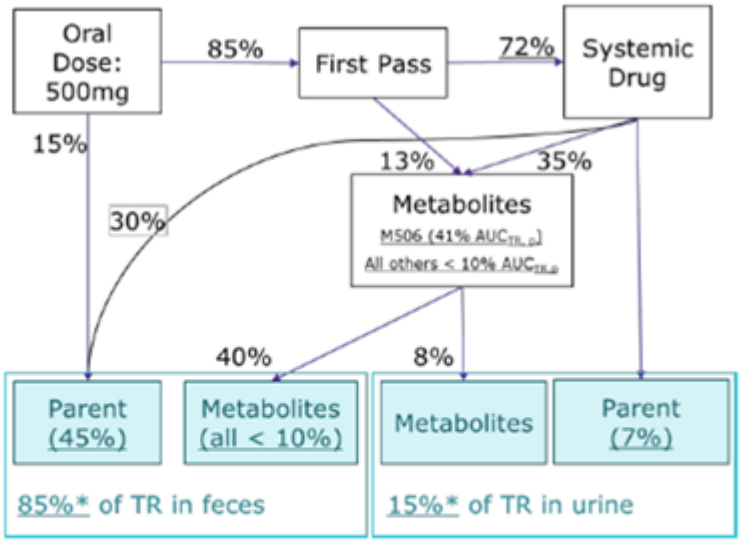
Figure 5: Main Metabolic Pathway of Tepotinib after Oral Administration of ^{14}C-Labeled Tepotinib in Humans



- Source: MSC2156119J - 14-GR004-C0 - Metabolite Pattern (Metabolite Report to Study EMR200095-007 CSR) Section 7.4.
- MSC2156119=tepotinib.

Source Study Reports: (refer to Study Reports 14-GR004-C0, DMPK 35-10, 18-DA0061-0, 14-GR108-V0, 15-GR019-P0, G-A-VIV-18-023 (18-DA0487-0)).

Figure 6: Major Routes of Excretion of ^{14}C-Labeled Tepotinib as Percent of ^{14}C-Labeled Dose in Urine and Feces (Means)



Source: Report 19-DA0128-0, Section 4.2. Underlined information from Study EMR200095-007.
TR=total radioactivity.
*Amounts in feces and urine adjusted for recovery (92%).
Percentages refer to total dose administered, unless noted otherwise.
Numbers are approximate and based on assumptions as presented in the text.

Pharmacokinetics of metabolites

Chiral M506, an oxidative metabolite, is the only major plasma metabolite. M506 was later identified as mixture of the stereoisomers MSC2571109A and MSC2571107A. In the mass balance study (EMR200095-007) the M506 R-enantiomer MSC2571109A accounted for 64.6% and the S-enantiomer MSC2571107A for 4.5% of the exposure of the parent drug. In Study MS200095-0012, the metabolite $AUC_{0-\infty}$ to tepotinib $AUC_{0-\infty}$ ratio was approximately 54% for MSC2571109A and approximately 3% for MSC2571107A (TF2 and TF1 formulations). Therefore, MSC2571107A can be considered a minor metabolite and MSC2571109A a major metabolite.

The applicant concludes that there was only a negligible contribution of the major circulating metabolite (MSC2571109A) to the overall efficacy of tepotinib in humans.

Both MSC2571109A and MSC2571107A were measured in several studies following single and multiple doses of tepotinib.

In Study MS200095-0039, after a single dose of 500 mg tepotinib (TF2) administered after a normal breakfast during concomitant treatment with omeprazole, the median t_{max} of MSC2571109A was 24.0 h (range: 24 to 48 h) and the geometric mean $t_{1/2}$ was 31.7 h (95% CI: 26.9 to 37.4 h). In Study MS200095-0044, corresponding values for t_{max} and $t_{1/2}$ in the fed state (high-fat meal) were similar (24 hours (range 24 to 48 h) and 33.3 hours for TF2 (Part B of the study) and 24 hours (range 16-48 h) and 34 hours for TF3 (Part C). The $t_{1/2}$ for MSC2571109A is similar to the $t_{1/2}$ of tepotinib and suggests formation rate limited PK for MSC2571109A.

The steady state exposure of metabolite MSC2571109A following daily doses of 500 mg tepotinib (TF1) in study MS200095-006 was as follows (GM(%CV)): Cmax, ss 444 ng/ml (45.8) and $AUC_{T,ss}$ 7530 ng*h/ml (52.6).

Dose proportionality and time dependencies

In study EMR200095-001, less than dose-proportional increase with increasing dose was observed with the CF2 formulation over the entire studied dose-range. In the lower dose range of 30 to 300 mg,

dose-proportionality was supported with this formulation, while a less than dose-proportional increase was observed at higher doses.

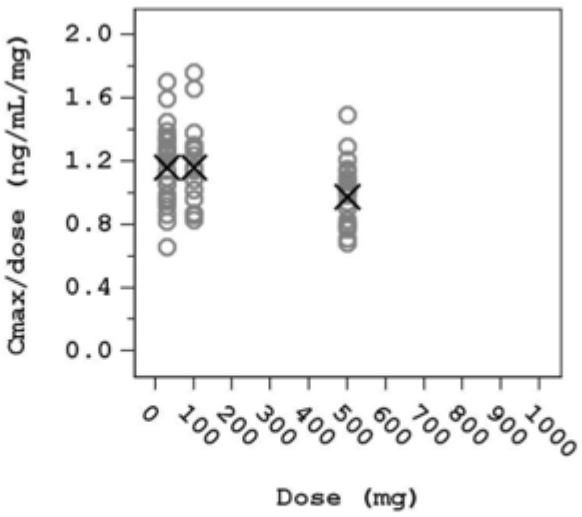
In study EMR200095-004 with TF1 formulation, dose-normalized values for C_{max} and AUC_{τ} showed a trend that tepotinib exposure increases less than dose proportionally across dose levels of 300 to 1,000 mg.

In study EMR200095-006 with TF1 formulation, mean tepotinib exposures (AUC_{τ} and C_{max}) at steady state (C1D15) for the 500 mg dose were slightly less than dose proportional (15% to 18%), compared with the 300 mg dose.

In study EMR200095-007, CL/f, Vz/f values and also dose adjusted exposure parameters, i.e. Cmax, $AUC_{0-\infty}$, and AUC0-t estimated after single dose treatment with 100 mg (part C) and 500 mg (part B) of TF1 were comparable (6-15% difference in dose-adjusted AUC and Cmax) and indicate that there is no dose-dependent PK of tepotinib in the dose range of 100 to 500 mg with TF1 formulation.

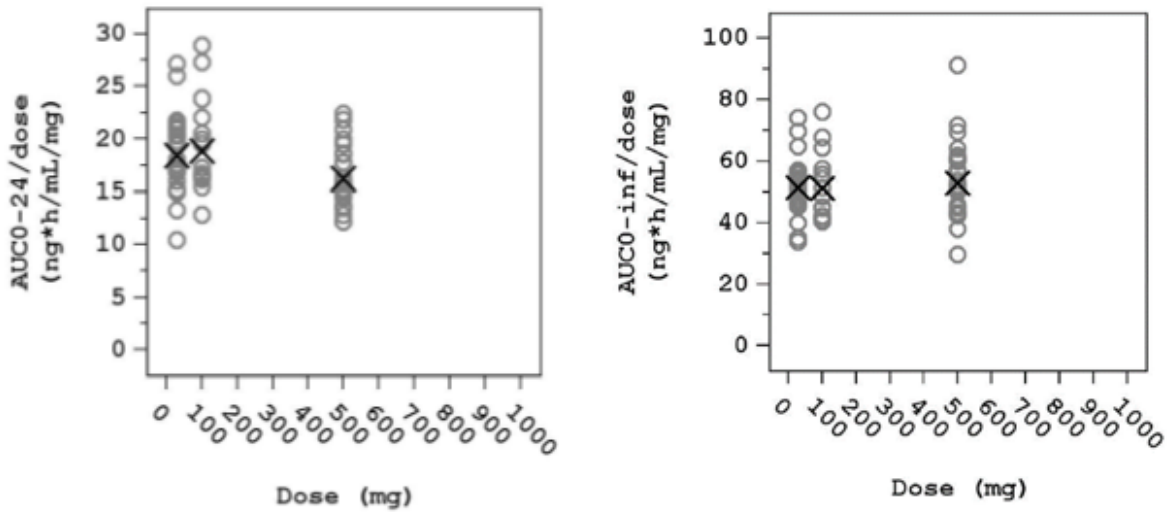
Single dose data of dose-adjusted Cmax and AUC from studies EMR200095-002, -007 and -0012 with TF1 in fed (high-fat high-calorie breakfast) conditions are summarised in the figures below.

Figure 7: EMR200095-002, -007, -0012: Dose-Normalized C_{max} after Single Doses of Tepotinib Administered as TF1



Source: Integrated PK Data Analysis Report, March 2020, Figure 5.
TF1=Tablet Formulation 1.
Individual values and geometric means for C_{max}.
O=individual value.
x=geometric mean.

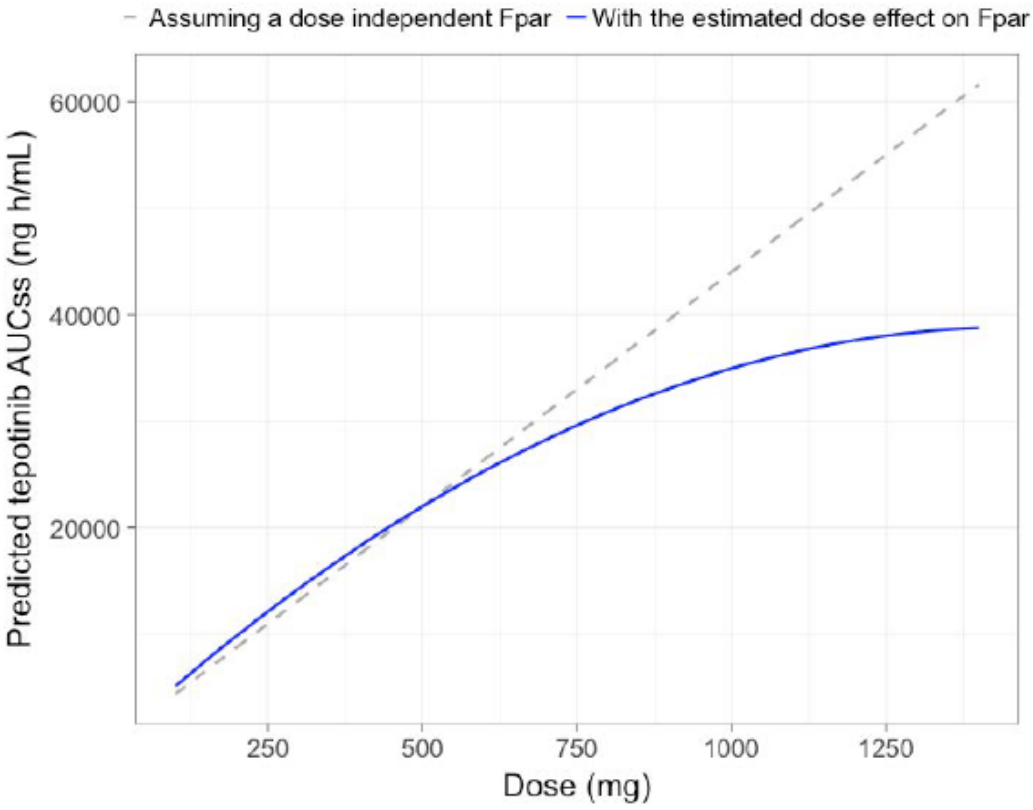
Figure 8: EMR200095-002, 007, 0012: Dose-Normalized AUC0-24 and AUC0-∞ after Single Doses of Tepotinib Administered as TF1



Source: Integrated PK Data Analysis Report, March 2020, Figure 6 and Figure 7.
TF1=Tablet Formulation 1.
Individual values and geometric means for AUC_{0-24} (A) and $AUC_{0-\infty}$ (B).
O=individual value.
x=geometric mean.

Dose linearity was investigated in the population PK analysis where it was included in the model as a less than dose proportional change in bioavailability with increasing dose, across the entire dose range included in the analysis (30 to 1,400 mg). The estimated effect of dose on tepotinib AUC_{ss} from the population PK analysis is illustrated in Figure 9 and indicates a lack of relevant deviation from dose linearity up to 500 mg.

Figure 9: Predicted Tepotinib AUC_{ss} Versus Dose



Source: Pharmacometrics Pooled Population PK Report, April 2020, Figure 33.
AUC_{ss}=steady state AUC, F_{par}=bioavailability of parent drug.
The blue line represents the relationship between AUC_{ss} and dose according to the final tepotinib model while the grey dashed line displays the theoretical relationship between tepotinib AUC_{ss} and dose if there were no impact of dose on F_{par}.

The applicant concludes that deviation from dose-linear exposure for the capsule formulation CF2 was observed across the dose range up to 1,400 mg in Study EMR200095-001. However, data from the studies using the tablet formulations at doses up to 500 mg showed dose-linear exposure in the clinically relevant dose range.

After multiple dosing of 500 mg tepotinib as TF1, median R_{acc} C_{max} was 2.539 and the median R_{acc} $AUC_{0\text{-}24h}$ was 3.306. The following values of C_{max} and $AUC_{0\text{-}24\ h}$ at steady state were reported: C_{max}: 1291 ng/ml and $AUC_{0\text{-}24h}$: 27437.7 ng/mL*h (Study EMR200095-001).

PK data for tepotinib at steady state following a dose of 500 mg (TF2, taken with standardised breakfast) in study MS200095-0032 was as follows: $AUC_{0\text{-}24\ h,\ ss}$ was 18112 ng/mL*h and $C_{max,\ ss}$ was 891 ng/ml.

The stationarity of tepotinib PK with respect to time was not studied directly but the applicant states that inspection of the goodness of fit plots from the population PK analysis revealed no trends in the residuals with respect to time, indicating that tepotinib PK characteristics are constant with respect to time.

Intra- and inter-individual variability

When the proposed commercial formulation of tepotinib, TF3, was administered as single 500 mg doses to healthy volunteers in the fed state (high-fat meal), the interindividual variability (GeoCV%)

was 17.0% for C_{max}, and 25.0% and 25.5% for AUC_{0-t} and $AUC_{0-\infty}$, respectively (Study MS200095-0044).

Across Studies EMR200095-002, EMR200095-007, and MS200095-0012 (all in healthy volunteers), the mixed intraindividual variability (CV%) ranged between 10.0% and 12.8% in the fed state for doses between 30 and 500 mg. Single doses of 500 mg were tested under fasted conditions in healthy participants in part A of Study MS200095-0044, in which TF3 was compared to TF2. The mixed intraindividual variability was 16% for AUC_{0-t}, and 14% for C_{max}. The maximum value for the mixed intraindividual variability was observed for C_{max} (23.7%) for a dose of 30 mg.

The interindividual variability in CL for patients was estimated to be 33.5%. No direct estimate of the intraindividual variability in tepotinib CL was obtained in the population PK analysis, but, given that the residual variability was 33.7% (which includes intraindividual variability as well as variability due to the tepotinib assay, potential model misspecification and any errors in correct documentation of PK sample timing), it may be concluded that the patient intraindividual variability in tepotinib PK is less than the interindividual variability.

Pharmacokinetics in target population

In the population PK analysis including 613 study participants (175 healthy participants and 438 patients with solid tumours) only colorectal cancer and hepatocellular carcinoma statistically significantly influenced CL/F of tepotinib.

The predicted typical individual PK parameters for tepotinib based on the pop-PK analysis is described in *Table 8*.

Table 8: Descriptive Statistics for the Bootstrap Predicted Tepotinib Typical Individual PK Parameters in Cancer Patients

Parameter	Mean	SE	5th, 95th Percentile
CL_{par}/F (L/h)	19.3	0.6	18.3; 20.2
Relative F_{par} actual doses	1.12	0.04	1.06; 1.18
Relative F_{par} 500 mg	0.94	0.01	0.92; 0.96
Relative F_{par} 250 mg	1.04	0.02	0.99; 1.08
AUC_{ss} 500 mg (ng × h/mL)	22,272	695	21,225; 23,447
AUC_{ss} 250 mg (ng × h/mL)	12,277	397	11,701; 12,914
$C_{max,ss}$ 500 mg (ng/mL)	1,236	40	1,175; 1,299
$C_{max,ss}$ 250 mg (ng/mL)	683	33	627; 737
$C_{trough,ss}$ 500 mg (ng/mL)	952	34	903; 1,008
$C_{trough,ss}$ 250 mg (ng/mL)	523	26	481; 557
V_{ss}/F (L)	2,091	759	1,184; 3,530
t_{ss} (h)	128.3	1.9	125.5; 131.7
$t_{1/2,eff}$ (h)	32.1	0.5	31.4; 32.9

Source: Pharmacometrics Pooled Population PK Report, April 2020, Table S3.

AUC_{ss} 500/250 mg=steady state AUC for 500/250 mg, CI=confidence interval, CL_{par}=apparent CL of parent drug, $C_{max,ss}$ 500/250 mg=maximum concentration at steady state for 500/250 mg, $C_{trough,ss}$ 500/250 mg=trough concentration at steady state for 500/250 mg, F_{par} actual doses= bioavailability of parent drug for the actual doses in the analysis dataset, F_{par} 500/250 mg= bioavailability of parent drug for 500/250 mg, SE=standard error, T_{ss}=time to steady state, $t_{1/2eff}$=effective half-life, V_{ss}/F=apparent volume of distribution at steady state.

Note: The results are based on 100 bootstrap samples. The mean is the bootstrap estimate of the typical individual value of the parameter, the SE is the bootstrap estimate of the precision in the typical individual value of the parameter (computed as the StD of the 100 bootstrap estimates) and the 5th and 95th provide the 90% bootstrap CI for the parameter.

Special populations

Impaired renal function

No specific clinical pharmacology study has been performed that investigates the potential influence of renal impairment on the PK of tepotinib.

In the mass balance study using ^{14}C-tepotinib (Study EMR200095-007), urinary excretion was identified as a minor route of elimination with only 13.6% of the total radioactivity found in the urine and with 7% of the administered radioactive dose as parent drug). The applicant concludes that this indicates that decreased renal function is unlikely to result in clinically significant change in exposure.

Patients with moderate or severe renal impairment were excluded in the early clinical studies (CrCL ≤ 60 mL/min in Study EMR200095-001 and CrCL < 60 mL/min in studies EMR200095-003, -004, -005, -006). However, in the pivotal VISION study, inclusion of patients with moderate renal impairment (i.e., CrCL ≥ 30 mL/min) was permitted.

In the population PK analysis, renal impairment was assessed using eGFR as determined by the MDRD formula. The apparent CL of tepotinib was found positively correlated to eGFR, but the influence on exposure appears to be limited (eGFRs of 30, 60, 80 to 110 mL/min/1.73m2 for a typical individual receiving 500 mg of tepotinib leads to CLpar values of 16.2, 18.6, 19.7 and 20.9 L/h, respectively).

Impaired hepatic function

In study MS200095-0028, PK of tepatinib and metabolites were compared in healthy subjects and subjects with mild or moderate hepatic impairment following a single dose of 500 mg tepotinib (TF2 formulation) with a standardised breakfast. Tepotinib exposures based on the total plasma concentrations (AUC and C_{max}) were similar in healthy participants and patients with mild hepatic impairment (Child-Pugh Class A). In patients with moderate hepatic impairment (Child-Pugh Class B), the mean total plasma AUC and C_{max} values were approximately 13% and 29% lower respectively, than those in healthy participants. Mean half-life of tepotinib was 38 hours in healthy subjects, 43 hours in subjects with mild hepatic impairment and 54 hours in subjects with moderate hepatic impairment.

Regarding unbound tepotinib, the mean $AUC_{0-\infty,u}$ were about 13% and 24% higher in patients with mild and moderate hepatic impairment, respectively, compared to healthy participants. Observed mean $CL/F_{,u}$ values were slightly decreased by about 5% and 17% in patients with mild and moderate hepatic impairment, respectively, compared to healthy participants which is within the observed exposure variability (CV of 23.8%, 24.2% and 27.7% for $AUC_{0-\infty,u}$, $C_{max,u}$ and $CL/F_{,u}$ in healthy controls).

For subjects with moderate hepatic impairment (Child-Pugh class B), exposure to MSC2571109 based on AUC and C_{max} ratios was approximately 37% and 15% higher, respectively, compared to healthy subjects. The mean half-life of MSC2571109 was 49 hours in healthy volunteers, 54 hours in subjects with mild hepatic impairment and 82 hours in subjects with moderate hepatic impairment.

Exposure to the minor metabolite MSC2571107 based on AUC and Cmax ratios was similar in subjects with mild hepatic impairment compared to healthy subjects, and for subjects with moderate hepatic impairment exposure was similar for $AUC_{0-\infty}$, while C_{max} was approximately 27% lower compared to healthy subjects. The mean half-life was 49 hours in healthy volunteers, 48 hours in subjects with mild hepatic impairment and 82 hours in subjects with moderate hepatic impairment.

The pharmacokinetics of tepotinib have not been studied in patients with severe (Child Pugh Class C) hepatic impairment.

Sex, race/ethnicity, weight, age

In the population PK analysis including 613 study participants (439 male and 174 female participants), sex was not found to influence the parameters of the tepotinib population PK model.

The population PK analysis did not find ethnicity to be a statistically significant covariate on the exposure of tepotinib. No dose adjustments are recommended for patients based on their ethnicity.

An influence of body weight on the apparent central F_{par} was detected in the population PK analysis where 613 study participants with weights ranging from 35.5 to 136 kg were included. The influence was small and was predicted to result in a decrease in AUC_{ss} of 18% if weight changed from the mean weight of 72.9 kg to 103 kg (the 95th percentile of the weight distribution). No dose adjustment is proposed based on body weight.

Based on the available clinical data, no dose adjustments are suggested for elderly patients. In the population PK analysis including 613 study participants (aged 18 to 89 years), age was not found to influence the parameters of the tepotinib population PK model.

Table 9: Age categories for participants in PK trials

	Age Category (years)			
Study	Age < 65 n/N (%)	Age ≥ 65 - <75 n/N (%)	Age ≥ 75 - <85 n/N (%)	Age ≥ 85 n/N (%)
Rich PK studies				
EMR200095-001	94/149 (63.1%)	40/149 (26.8%)	15/149 (10.1%)	0/149 (0.0%)
EMR200095-002	28/28 (100.0%)	0/28 (0.0%)	0/28 (0.0%)	0/28 (0.0%)
EMR200095-003	6/12 (50.0%)	5/12 (41.7%)	1/12 (8.3%)	0/12
EMR200095-004 Phase Ib	22/27 (81.5%)	5/27 (18.5%)	0/27	0/27
EMR200095-005 Phase I	4/17 (23.5%)	10/17 (58.8%)	3/17 (17.6%)	0/17
EMR200095-006 Phase I	9/18 (50.0%)	6/18 (33.3%)	3/18 (16.7%)	0/18
EMR200095-007	27/27 (100.0%)	0/27	0/27	0/27
MS200095-0012	24/24 (100.0%)	0/24	0/24	0/24
MS200095-0028	15/18 (83.3%)	3/18 (16.7%)	0/18	0/18
MS200095-0030	12/12 (100.0%)	0/12	0/12	0/12
MS200095-0032	20/20 (100.0%)	0/20	0/20	0/20
MS200095-0038	18/18 (100.0%)	0/18	0/18	0/18
MS200095-0039	12/12 (100.0%)	0/12	0/12	0/12
MS200095-0044	66/66 (100.0%)	0/66	0/66	0/66
Sparse PK studies				
EMR200095-004 Phase II	34/45 (75.6%)	10/45 (22.2%)	1/45 (2.2%)	0/45
EMR200095-005 Phase II	21/49 (42.9%)	20/49 (40.8%)	8/49 (16.3%)	0/49
EMR200095-006 Phase II single	9/15 (60.0%)	6/15 (40.0%)	0/15	0/15
MS200095-0022	67/279 (24.0%)	103/279 (36.9%)	89/279 (31.9%)	20/279 (7.2%)
Total (n)	**488**	**208**	**120**	**20**

The pharmacokinetics of tepotinib has not been studied in subjects less than 18 years of age.

Pharmacokinetic interaction studies

Tepotinib as victim of drug interactions

Tepotinib is a substrate of P-gp but not of BCRP, MATE1, MRP2, OATP1B1, OAT1B3, OCT1, OCT2, or MATE2K. The metabolite MSC2571109 is not a substrate of MATE1, OATP1B1, OAT1B3, OCT1, OCT2, or MATE2K. No in vivo study with inducers or inhibitors of P-gp has been performed. The applicant argues that the potential of P-gp inhibitors to increase absorption is small, and that P-gp inhibitors could lead to a worst-case increase in exposure of 1.43-fold (due to inhibition of biliary secretion). In the FIH Study EMR200095-001, the applicant concludes that the maximum tolerated dose was not reached, even at the highest administered dose of 1,400 mg (where exposure was almost double that of the proposed clinical dose of 500 mg once daily) and that therefore, the potential impact of P-gp inhibition on tepotinib exposure is not considered clinically relevant.

In vitro metabolism data indicate that CYP3A4 and CYP2C8, and possible other enzymes such as FMOs, are involved in the metabolism of tepotinib. In the formation of the major metabolite, several CYPs (mainly CYP3A4, 2C8 and 1A2) and also cytosolic enzymes may be involved. No in vivo studies with CYP inhibitors or inducers have been performed. The applicant argues that no single identified metabolic pathway in excreta comprises more than 25% of the administered dose and therefore, the DDI potential with tepotinib as a victim of co-administered drugs that interact with drug-metabolizing enzymes is considered low.

As tepotinib has pH dependant solubility, an *in vivo* study investigating the effect of multiple doses of 40 mg omeprazole on single-dose PK of tepotinib (500 mg, TF2 formulation, given with a standardised non-high fat breakfast) has been performed (Study MS200095-0039). Omeprazole had no marked effect on the PK of tepotinib in fed conditions (90% CI of test/reference ratios for AUC and C_{max} were within conventional BE criteria).

Tepotinib as perpetrator of drug interactions

The following cut-offs are used for tepotinib for evaluation of interaction potential in vivo:

50*Cmax(u)[a] (µM)	25*Inlet Cmax(u)[b] (µM)	0.1*Dose/250 ml[c] (µM)
2.6	1.9	365.4

a) Input parameters were C_{max} 1291 ng/ml from study EMR200095-001, fu=0.02, Mw=492.58 g/mol (tepotinib base).

b) Input parameters F=72%, ka=0.00267/min (0.16/h), Blood/Plasma ratio 1.

c) Dose = 450 mg (tepotinib base)

The following cut-offs are used for the major metabolite MSC2571109 for evaluation of interaction potential in vivo:

50*Cmax(u) (µM)
0.5

Input parameters were Cmax 444 ng/ml from study EMR200095-006, fu=0.012, Mw=506.55 g/mol.

The in vitro direct inhibition data by tepotinib and the major metabolite MSC2571109 is summarised in the table below:

	Tepotinib	**MSC2571109A**

	Ki (µM)	Ki (µM)
Enzymes		
CYP1A2	> 25	> 7.5
CYP2B6	> 25	> 7.5
CYP2C8	11.0	> 7.5
CYP2C9	13.5	4.4
CYP2C19	15.0	> 7.5
CYP2D6	> 25	> 7.5
CYP3A	12.5*	> 7.5
UGT1A1	>7.5	0.55
UGT1A3	>7.5	2.9
UGT1A4	>7.5	3.1
UGT1A6	>7.5	>7.5
UGT1A9	1.9*	1.8
UGT2B7	>7.5	>7.5
UGT2B15	>7.5	4.8
UGT2B17	3.05	1.1
Transporters (demanded)		
P-gp	0.21*	Not studied
BCRP	0.95*	Not studied
OATP1B1	88.5	0.4**
OATP1B3	17.5	> 2.5
OAT1	135	> 2.5
OAT3	> 150	1.65
OCT2	33	0.02*
Transporters (optional)		
OCT1	1.15*	0.3
MATE1	1.8*	>2
MATE2-K	0.55*	0.18*
BSEP	>6.4	Not studied

*Value below relevant cut-off

**Value below relevant cut-off but borderline

Assuming Ki = IC50/2 (except for CYP2C8 where Ki was determined)

At clinically relevant concentrations neither tepotinib nor the major circulating metabolite MSC2571109A represent a risk of inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1. Based on in vitro-data there is a risk of direct inhibition of CYP3A4 in the intestine by parent drug tepotinib.

For CYP3A4 TDI was observed for the major circulating metabolite, in particular when looking at testosterone data.

Tepotinib or the major metabolite MSC2571109A do not inhibit UGT1A1/3/4/6, or 2B7/15/17 at clinically relevant concentrations. Tepotinib may be an inhibitor of UGT1A9 at clinically relevant concentrations.

For tepotinib, induction of CYP3A4 was observed in *in vitro* studies. Induction of CYP2B6 and CYP1A2 was not observed. For the metabolite, induction of CYP3A4 and CYP2B6 was observed. Induction of CYP1A2 was not observed.

An in vivo-study has been performed, investigating the effects of multiple doses of tepotinib on the sensitive CYP3A4 substrate midazolam (Study MS200095-0030). No effect was seen on the PK of midazolam following 10 days of treatment with tepotinib, since results for AUC and Cmax were within acceptance criteria for BE.

No study investigating the effect of tepotinib on oral contraceptives has been performed.

Tepotinib inhibits P-gp and BCRP at concentrations relevant for both intestinal and systemic exposure. Tepotinib may also be an in vivo inhibitor of OCT1, MATE1 and MATE2K but is not an inhibitor of OAT1 and OAT3, OATB1B1 and 1B3, BSEP or OCT2 at concentrations relevant for evaluation of potential for in vivo interaction.

Metabolite MSC2571109A may be an in vivo relevant inhibitor of MATE2K and OCT2, but is not an inhibitor of MATE1, OATB1B1 (borderline value, see discussion) and OATPIB3, OAT1 and OAT3, at concentrations relevant for evaluation of potential for in vivo interaction.

Thus, parent drug or metabolite inhibit P-gp, BCRP, OCT1 and 2 and MATE1 and 2 at clinically relevant concentrations.

An in vivo study has been performed in order to assess the in vivo effects of tepotonib administered once daily for 8 days on single dosed of dabigatran etexilate, a sensitive substrate for intestinal P-gp inhibiton, given with a standardised continental breakfast (Study MS200095-0032). Multiple dose treatment with tepotinib increased total dabigatran exposure by 51% for AUC0-t, by 45% for AUC0-∞ and by 38% for Cmax.

No in vivo studies have been performed with BCRP substrates or with substrates of OCT1 and 2 and MATE1 and 2.

Exposure relevant for safety evaluation

In study EMR200095-001, following multiple doses of 500 mg with TF1 formulation in patients, the following values of C_{max} and $AUC_{0\text{-}24\ h}$ at steady state were reported:

C_{max}: 1291 ng/ml (2.62µM)

$AUC_{0\text{-}24h}$: 27437.7 ng/mL*h (55.7 µM*h)

This is the highest exposure seen in a multiple dose study with a 500 mg dose, and has been used for calculation of DDI cut-offs. In the pop-PK analysis, the mean $AUC_{0\text{-}24,ss}$ was 22272 ng*h/ml and the mean $C_{max,ss}$ was 1236 ng/ml with a dose of 500 mg.

For the major metabolite MSC2571109A, the following exposure values have been reported (study EMR200095-006, 500 mg tepotinib with TF1 formulation in patients, cycle 1 day 15):

$AUC_{0\text{-}24h}$: 7530 ng*h/ml
C_{max}: 444 ng/ml

Pharmacokinetics using human biomaterials

2.6.2.2. Pharmacodynamics

Mechanism of action

No mechanism of action studies have been submitted by the applicant.

Primary and Secondary pharmacology

Population PK/PD analysis of Tepotinib target inhibition to inform Phase II dose selection

The inhibition by tepotinib of the phospho-MET in solid tumor tissues, a proximal biomarker, was determined by quantitatively measuring the levels of c-MET auto-phosphorylation (Y1234/Y1235) in paired tumor biopsies (pre- and on-treatment) from subjects in the EMR200095-001.

Data from 13 patients with evaluable pre-treatment and on-treatment phosphoc-MET level were included in the analysis. Dose level ranged from 60 mg/daily to 1000 mg/daily.

The observation of phospho-c-MET in human solid tumors was fitted by a previously developed turnover model with full inhibition effect (Imax), which was structurally determined based on phospho-MET inhibition data from the mouse KP-4 cell line xenograft tumors.

Preclinical target inhibition and efficacy data suggested that greater than 95% of target inhibition was expected at the dose level achieving tumor stasis in KP-4 cell-line xenograft mice.

Accordingly, a conservative PD criterion of sustained close-to-complete inhibition (≥ 95%) of the phosphorylation of c-Met was introduced.

A population PK model, including PK profiles from 308 subjects in seven Phase 1/1b trials (EMR200095-001 ~ EMR200095-007) has been established. The empirical Bayesian estimates of individual parameter from the pop-PK analysis were used to predict the time-profile of plasma concentration, which was correlated with the pharmacodynamic endpoint in the later PK/PD analysis.

Clinical PK/PD simulations indicated that 500 mg dose of tepotinib was expected to maintain biologically meaningful target inhibition with ≥95% phospho-MET inhibition any timepoint at steady state in vast majority (>90%) of patients. This result was supporting 500 mg q.d. dose regimen as the recommended phase II dose.

Exposure-response

3 similar exposure response reports (1 original report and 2 adendum reports) were provided. The addendum was updates of the analyses as more data was available. The latest addendum (SEP 22, 2020, Data cut-off Date: 01 July 2020) is described here.

Objective

The aim of this analysis is to graphically explore the relationships between the exposure of tepotinib derived from the pharmacokinetic (PK) model and each efficacy endpoint (OR, DOR, and PFS).

Dataset

The data for this analysis originated from the 01 July 2020 data cut-off from study MS200095-0022 (VISION), cohort A. The exposure-efficacy analyses presented are based on the 01 July 2020 cut off which provide at least 15 months of follow up on a set of subjects having their first dose prior to 02 Apr 2019 as well as provide at least 9 months of follow up on a larger set of subjects having their first dose prior to 02 Oct 2019.

PK metric for analysis

Tepotinib 24-hour area under the curve at steady state ($AUC_{\tau,ss}$) was used as the representative exposure metric in the analysis of all efficacy endpoints. The exposure metric of tepotinib $AUC_{\tau,ss}$ was predicted for all subjects in the analysis data set, using the individual estimated parameters of the tepotinib population PK model (V 1.0)

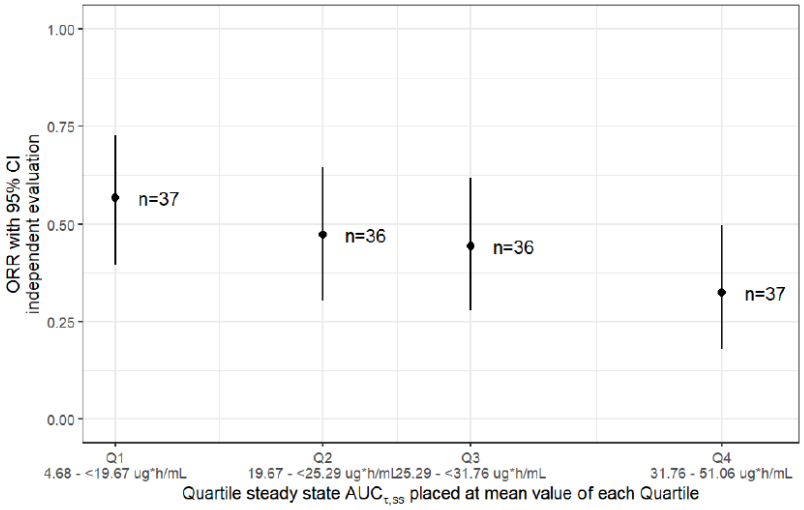
Method

The analysis was a graphical analysis designed to explore the relationship between tepotinib exposure and the efficacy in solid tumour non-small cell lung cancer (NSCLC) patients with MET exon 14 (METex14) skipping alterations.

The potential influence of tepotinib exposure on OR, for both Investigator Assessment of OR and OR determined by independent evaluation, was explored graphically. This was done by estimating means across subjects of objective response rate (ORR) and using the Clopper-Pearson method computing the 95% confidence intervals for ORR for each quartile of tepotinib $AUC_{\tau,ss}$.

Results

Increasing $AUC_{\tau,ss}$ quartile was not associated with an increased ORR (*Figure 10*). There was no apparent association between $AUC_{\tau,ss}$, and DOR (*Figure 11*). There was no apparent association between $AUC_{\tau,ss}$, and PFS (*Figure 12*).



Based on pooled data from patients positive for TBx+ (tumour biopsy) and/or LBx+ (liquid biopsy). The lines represent the Clopper-Pearson 95% CI (confidence interval) and the points are the observed ORR (objective response rate) per quartile. n is the number of subjects in each quartile. The values are placed at the mean value for each quantile on the x-axis.

Figure 10. ORR based on independent evaluation by tepotinib steady state AUC (AUCτ,ss)quartile in subjects receiving first dose before 02Oct2019 (n=146)

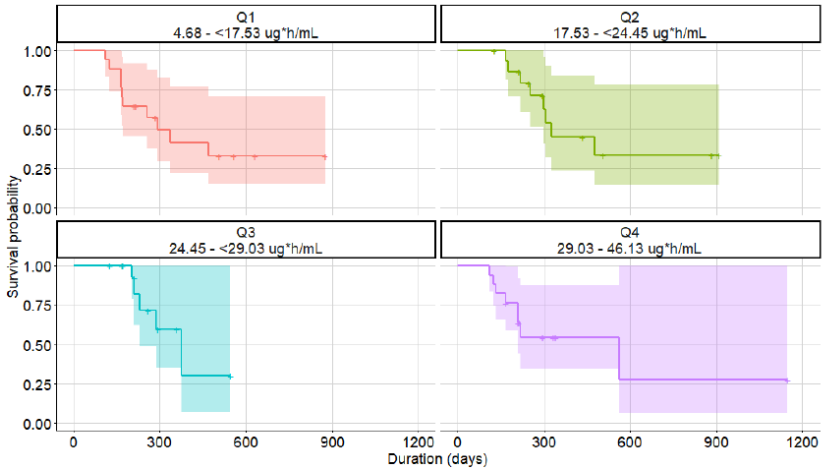


Figure 11. KM plot of DOR based on independent evaluation, stratified by tepotinibsteady state AUC (AUCτ,ss) quartile - in subjects receiving first dose before 02Oct2019 (n=66)

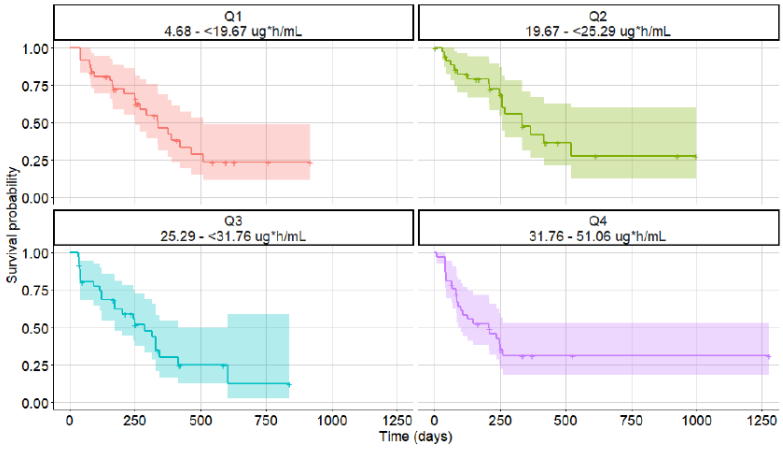


Figure 12. KM plot of PFS based on independent evaluation, stratified by tepotinib steadystate AUC ($AUC_{T,ss}$) quartile - in subjects receiving first dose before 02Oct2019(n=146)

Exposure safety analysis

The aim of this analysis was to evaluate the relationship between tepotinib exposure, as derived from a population pharmacokinetic (PK) model and some pre-specified safety endpoints in solid tumour patients treated with tepotinib monotherapy. The safety endpoints included were; time to the first oedema event, maximum severity grade of oedema, serum lipase, serum amylase, serum albumin, serum creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations. In addition, the impact of tepotinib on serum creatinine following a single dose in healthy subjects was evaluated.

The exposure-safety analysis included data from Studies EMR200095-001, EMR200095-003, EMR200095-004, EMR200095-005 and VISION (data cutoff 01 January 2020) in which all patients

499 study patients were included in the analysis with 201 coming from the VISION study.

Exposure used in exposure-safety

The primary individual exposure metric used in the exposure-safety analyses was tepotinib daily AUC. For serum creatinine, the MSC2571109A daily AUC was also used. AUC were predicted from individual parameter estimates from the tepotinib and MSC2571109A population PK models developed with the 18 February 2019 cut off data but also using the data from the VISION study with a data cut off between 18 February 2019 and 01 January 2020.

Graphical exploratory analysis ALT, AST, serum lipase, amylase levels.

No apparent relationship was found between tepotinib exposure and ALT, AST, serum lipase, or amylase level (not shown, see also PK AR).

Serum albumin

No apparent trend in the decreasing albumin concentrations with increasing tepotinib exposure (*Figure 13*).

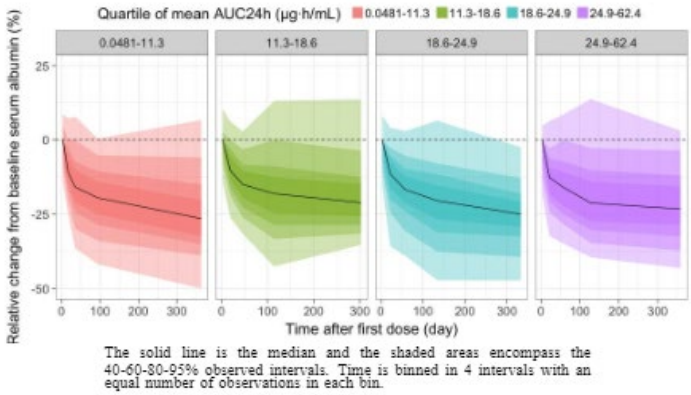


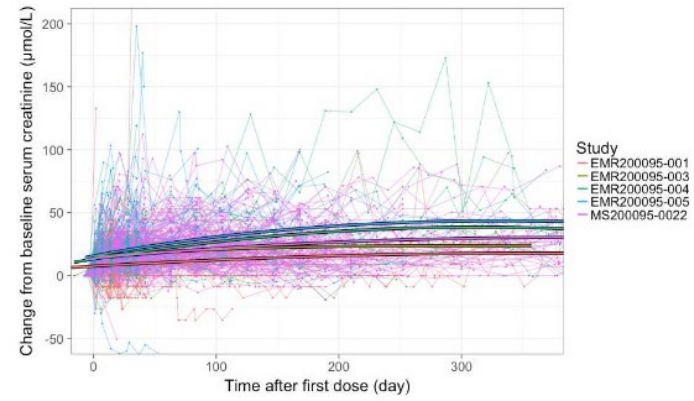
Figure 13. Relative median change from baseline serum albumin versus time after first dose stratified by mean AUC24h quartile

In addition to graphical analysis, time course of the change in serum albumin concentration was described using an indirect response model. The impact of tepotinib was assumed to inhibit the formation rate (Kin) of albumin in a Michaelis-Menten fashion.

Tepotinib exposure caused an approximate 26% maximum decrease in serum albumin. The AUC50 associated with the effect is very small (0.215 µg × h/mL) and therefore the onset of the decrease in albumin concentrations is driven mainly by the equilibrium between albumin formation and elimination.

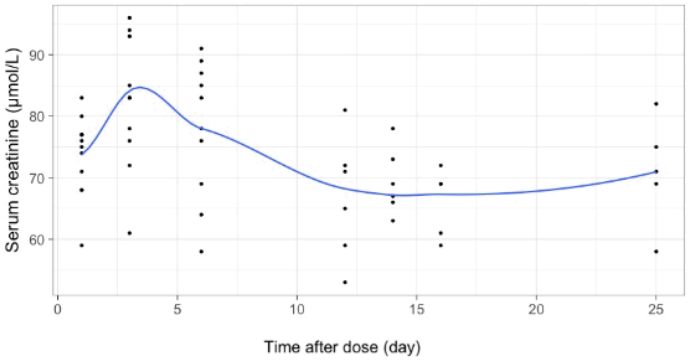
Serum creatinine

The graphical analysis of serum creatinine concentrations found a consistent trend towards an increase in the median observed serum creatinine concentration over time in all studies. The increases reached a plateau after continued tepotinib administration (*Figure 14*), and the time course following administration of single doses of 500 mg tepotinib in healthy participants suggests that the effect is reversible (*Figure 15*).



Source: Pharmacometrics Exposure-Safety Report, April 2020, Figure 44.
LOESS=locally estimated scatterplot smoothing.
Each line represents the data for 1 patient and is colored by study. Solid lines are LOESS smooths colored by study.
The y-axis is truncated at -50 and 150 µmol/L and the x-axis at 365 days.

Figure 14. Observed Change from Baseline Serum Creatinine Concentration Versus Time After First Dose Stratified by Study



Source: Pharmacometrics Exposure-Safety Report, April 2020, Figure 53 (top panel).
LOESS=locally estimated scatterplot smoothing.
Dots represent observations. The solid line is a LOESS smooth.

Figure 15. Observed Individual Serum Creatinine Over Time after a Single Tepotinib Dose of 500 mg in Healthy Participants in Study EMR200095-007

Time to event model Edema

Based on the graphical exploratory analysis, a model-based time to event (TTE) analysis of the time to the first peripheral edema event was performed. The developed TTE base model (before consideration of covariates) was described by a constant hazard (exponential distribution). None of the tepotinib exposure-response models tested had a discernible significant impact on the hazard of time to first peripheral edema event.

The impact of covariates on the model parameter (hazard of time to first peripheral edema event) was evaluated using the SCM procedure. The only covariate included in the final model was an influence of age on the time to first peripheral edema event (*Table 10*).

Table 10. Parameter Estimates of the Final Time-to-Event Model for Time to First Peripheral Edema Event

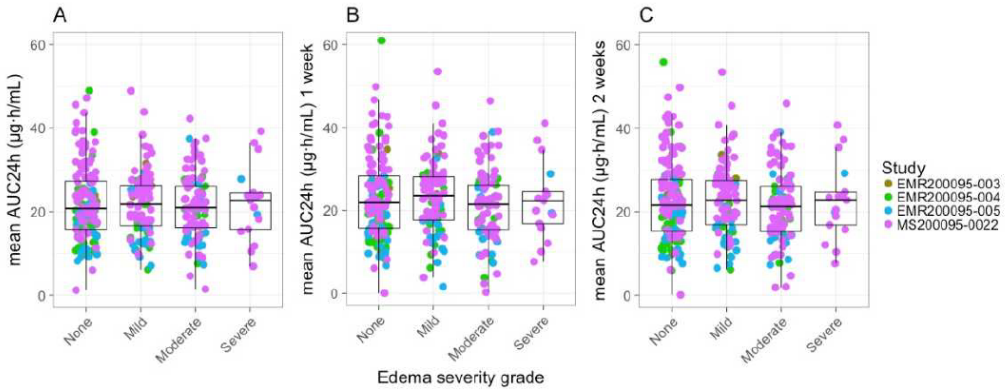
	Value	RSE (%)	90% CI
h_0: base hazard	0.00761	6.59	0.007; 0.008
θ_2: age effect on base hazard	0.0309	19.2	0.020; 0.044

Source: Pharmacometrics Exposure-Safety Report, April 2020, Table 17 and Table 18.
RSE=relative standard error; CI=confidence interval.

Results exposure-safety Edema

These results from the time to event model suggest that the risk of developing oedema may have reached the plateau at very low exposure level of tepotinib, therefore it could not be properly quantified. Advanced age was associated with a small increase in the risk of developing oedema independent of tepotinib treatment.

The distribution of exposure was similar across the maximum severity grade of peripheral edema events (*Figure 16*). The lack of association between exposure and maximum severity grade was consistent across exposure metrics. In light of the exploratory nature of the analysis and the limited data to support it, no clear conclusion regarding the impact of tepotinib exposure on peripheral edema can be drawn.



Source: Pharmacokinetics Exposure – Safety Report, April 2020, Figure 11.

IQR=interquartile range.

In the box plots, the middle line corresponds to the median, the upper and lower hinges correspond to the first and third quartiles (the 25th and 75th), the upper whisker extends from the hinge to the highest value that is within 1.5 IQR of the hinge, or distance between the first and third quartiles, the lower whisker extends from the hinge to the lowest value within 1.5 IQR of the hinge.

Figure 16: Mean AUC24h up until Time of Edema Event (A), during 1 W eek prior to Edema Event (B), and during 2 Weeks prior to Edema Event (C) by Edema Severity Grade (Maximum Severity per Patient), Colored by Study, Excluding Study EMR200095-001

Exposure-QT

Two exposure-QTc analyses were provided, one using data from different doses for 4 early studies, and the other using data from vision study. The analyses are described below.

Exposure-QT – integrated study (data from 4 studies)

A total of 285 subjects have been pooled across these 4 studies for the PK-ECG dataset, which included 144 subjects from EMR200095-001 study, 12 subjects from EMR200095-003 study, 70 subjects from EMR200095-004 study and 59 subjects from EMR200095-005 study. Of these subjects, 169 subjects had matched parent and metabolite concentration, 55 subjects were from EMR200095-001 study, 12 subjects from EMR200095-003 study, 43 subjects from EMR200095-004 study and 59 subjects from EMR200095-005 study. Effect of tepotinib and metabolite on QTcF was evaluated using a subset of the pooled dataset using only datapoint having matched tepotinib concentration with MSC2571109A concentration.

When considering the tepotinib drug effect alone, the upper bound of the 90% CIs of the predicted mean ΔQTcF were 3.57 msec at the observed geometric mean steady state Cmax at the proposed clinical dose of 500 mg, and 7.54 msec at the geometric mean steady state Cmax at the highest administered dose of 1,400 mg (*Table 11*).

Table 11. Predicted ΔQTcF at Observed Mean Cmax of Tepotinib at Steady State

Dose Level	Dataset	geoMean C_{max} (ng/mL)	Predicted Mean ΔQTcF (msec)	90% CI of ΔQTcF (msec) Bootstrapped	
				Lower Bound	Upper Bound
500 mg	Pooled data	1,000.2	2.00	0.48	3.57
500 mg	Study EMR200095-001	980.4	3.16	1.19	4.99
1,400 mg	Pooled data	1,818.5	4.63	1.52	7.54
1,400 mg	Study EMR200095-001	1,818.5	5.68	1.98	8.92

Source: Integrated ECG Report, August 2019; Table R13 and Table 4.3.
CI=confidence interval.

Additionally, when considering the effects of tepotinib, MSC2571109A, and interaction between tepotinib and MSC2571109A, the predicted mean ΔQTcF and the upper bound of associated 90% CIs at 500 mg and 1,000 mg were also similar to the predictions from the pooled data across all 4 studies and did not exceed 10 msec (*Table 12*).

Table 12. Predicted ΔQTcF at Observed Mean Cmax of Tepotinib and MSC2571109A with Interaction Term (Tepotinib Concentration*MSC2571109A Concentration) at Steady State

Dose Level	Dataset	geoMean C_{max} for Tepotinib (ng/mL)	geoMean C_{max} for MSC2571109A (ng/mL)	Predicted Mean ΔQTcF (msec)	90% CI of ΔQTcF (msec) Bootstrapped	
					Lower Bound	Upper Bound
500 mg	Pooled data	1,000.2	319.3	3.08	1.25	4.34
500 mg	EMR200095-001	980.4	323.9	4.36	1.54	6.43
1,000 mg	Pooled data	1,199.4	384.4	5.18	2.59	6.75
1,000 mg	EMR200095-001	1,199.4	384.4	5.92	2.37	7.98

Source: Integrated ECG Report, August 2019; Table R15 and Table 4.4.
CI=confidence interval.

Exposure-QTc Analysis of the VISION study

The QT data and plasma concentration data for tepotinib and MSC2571109A from time-matched PK samples was subjected to exposure-QTc analysis. ECG and drug concentration data collected until the data cut off date of 19 July 2019 were used for the analysis. A total of 1,083 ECGs and PK data pairs recorded at the scheduled timepoints from 107 patients were included.

Time-matched plasma concentration of tepotinib and/or its metabolite MSC2571109A and corresponding ΔQTcF data were used to quantify the relationship between exposure and response (ΔQTcF). The actual time of PK sample collection were recorded. The scheduled ECG timepoints are shown in *Table 13*.

Table 13. ECG sampling VISION study.

Visit Name	Visit Code as entered in QECGBuild	Number of ECGs per visit
Cycle1Day1Predose (Baseline)	C1D1PRE	3
Cycle1Day1Postdose4hours	C1D1PD4H	3
Cycle2Day1Predose	C2D1PRE	3
Cycle2Day1Postdose4hours	C2D1PD4H	3
Unscheduled (for Unscheduled visit between C1 and C2)	UNS	As applicable

A prespecified linear mixed effects model was used to evaluate the relationship between plasma concentration of tepotinib only on QTcF by including ΔQTcF as the dependent variable, with centred baseline QTcF value, concentration of tepotinib as fixed effects, and both intercept and slope for concentration of tepotinib as subject-specific random effects.

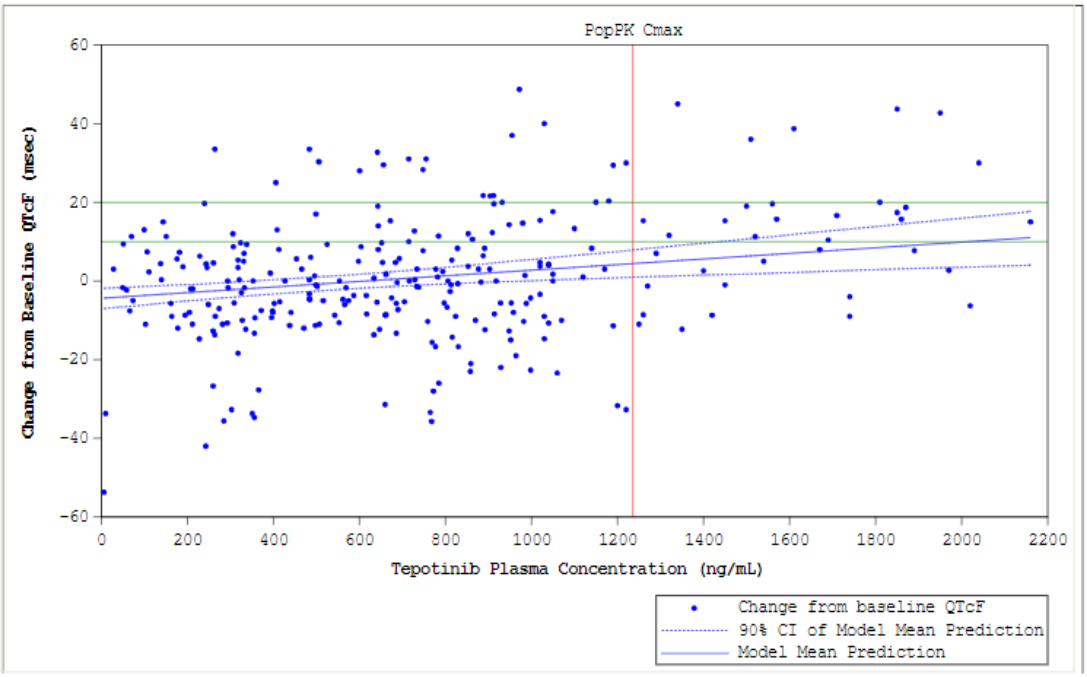
At the population pharmacokinetics (PopPK) model-derived mean steady state Cmax value of 1,236 ng/mL for tepotinib for the 500 mg dose, the predicted mean ΔQTcF was 4.41 msec and the upper bound of its 90% CI was 7.87 msec (*Table 14*).

Table 14. Predicted ΔQTcF at Mean Cmax of Tepotinib for the 500 mg Dose at Steady State (VISION, Cohort A

Dose Level	PopPK $C_{max\ ss}$ (ng/mL)	Predicted Mean ΔQTcF (msec)	90% CI of ΔQTcF (msec) (Bootstrapped)	
			Lower Bound	Upper Bound
500 mg	1,236	4.41	0.97	7.87

Source: VISION study, Expert ECG Report, Table R2.
CI=confidence interval, PopPK=population pharmacokinetics.

Individual ΔQTcF and tepotinib plasma concentration for all subjects from all timepoints has been plotted and the model derived relationship between the population mean ΔQTcF versus concentration has been plotted along with its two-sided 90% confidence intervals (CIs) (*Figure 17*).



Source: Figure 2.1
Note 1: The model -derived predicted population mean change from baseline QTcF (ΔQTcF) is shown as the continuous blue line and the two-sided 90% bootstrapped confidence limits of predicted mean ΔQTcF are shown as broken lines for study subjects.
Note 2: The vertical red line corresponds to the PopPK mean $C_{max\ ss}$ in the 500 mg dose.
Note 3: The green horizontal lines represent the regulatory threshold of concern of 10 msec, and additional 20 msec as reference line.

Figure 17. Model Derived Predictions for Tepotinib Concentration-QTcF Analysis with Individual QTcF Change from Baseline (ΔQTcF)

Tepotinib and metabolite MSC2571109A exposure-QTc model

As the concentration-QT analysis of pooled data from 4 previous studies (EMR200095-001, EMR200095-003, EMR200095-004 and EMR200095-005) had shown that a significant effect of interaction between concentrations of tepotinib and its metabolite MSC2571109A on ΔQTcF, this model was specifically studied using data from the present study. The upper bound of the two-sided 90% bootstrapped confidence interval of the mean ΔQTcF was 9.35 ms at the PopPK model-derived steady-state mean Cmax,ss value of 1236ng/mL for tepotinib and 416 ng/mL for metabolite MSC2571109A (*Table 15*).

Table 15. Predicted QTcF at Mean Cmax of Tepotinib and MSC2571109A with Interaction

PopPK Mean $C_{max\ ss}$ (ng/mL) (Tepotinib)	PopPK Mean $C_{max\ ss}$ (ng/mL) (MSC2571109A)	Predicted Mean ΔQTcF (msec)	90% Confidence Interval of ΔQTcF (msec) (Bootstrapped)		90% Confidence Interval of ΔQTcF (msec) (Asymptotic)	
1236	416	5.13	1.39	9.29	0.91	9.35

2.6.3. Discussion on clinical pharmacology

The bioanalytical methods for analysis of tepotinib and metabolites in plasma were adequately validated and cross-validations were performed between methods and laboratories.

Population PK analysis

The modelling of the parent drug is considered to be the main focus. The metabolite is considered of less importance, as the non-clinical data support that MSC2571109A has a negligible contribution to the clinical efficacy of tepotinib (see non-clinical section). 3014 observations below the LOQ for tepotinib and 1663 observations below LOQ for MSC2571109A were excluded. Re-estimation of both tepotinib and MSC2571109A models using an updated dataset had only a minor impact on the previously reported PK models. Parameter estimates were similar, including for clearance (20,5 L/h compared to 20,4 L/h previously for tepotinib and 40,7 L/h compared to 40,2 L/h previously for MSC2571109A).

The applicant has run the final models using the M3 method as requested, and the model predictive performances are acceptable. The applicant has also run a model with outliers (CWRES >5). Parameter estimates for both the model with M3 and the model with outliers included are similar to the original final model which can therefore be accepted.

The shrinkage on final parameters was high (>30%) for almost all random effects parameters however part of the shrinkage originates from inappropriate inclusion of individual parameters like CLpar for healthy volunteers and Fpar for healthy volunteers that could not be estimated for patients. The applicant's method of handling missing covariates is considered acceptable.

The relative BA/BE studies were generally performed in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr).

The pivotal BE study together with requested additional analysis using a conservative estimation approach for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} confirmed bioequivalence between TF3 and TF2 in the fasted state.

The pivotal BE study comparing TF3 to TF2 was performed in the fasted state, while the guideline recommends a study in the fed state for products such as tepotinib where the SmPC recommends intake only in the fed state. Food effect of both formulations was however studied in separate parts of the same study. Thus, it is possible to compare the exposure of both formulations also in the fed state.

Although it is not optimal that the BE study comparing TF3 to TF2 was performed in the fasted state, this guideline deviation can be accepted since food effect was studied for both formulations and was largely similar, and also considering that the TF3 formulation was introduced in the VISION study. Based on the totality of data, bioequivalence is sufficiently demonstrated between TF3 and TF2.

As TF2 was within bioequivalence criteria compared to TF1 in the fed state and as TF3 is bioequivalent to TF2 in the fasted state (see above) and with largely similar food effect observed for TF3 as for TF2, absolute bioavailability of the proposed commercial formulation TF3 is expected to be similar to that observed for TF1.

The effect of food on the commercial formulation was investigated with a high-fat high-calorie meal as defined in relevant guidelines, which is considered to represent worst-case food effect. The product has been taken with food in the pivotal study with no restriction on the type of food in the clinical trials and is recommended to be taken with food. This is supported considering the available data.

The fu results from the mass balance study and HI study were in agreement with the *in vitro* results.

For parent drug a slight concentration dependency was observed and thus it is considered more relevant to use the blood-to-plasma ratio determined at 1.0 µM (closest to the steady state C_{max}), which was 1.0. Blood/plasma ratio from the mass balance study is consistent with the in vitro data.

Following a single oral administration of a radiolabelled dose of 500 mg tepotinib, 78% was excreted via the faeces and 14% in urine. In total, 52% of the radioactive dose was excreted unchanged (7% in urine and 45% in faeces). Metabolism and biliary excretion of parent drug may be considered major elimination pathways, while renal elimination is a minor pathway.

Tepotinib has been identified as a substrate of P-gp but not of other transporters. Normally, major elimination pathways are confirmed using in vivo studies with inhibitors of enzymes or transporters as relevant, but no in vivo study with a P-gp inhibitor has been performed in order to confirm if biliary secretion via P-gp is a major elimination pathway.

In faeces and urine, no single metabolite amounted to more than 10% of the excreted dose. According to the suggested metabolism schedule, no sequential metabolism seems to occur so that several metabolites should be summed up in order to clarify the contribution of a specific metabolic pathway, and even if some metabolites should be summed up, there will not be one major pathway. Thus, although metabolism overall is a major elimination pathway, it can be agreed that no single metabolic pathway seems to contribute more than 25% of drug elimination. *In vitro* metabolism data indicate that CYP3A4 and CYP2C8, and possibly other enzymes such as FMOs, are involved in the metabolism of tepotinib. In the formation of the major metabolite, several CYPs (mainly CYP3A4, 2C8 and 1A2) and also cytosolic enzymes may be involved.

No clinical studies investigating the effect of CYP inhibitors or inducers on tepotinib exposure have been performed. This is agreed considering that there is no single metabolic pathway that seems to contribute more than 25% of drug elimination.

Moderate HI did not affect the exposure of tepotinib and metabolites MSC2571109 and MSC2571107 to a large extent, but it is not known if the effects would be larger in case of severe HI.

Renal clearance has not been reported; thus it is not possible to conclude if active renal secretion occurs. However, as renal elimination of parent drug is a minor elimination pathway, this is not considered critical.

Overall, the elimination pathways of tepotinib are considered sufficiently well characterized, although the planned *in vivo* study with the CYP3A4 and P-gp inhibitor itraconazole (see DDI part) may provide additional confirmation.

At first, the chiral metabolite M506 was identified as a major metabolite in plasma. It was later concluded that the R-enantiomer MSC2571109A had much higher exposure (65% of parent drug) than the S-enantiomer MSC2571107A (4.5% of parent drug). Thus, the R-enantiomer MSC2571109A is considered to be the only major metabolite in plasma and needs to be investigated for enzyme inhibitory potential. The major metabolite was excreted in faeces but only accounted for 3% of the dose. The PK of the major metabolite MSC2571109A and also of the minor metabolite MSC2571107A has been characterised in several clinical studies. The applicant has concluded that the major metabolite does not contribute significantly to the overall pharmacological activity of tepotinib. This is agreed as discussed in the non-clinical part.

Dose-proportionality and time dependency

With the CF2 formulation, a less than proportional increase in exposure with increasing dose was observed, at least at doses above 300 mg. With the tablet formulations, overall, data indicate an approximately dose-proportional increase in exposure at doses up to 500 mg. The population PK analysis also supports this conclusion regarding the tablet formulation.

Considering a half-life of 32 hours (based on the pop-PK analysis) and a dosage interval of 24 hours, an accumulation ratio of 2.5 would be expected. This is similar to what has been observed (2.5 for Cmax and 3.3 for AUC at a dose of 500 mg; accumulation ratios in the range 1.8 to 3.6 were observed for AUC and Cmax in the dose range 300 to 1400 mg with formulations CF2 and TF1 in study EMR200095-001). Thus, there are no signs of significant time dependency.

Time dependency was evaluated in the popPk analysis. It is agreed that no trends in the residuals with respect to time are seen and that this also indicates that tepotinib PK characteristics are constant over time.

Intra- and inter-individual variability

The inter-individual variability in healthy volunteers was low to moderate. No direct estimate of intra-individual variability has been reported, but no concern is raised regarding this.

Pharmacokinetics in target population

The popPK is used to support that no dose adjustment is special populations are needed as well as provide supportive information regarding food effect and formulation effects on PK.

The boundary range of 80-125% is based on standard bioequivalence consideration, whereas the applicant has developed Exposure-response models that may potentially better inform the clinical relevance of the covariate effects and the acceptability range. This constitutes a limitation in the conclusion as it cannot be ascertained that these boundaries are the most appropriate ones for tepotinib however this issue is not further pursued.

Special populations

Renal elimination is a minor elimination pathway for tepotinib. Severe renal impairment can however sometimes affect the elimination of hepatically eliminated drugs, likely due to an inhibiting effect of uremic toxins on metabolising enzymes and transporters. A PK study in severe renal impairment is therefore generally recommended even for substances that are primarily eliminated hepatically. No such study has been performed. Given the low extent of renal elimination of tepotinib, an effect of mild or moderate RI on the PK of tepotinib is not expected. The pop-PK analysis (in which 24 patients with moderate renal impairment were included) supports the conclusion that no dose adjustment is needed in patients with mild or moderate RI (creatinine clearance 30 to 89 mL/min), even though patients with eGFR between 30 and 40 ml/min/1.73m2 were not included in the analysis. In addition, the dose is adjusted based on toxicity. The pharmacokinetics and safety of tepotinib in patients with severe renal

impairment (creatinine clearance below 30 mL/min) have not been studied. The use of tepotinib in patients with severe renal impairment is therefore not recommended (see section 4.2 of the SmPC). Renal function estimates that rely on serum creatinine (creatinine clearance or estimated glomerular filtration rate) should be interpreted with caution.

As discussed in the section on Interactions, based on *in vitro* data, tepotinib or its major metabolite may inhibit OCT2 and MATE1 and 2, which are involved in the active renal secretion of creatinine. This may affect the interpretation of renal function data based on creatinine and that increases in creatinine may at least partly be due to transporter effects rather than true decreases in GFR. Renal function estimates that rely on serum creatinine (creatinine clearance or estimated glomerular filtration rate) should be interpreted with caution considering this effect. In case of blood creatinine increase while on treatment, it is recommended that further assessment of the renal function be performed to exclude renal impairment (see section 4.4 of the SmPC).

No conclusions from the popPK for NCI ODG class 2 and 3 can be drawn since too few patients with NCI ODG class 2 and 3 were included. A dedicated study has been performed where the effect of mild or moderate hepatic impairment on the PK of tepotinib and its metabolites was investigated. The effect of severe HI has not been assessed. Subjects in the moderate group can be considered to have an adequate range of decrease in serum albumin and increase in serum bilirubin (although no effect of prothrombin time was observed in these subjects), and thus be representative of the moderate HI group as regards to markers expected to be related to drug elimination capacity. There were no large effects of mild or moderate HI on the PK of tepotinib.

The increase in unbound tepotinib concentrations in patients with mild and moderate hepatic impairment is within the observed exposure variability in healthy volunteers and the increases are not clinically relevant based on overall favourable safety profile where a maximum tolerated dose was not reached up to the highest administered dose of 1,400 mg, i.e. at AUC almost 2-fold of those at the proposed clinical dose of 500 mg. No dose adjustment is recommended in patients with mild (Child Pugh Class A) or moderate (Child Pugh Class B) hepatic impairment. The pharmacokinetics and safety of tepotinib in patients with severe hepatic impairment (Child Pugh Class C) have not been studied. The use of tepotinib in patients with severe hepatic impairment is therefore not recommended (see section 4.2 of the SmPC).

A population kinetic analysis did not show any clinically meaningful effect of age (range 18 to 89 years), race, gender or body weight, on the pharmacokinetics of tepotinib. No dose adjustments are recommended beyond those based on tolerability. Data on ethnicities other than Caucasian or Asian are limited (see section 5.2 of the SmPC).

Interactions

Tepotinib as victim of drug interactions

The methodology used in the *in vitro* studies is adequate.

Tepotinib is a substrate for P-glycoprotein (P-gp). Strong P-gp inducers may have the potential to decrease tepotinib exposure. Strong CYP inducers may also decrease tepotinib exposure. Without a DDI study it is not possible to conclude if a clinically relevant effect on tepotinib exposure would be seen with CYP inducers. Concomitant use of strong CYP and P-gp inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) should be avoided. The applicant is recommended to conduct a study investigating the effects of the CYP and P-gp inducer carbamazepine on tepotinib and submit the results when available.

The applicant has discussed that the potential of P-gp inhibitors to increase absorption is small (could cause 15% increase in exposure), and that P-gp inhibition of elimination pathways could lead to a

worst case increase in exposure of 1.43-fold (due to inhibition of biliary secretion). Thus, the combined effect of increased absorption and decreased biliary secretion caused by a P-gp inhibitor (worst-case scenario) would be expected to result in approximately 1.6-fold increase in tepotinib exposure which may increase the incidence and severity of adverse reactions of tepotinib. As discussed in the Clinical Safety part, it is not agreed that there are no safety issues with around 2-fold increase in exposure. It is agreed that the DDI potential with tepotinib as a victim of co-administered drugs that interact with drug-metabolizing enzymes is low regarding CYP inhibitors, although the impact of a combined inhibition of CYP3A4 and P-gP may be relevant. As long as no clinical data on P-gp and 3A4-inhibitors are available, substances that are both strong inhibitors of 3A4 and P-gp inhibitors (e.g. itraconazole, ketoconazole, ritonavir, saquinavir, nelfinavir) should be avoided. The applicant is recommended to perform a DDI study with itraconazole, which inhibits both 3A4 and P-gp, to investigate the magnitude of this interaction.

Also for P-gp inhibitors that are not strong inhibitors of CYP3A (e.g. quinidine, verapamil) an increase in exposure for tepotinib cannot be excluded. Therefore, caution and monitoring for adverse reactions is advised in case of concomitant use (see sections 4.4 and 4.5 of the SmPC).

Co-administration of omeprazole under fed conditions had no clinically relevant effect on the pharmacokinetic profile of a single dose of tepotinib 450 mg and its metabolites (geometric mean ratio for tepotinib of 110% for AUC_{inf} (90% CI: 102; 119) and of 104% for C_{max} (90% CI: 93; 117); similar effect on metabolites observed).

Tepotinib as perpetrator of drug interactions

In vitro inhibition of all mandatory CYP enzymes has been studied for both tepotinib and the major metabolite MSC2571109. In addition, UGT inhibition has been studied.

Based on in-vitro data there is a risk of direct inhibition of CYP3A4 in the intestine by parent drug tepotinib, but at clinically relevant concentrations neither tepotinib nor the major circulating metabolite MSC2571109A represent a risk of inhibition of other CYP enzymes. There is no need to use PBPK or mechanistic static modelling to exclude clinically relevant interactions with tepotinib or MSC2571109A as CYP inhibitors, since inhibition of CYPs (except CYP3A4) can be excluded based on the basic model. Thus, these models have not been assessed. For CYP3A4 TDI was observed for the major circulating metabolite, in particular when looking at testosterone data, but considering the cut-off for systemic interaction potential a clinically relevant interaction is not likely.

Tepotinib or the major metabolite MSC2571109A do not inhibit UGT1A1/3/4/6, or 2B7/15/17 at clinically relevant concentrations. The Ki for UGT1A9 for parent drug was slightly below the cut-off, thus data suggests that tepotinib may be an inhibitor of UGT1A9 at clinically relevant concentrations. The clinical relevance of this finding is unknown, but no warning is considered necessary in section 4.5.

For tepotinib, induction of CYP3A4 was observed. Induction of CYP2B6 and CYP1A2 was not observed. Although there were some issues with stability during the induction experiments, taken together, the risk of *in vivo* induction of CYP1A2 or CYP2B6 by parent drug is considered low and it is agreed to conclude no induction of CYP1A2 or CYP2B6 by parent drug.

It is not a request according to the DDI guideline to investigate the induction effect of metabolites, but the applicant has performed such studies. Also, for the metabolite, induction of CYP3A4 was observed. Clinically relevant induction of CYP1A2 can be excluded. Although there were issues with stability during the experiments, taken together, the risk of *in vivo* induction of CYP2B6 by the metabolite is considered low, and considering also that there is no request to investigate induction potential of metabolites, it is agreed to conclude no induction of CYP2B6.

Multiple administrations of 500 mg tepotinib orally once daily had no clinically relevant effect on the pharmacokinetics of the sensitive CYP3A4 substrate midazolam. The results of this study can also be extrapolated so that induction of other PXR regulated enzymes and transporters can also be excluded.

The DDI guideline states that regardless of the *in vitro* induction study results, a potential human teratogen needs to be studied *in vivo* for effects on contraceptive steroids if the drug is intended for use in fertile women. In the absence of a DDI study, it is currently unknown whether tepotinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore women using systemically acting hormonal contraceptives should add a barrier method during tepotinib treatment and for at least 1 week after the last dose with oral contraceptives (see section 4.5 and 4.6 of the SmPC).

The effect of tepotinib on all mandatory transporters has been investigated. For the metabolite, the effect on P-gp and BCRP has not been investigated, but this is acceptable since inhibition is observed for parent drug. In addition, investigation of transporter inhibition by metabolites is not mandatory. In addition, inhibition of the optional transporters OCT1, MATE1 and MATE2-K has been investigated for both tepotinib and metabolite, as well as inhibition of BSEP by tepotonib. The methodology used is generally acceptable, but the applicant is recommended to provide further *in vitro* data assessing the impact of an adequate pre-incubation step on the inhibitory potential of tepotinib on OATP1B1, OATP1B3, OAT1 and OAT3 transporters. Based on in vitro studies, tepotinib or its metabolite inhibit P-gp, BCRP, OCT1 and 2 and MATE1 and 2 at clinically relevant concentrations. Tepotinib or its metabolite may have the potential to alter the exposure of substrates of the transporters OCT1 and 2 and MATE1 and 2. The most clinically relevant example of substrates of these transporters is metformin. Monitoring of the clinical effects of metformin is recommended during co-administration with tepotinib. Tepotinib can inhibit the transport of substrates of the BCRP in vitro. Monitoring for adverse reactions of sensitive BCRP substrates (e.g. rosuvastatin, methotrexate, topotecan) is recommended during co-administration with tepotinib (see sections 4.5 and 5.2 of the SmPC).

For the metabolite, the Ki value for OATP1B1 (0.4μM) is slightly below the relevant cut-off (0.5), but as the results are very borderline and since there was no inhibition of OATP1B1 by tepotinib at clinically relevant concentrations (considering also that studies of effects of metabolites on transporters are not mandatory), the risk of inhibition of OATP1B1 at clinically relevant concentrations is considered very small. In addition, no safety signal has been observed based on statin data. Therefore, the risk of OATP1B1 inhibition is not mentioned in section 5.2 of the SmPC.

Dose adjustment of dabigatran etexilate, a sensitive P-gp substrate, may be needed in case of concomitant use. Caution and monitoring for adverse reactions of other P-gp-dependent substances with a narrow therapeutic index (e.g. digoxin, aliskiren, everolimus, sirolimus) is recommended during co-administration with tepotinib (see section 4.5 of the SmPC).

Pharmacokinetics-Pharmacodynamics (PK/PD)

Exposure-efficacy

There appears to be a flat exposure-response relationship for OR, DOR, and PFS within the observed exposure range after administration of a 500 mg tepotinib.

Performing the exposure-response analysis using only tepotinib (not active moiety including metabolite) is accepted (see non-clinical AR). It is noted that a previous version of the popPK model V1.0 (report not found) appears to have been used to derive the individual AUCs. Exposure-response analysis on dataset with only 1 dose (500 mg) and dose reduction/interruption limits the usefulness of the analysis. These issues are not further pursued as the exposure-response analysis is considered to provide limited value.

Exposure safety

Several studies were included in the exposure-safety analysis, but the VISION study provided most data (around 40% of the data). Further, with only one dose and dose reductions in the VISION study, the value of the in data for the analysis is limited. Therefore, the exposure-safety analysis should be interpreted as exploratory and supportive only.

Regarding increase in creatinine and hypoalbuminaemia, the analysis indicates similar results as observed in the clinical safety. This is reflected in the SmPC based on clinical data. The time course following administration of single doses of 500 mg tepotinib in healthy participants suggests that the effect on serum creatinine is reversible.

The applicant concludes that due to the exploratory nature of the analysis and the limited data to support it, no clear conclusion regarding the impact of tepotinib exposure on peripheral edema can be drawn. This is generally agreed with. If anything, the analysis indicate that dose reduction may not be sufficient to decrease oedema.

Exposure-QTc

A concentration-dependent increase in QTc interval was observed in the concentration-QTc analysis. At the recommended dose, no large mean increases in QTc (i.e. > 20 ms) were detected in patients with various solid tumours. The QTc effect of tepotinib at supratherapeutic exposures has not been evaluated. Limitations of the analysis include: no positive control and, no placebo control.

Regarding the exposure-QTc for the VISION study, the applicants concludes that the 90% two-sided upper confidence bound of mean ΔQTcF did not exceed the threshold of regulatory concern of 10msec for Cmax for 500 mg dose, however the popPK derived Cmax used to draw this conclusion by the applicant is the mean Cmax. Thus, many patients will have Cmax above this value for the 500 mg dose. Already a slightly higher Cmax than the mean Cmax would yield a 10 ms increase for the upper CI. Also, the sampling PK/ECG sampling in the VISION study does not appear to be at the time of Cmax (samples taken at 4 h, with time for Cmax around 8-12 h). The exposure-QTc for the VISION study indicate a relevant QT-prolongation already at exposures for the 500 mg dose. The CHMP considers that QTc-prolongation is an important identified risk (see clinical safety).

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology data submitted support the approval of tepotinib. The applicant is recommended to conduct and submit additional DDI studies post-authorisation (studies with the CYP3A4 and P-gp inhibitor itraconazole and with the inducer carbamazepine) and the applicant is also recommended to submit additional *in vitro* data assessing the impact of an adequate pre-incubation step on the inhibitory potential of tepotinib on OATP1B1, OATP1B3, OAT1 and OAT3 transporters.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

As a justification for the proposed clinical dose of 500 mg tepotinib once daily in patients with advanced NSCLC harbouring METex14 skipping alterations, the applicant explains that clinical PK and Pd data from the Phase I, first-in-human, dose-escalation study (Study EMR200095 001) were used to adapt the nonclinical PK/Pd model to the human setting. The human PK/Pd model simulations suggested that a tepotinib dose of 500 mg once daily is sufficient to achieve sustained inhibition of

phospho-MET at a level > 95% in more than 90% of a mixed solid tumour population. Although limited activity and 6 and 0 DLTs in the respective studies was seen, the safety and tolerability data from Study EMR200095 001 and from Study EMR200095 003 were further considered to support the selection of 500 mg once daily tested in Phase II studies.

2.6.5.2. Main study

A Phase II single-arm trial to investigate tepotinib in advanced (locally advanced or metastatic) non-small cell lung cancer with MET exon 14 (METex14) skipping alterations or MET amplification (VISION).

Methods

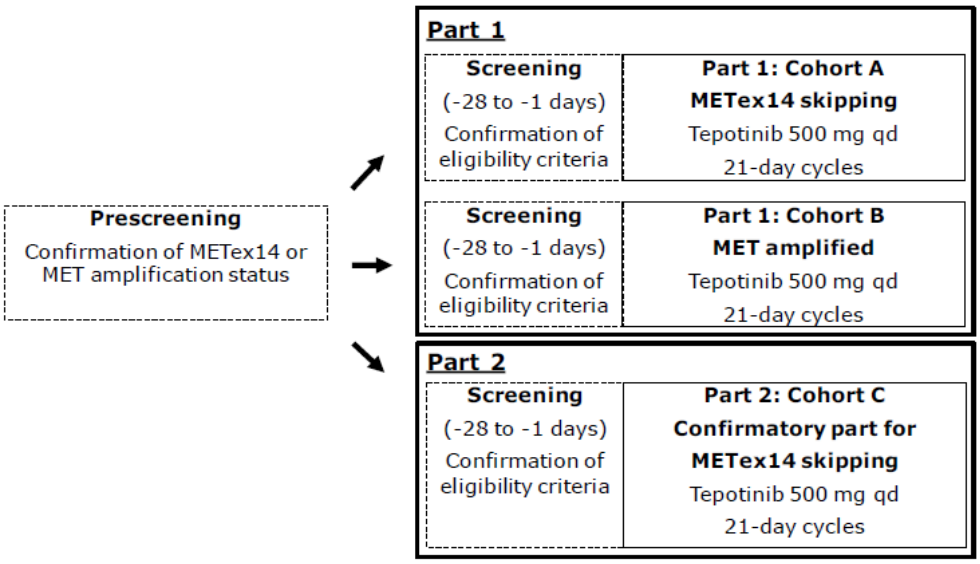


Figure 18: Study MS200095-0022 design

- **Study Participants**

Inclusion criteria:

The VISION trial, was initiated as a 2L+ trial in NSCLC patients with MET exon 14 skipping alterations. In effect, due to several protocol changes from amendment 4 and forth, the trial shifted from a 2L+ to a 1L+ trial in a broader population (also MET amplifications, cohort B) and allowed also liquid biopsies for inclusion. Accordingly, criteria (1) and (2) were deleted and criteria **9, 10** and **11** were added subsequently:

(1.) Histologically confirmed advanced adenocarcinoma of the lung, having failed at least one but not more than 2 lines of systemic therapy, including a platinum-doublet-containing regimen;

(2.) METex14 skipping alterations, as determined by the central laboratory. Both, archival and fresh biopsies are acceptable;

- In case METex14 skipping alteration has been observed in a subject in a pre-trial setting, it should be ensured that sufficient tissue is available for re-testing and for a potentially required bridging trial (regulatory need for assay approval) before trial entry. Only subjects with METex14 skipping mutation based on trial central testing will be enrolled into the trial

3. Signed, written informed consent by subject or legal representative prior to any study-specific screening procedure;

4. Male or female, ≥ 18 years of age (or reached the age of majority according to local laws and regulations, if the age of majority is > 18 years of age [i.e., ≥ 20 years of age in Japan]);

5. Measurable disease by IRC in accordance with RECIST Version 1.1;

6. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1;

9. Histologically or cytologically confirmed advanced (locally advanced or metastatic) NSCLC (all types including squamous and sarcomatoid);

10. Treatment naïve patients in first-line or pre-treated patients with no more than 2 lines of prior therapy;

11. Subjects with MET alterations, namely:

- METex14 skipping alterations in plasma and/or tissue, as determined by the central laboratory or by an assay with appropriate regulatory status, were enrolled into the study. For these subjects, sufficient tumour tissue and/or plasma was requested to allow additional testing;
- MET amplification only in plasma defined by a positive LBx test, as determined by the central laboratory or by an assay with appropriate regulatory status;
- Based on the outcome of the interim analysis in 12 LBx selected subjects: MET amplification only in tissue defined by a positive TBx with a gain of at least 4 copies of the MET gene, as determined by the central laboratory or by an assay with appropriate regulatory status.

Exclusion criteria:

Note: Exclusion criteria 1, 2, and 6 were deleted and 23 to 25 added in CSP Amendment 4. Exclusion criteria 3 was updated in CSP Amendment 8.

<u>Cancer-related</u>

(1.) Subjects with characterized EGFR (documented results; local testing acceptable) that predict sensitivity to EGFR-therapy, including, but not limited to exon 19 deletions and exon 21 alterations;

(2.) Subjects with characterized ALK rearrangements (documented results; local testing acceptable);

3. Subjects with symptomatic brain metastases who were neurologically unstable, and/or had required an increase in steroid dose within 2 weeks and/or had received prior stereotactic radiosurgery/gamma knife within 2 weeks and/or other prior treatment for brain metastases within 4 weeks prior to the start of therapy. Subjects with leptomeningeal disease were ineligible;

4. Any unresolved toxicity Grade 2 or more according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, from previous anticancer therapy;

5. Need for transfusion within 14 days prior to the first dose of study treatment;

(6.) Prior chemotherapy, biological therapy, radiation therapy, or other investigational anticancer therapy (not including palliative radiotherapy at focal sites) within 21 days prior to the first dose of trial treatment;

7. Subjects who had brain metastasis as the only measurable lesion;

23. Subjects with characterized EGFR activating mutations that predict sensitivity to anti-EGFR therapy;

24. Subjects with characterized ALK rearrangements that predict sensitivity to anti-ALK therapy;

25. Prior chemotherapy, biological therapy, radiation therapy, hormonal therapy for anticancer purposes, targeted therapy, or other investigational anticancer therapy (not including palliative radiotherapy at focal sites) within 21 days prior to the first dose of study treatment.

METex14 skipping

Prospective testing of MET exon 14 skipping mutations was performed centrally on circulating free DNA (cfDNA) obtained from plasma (liquid biopsy [LBx]) with the use of next-generation sequencing (NGS) panel Guardant360® Test Version 2.10 and ArcherDX MET Variant Test or by evaluating RNA obtained from fresh or archival (formalin-fixed, paraffin-embedded) tumor-biopsy tissue (TBx) with the use of the Oncomine Focus Assay 2.10 and the ArcherDX MET Variant Test.

For circulating free DNA/cfDNA/LBx positive METex14 status was defined as mutations occurring in 12 bp regions centered on the splice donor and acceptor sites.

For tumour tissue RNA/TBx positive METex14 status was defined by detecting a sequence at the Exon 13 to Exon 15 boundary by amplicon NGS.

- **Treatments**

500 mg tepotinib once a day, which corresponds to 500 mg tepotinib hydrochloride hydrate and is equivalent to 450 mg tepotinib (the free base form).

- **Objectives/endpoints**

The primary endpoint is objective response (confirmed complete response [CR] or partial response [PR]) determined according to RECIST Version 1.1, based on independent review (IRC). Patients were identified as having an OR if they achieved either a confirmed complete response or partial response from first administration of study treatment to first observation of progressive disease. Confirmation took place by a tumor assessment at least 4 weeks (28 days) after the tumour assessments initially indicating complete response or partial response.

Primary and Secondary Efficacy Endpoints in the VISION Study

Type	Endpoint
Primary	**OR (confirmed complete response or partial response) as per IRC determined according to RECIST 1.1**
Secondary	
Antitumor activity	OR as per Investigator determined according to RECIST 1.1
	DOR as per IRC
	DOR as per Investigator
	Objective disease control as per IRC
	Objective disease control as per Investigator
	PFS as per IRC
	PFS as per Investigator
	OS
HRQoL	Patient-reported outcomes

DOR=duration of response, IRC=independent review committee, OR=objective response, OS=overall survival, PFS=progression-free survival, PROs=patient-reported outcomes, RECIST=Response Evaluation Criteria in Solid Tumors.

- **Sample size**

Study design and powering of the study was discussed within a CHMP scientific advice procedure (EMA/CHMP/SAWP/820655/2015). At that time the sample size estimation approach, the targeted efficacy, and the planning of a pilot phase for sample size adjustment was criticised. Demonstrating that ORR is greater than 10% was not considered sufficient and the applicant was advised to plan the study to be able to estimate ORR with reasonable precision and also that an impressive response rate would be required for consideration of approval.

In the study protocol version 1.0 (14 January 2016) the targeted sample size was 60 subjects with the aim to show an ORR in the range of 40% to 50% and to demonstrate that the lower limit of the corresponding exact 2-sided 95% CI (Clopper-Pearson) exceeds 20%. With a sample size of 60, a maximum width for the 95% CI of 26.4% was to be achieved.

With protocol version 4.0 (15 March 2017) a new liquid biopsy (LBx) methodology was introduced for the testing of METex14 skipping alterations by use of plasma ctDNA. The study was thereby to enrol subjects with METex14 skipping alterations identified in tumour tissue and/or in circulating tumour DNA (ctDNA) derived from plasma. In addition, the primary analysis was defined to be based on two separate primary analysis sets; the LBx analysis set of 60 subjects (defined as all subjects that had tested positive for METex14 skipping in plasma ctDNA) and the Tissue analysis set of 60 subjects (defined as all subjects tested positive for METex14 skipping in tumour tissue).

Enrolment was now to continue up to a maximum number of 120 subjects; due to an anticipated overlap of subjects in the two analysis sets, the total number of subjects was expected to be smaller (a total of 70 to 90 subjects). The aim was still to show an ORR in the range of 40-50% with the lower limit of the corresponding exact two-sided 95% CI exceeding 20% but in each of the two primary analysis sets.

In addition, the indication was changed which implied allowance of patients with histologic NSCLC subtypes beyond adenocarcinoma, and allowance of first-line treatment.

By the time of the finalization of protocol Version 4.0, 5 subjects had been enrolled in Cohort A.

With protocol version 5.0 (10 May 2018) an additional NSCLC MET amplification cohort was introduced, and enrolment was now to proceed into two cohorts of subjects with MET alterations identified in tumour tissue and/or in ctDNA derived from plasma:

- Cohort A with subjects tested positive for METex14 skipping alterations, regardless of MET amplification status
- Cohort B with subjects tested positive for MET amplification and negative for METex14 skipping alterations

Enrolment into cohort A could then continue until at least 60 subjects were included in each of the two primary analysis sets (the LBx analysis set, the TBx analysis set). Enrolment into Cohort B was to continue until at least 60 subjects were included in the LBx analysis set and at least 12 subjects in each of 2 TBx analysis sets.

By the time of the finalization of protocol Version 5.0, 41 subjects had been enrolled in Cohort A.

With protocol version 6.0 (26 March 2019) a third cohort was added (cohort C) to expand the METex14 population. Cohort C is intended to act as a confirmatory part for METex14 Skipping Alterations. For ease of reference, the study was now also divided into 2 parts (part 1: cohort A and B, part 2: cohort C).

By the time of the finalization of protocol Version 6.0, 102 subjects had been enrolled in Cohort A.

Sample size Cohort C (Study part 2)

Part 2: Cohort C was initiated once subject accrual for Cohort A had completed. The eligibility criteria and schedule of assessments for Cohort C is to be the same as for subjects enrolled in Cohort A. Subjects in Cohort C is to receive tepotinib as tablet formulation 3 (TF3).

For Cohort C, subjects with METex14 skipping alterations were to be enrolled such that at least 60 subjects are included in the LBx and TBx analysis sets, respectively, in total, at least 100 subjects. Regardless of material (LBx or TBx) used for inclusion into the study, at least 50 first line, at least 30 second line, and at least 20 third line subjects are to be enrolled.

Enrolment into Cohort C was ongoing at the time of data cut-off for the current report (01 July 2020). Cohort B has been halted following a pre-planned interim analysis.

- **Randomisation and Blinding (masking)**

N/A.

- **Statistical methods**

The CSR covers the analysis of all subjects enrolled in Cohort A based on an interim data cut-off (01 July 2020). The database lock for this analysis was 31 July 2020. The submitted Integrated Analysis Plan (IAP) is version 5.0 dated 22 July 2020 and should cover the analyses for efficacy and safety based on the data from the various cut-off dates. The IAP states that the statistical methods as described in the protocol were to be adopted.

The analysis included a subset of subjects who had a first dose of tepotinib before 02 April 2019 (these subjects had either been treated with tepotinib for at least 15 months, died or had prematurely discontinued study treatment for any reason, whichever came first) and a subset of subjects who had a first dose of tepotinib before 02 October 2019 (these subjects had either been treated with tepotinib for at least 9 months, died or had prematurely discontinued study treatment for any reason, whichever came first).

All statistical tests described in the IAP were to be regarded as exploratory. All p-values presented are two-sided and confidence intervals have a confidence probability of 95%.

Unless otherwise stated, the calculation of proportions was based on the number of subjects in the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

<u>Analysis sets</u>

Safety analysis sets (SAF): The SAF analysis set included all subjects who were administered at least 1 dose of tepotinib.

Intention-to-treat (ITT): The ITT analysis sets were to include all subjects who were administered at least 1 dose of tepotinib and had METex14 skipping alterations or MET amplification confirmed by a validated central laboratory assay.

For efficacy analyses, the following primary ITT analysis sets were defined taking into account also the assessment used to identify subjects with METex14 skipping alterations.

- ITT TBx or ITT LBx analysis set defined as all subjects tested positive for METex14 skipping alterations in tumour tissue or plasma ctDNA (including those tested positive for METex14 skipping alterations in both tumour tissue and plasma ctDNA)
- ITT LBx analysis set defined as all subjects tested positive for METex14 skipping alterations in plasma ctDNA

- ITT TBx analysis set defined as all subjects tested positive for METex14 skipping alterations in tumour tissue.

Subjects who tested positive in tissue and in plasma were assigned to both primary analysis sets.

Efficacy analyses were performed using also the following subsets:

The ITT-02 Apr 2019 analysis set (this approach ensured that the latest enrolled subject had a follow-up of at least 15 months, expected to provide 12 months of follow-up beyond a possible onset of response).

The ITT-02 Oct 2019 analysis set (this approach ensured that the latest enrolled subject had a follow-up of at least 9 months, expected to provide 6 months of follow-up beyond a possible onset of response).

Analysis of the primary endpoint

No formal statistical hypotheses were tested. The primary analysis was on ORR, defined as the proportion of subjects who achieved either a confirmed complete response or partial response based on independent review. The number of subjects achieving objective response, the ORR and the corresponding 2-sided exact Clopper-Pearson 95% CI have been presented.

The primary endpoint analysis was based on the primary analysis sets applying the ITT principle.

The primary analysis was based on 3 primary analysis sets: the L+ and/or T+ analysis set, the L+ analysis set, and the T+ analysis set (*defined above*).

Objective response based on Investigator assessment

Objective response (based on Investigator assessment) was derived and analysed identically to the primary endpoint. The independent review and investigator assessments of best overall response will be presented as cross-tabulations to show concordance between evaluations by cohort and for each analysis set.

Time-to-event endpoints (DOR, PFS and OS)

Duration of response, PFS and OS have been summarized descriptively. Kaplan-Meier plots have been presented. Duration of response and PFS were analysed based on independent review and was repeated using the data from the Investigator assessment. The time-to-event endpoints will be further explored using the different ITT analysis sets defined above.

IRC

An Independent Review Committee (IRC) conducted a blinded review of the tumour assessment images of all subjects using the same criteria based on a separate charter outlining details of the review process.

IDMC

An Independent Data Monitoring Committee performed periodic reviews to evaluate the safety of all subjects participating in the study. In addition to the outputs on safety data prepared for this purpose, outputs on efficacy data for each of the interim analyses were provided to the Independent Data Monitoring Committee to assess the benefit-risk ratio.

Cohort A and Cohort C

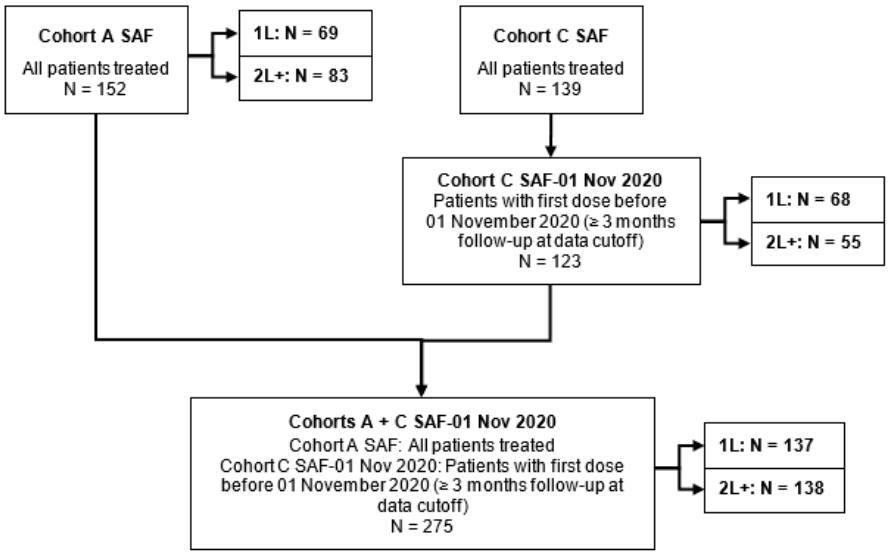
Cohort A and Cohort C will be independently and separately compared with an external control with regards to objective response rate (ORR) and duration of response (DOR).

Results

- **Participant flow**

The submission initially included data up to the cut-off date of 01 July 2020 from **255** advanced NSCLC patients harbouring METex14 skipping alterations treated with tepotinib in the VISION study.

During the procedure, the applicant submitted an update with a 01 February 2021 cut off, including patients who received their first tepotinib dose before 01 November 2020, i.e., patients with at least 3 months of follow-up, to ensure that each patient had received at least 2 post-baseline tumour assessments.



Source: VISION TLFs 01 February 2021 cutoff, Table 15.1.1.1bn and Table 15.1.1.2n.
1L=first line of therapy, 2L+=second or later line of therapy, SAF=safety analysis set, TLFs=tables, listings, and figures.

Figure 19: Key VISION study analysis sets analysed in this summary of efficacy (01 February 2021 Data cut-off)

- **Recruitment**

In total, 7869 patients were pre-screened (to determine MET alteration status), 168 subsequently screened for Cohort A (16 discontinued prior to treatment), 32 for Cohort B (8 discontinued prior to treatment; MET-amplified and negative for METex14 skipping mutations i.e., outside indication), 151 screened for Cohort C (10 discontinued prior to treatment, 2 were active in screening), leaving 152 Cohort A patients and 139 Cohort C patients to be included in pivotal data

First subject enrolled (signed screening informed consent form): 06 September 2016.

- **Conduct of the study**

The original CSP, dated 14 January 2016, was amended 8 times including 7 global amendments and 1 local amendment (implemented in France). For the original CSP and protocol amendments, refer to Appendix 16.1.1.

The seemingly most important amendment 4 (15 March 2017), involved several changes (selected):

- To introduce a new LBx methodology for the testing of METex14 skipping alterations by use of plasma ctDNA;
- To add an additional analysis set to the study which comprised subjects who tested positive for METex14 skipping alterations in plasma ctDNA by use of an LBx sample at prescreening;

- To change the indication of the study to NSCLC;
- To revise the inclusion criteria to allow for first-line treatment of subjects;
- To increase the number of subjects that could be enrolled;

In amendment 5 (10 May 2018; selected):

- To introduce an additional NSCLC MET amplification cohort (Cohort B) into the study;
- This protocol amendment also redefined the analysis sets to include the ITT L+ and/or T+ analysis set (also referred to as the combined analysis set) in efficacy analyses for Cohort A.

In amendment 6 (26 March 2019; selected):

- To introduce an additional NSCLC MET skipping alteration cohort into the study (Cohort C) as a confirmatory part for METex14 skipping alterations;
- To update inclusion criterion 9 to include cytologically confirmed NSCLC;
- To update the number of subjects to be enrolled in Cohort A (METex14 skipping alterations) to approximately 100;

In amendment 8 (17 January 2020; selected):

- To make provisions for halting enrolment into Cohort B with immediate effect;

- **Baseline data**

Table 16. Demographics and Baseline Characteristics, VISION Cohorts A + C – SAF-01 Nov 2020 (combined set)

	Overall N = 275 (100%)	1L N = 137 (100%)	2L+ N = 138 (100%)
Sex, n (%)			
Male	135 (49.1)	68 (49.6)	67 (48.6)
Female	140 (50.9)	69 (50.4)	71 (51.4)
Race, n (%)			
White	184 (66.9)	108 (78.8)	76 (55.1)
Black or African American	3 (1.1)	1 (0.7)	2 (1.4)
Asian	79 (28.7)	27 (19.7)	52 (37.7)
Not collected at site	7 (2.5)	1 (0.7)	6 (4.3)
Other	1 (0.4)	0	1 (0.7)
Missing	1 (0.4)	0	1 (0.7)
Ethnicity, n (%)			
Hispanic or Latino	2 (0.7)	1 (0.7)	1 (0.7)
Not Hispanic or Latino	267 (97.1)	135 (98.5)	132 (95.7)
Missing	6 (2.2)	1 (0.7)	5 (3.6)
Age (years)			
Mean (StD)	72.6 (9.10)	74.4 (8.58)	70.9 (9.31)
Median (Q1, Q3)	72.4 (66.6, 79.8)	74.6 (68.6, 80.7)	70.9 (64.5, 78.0)
Min, max	41; 94	47, 94	41, 89
Age groups, n (%)			
< 65 years	56 (20.4)	21 (15.3)	35 (25.4)
≥ 65 years	219 (79.6)	116 (84.7)	103 (74.6)
65 to < 75 years	101 (36.7)	48 (35.0)	53 (38.4)
75 to < 85 years	94 (34.2)	52 (38.0)	42 (30.4)
≥ 85 years	24 (8.7)	16 (11.7)	8 (5.8)
Country, n (%)			
Belgium	11 (4.0)	10 (7.3)	1 (0.7)
France	34 (12.4)	13 (9.5)	21 (15.2)
Germany	26 (9.5)	17 (12.4)	9 (6.5)
Italy	21 (7.6)	9 (6.6)	12 (8.7)
Japan	38 (13.8)	18 (13.1)	20 (14.5)
Poland	6 (2.2)	4 (2.9)	2 (1.4)
Spain	26 (9.5)	14 (10.2)	12 (8.7)
United States	54 (19.6)	24 (17.5)	30 (21.7)
South Korea	19 (6.9)	3 (2.2)	16 (11.6)
Taiwan	12 (4.4)	0	12 (8.7)
Netherlands	16 (5.8)	15 (10.9)	1 (0.7)
Israel	7 (2.5)	5 (3.6)	2 (1.4)
Switzerland	1 (0.4)	1 (0.7)	0
China	4 (1.5)	4 (2.9)	0
Geographic region, n (%)			
Europe	141 (51.3)	83 (60.6)	58 (42.0)
North America	54 (19.6)	24 (17.5)	30 (21.7)
Asia	80 (29.1)	30 (21.9)	50 (36.2)

Source: Section 2.7.3, Table 4.
1L=first line of therapy, 2L+=second or later line of therapy, max=maximum, min=minimum, Q1=quartile 1, Q3=quartile 3, SAF=safety analysis set, StD=standard deviation.

In Cohorts A + C SAF-01 Nov 20, 95.3% of patients had Stage IV (metastatic; combined Stage IV, including IVA and IVB) disease at study entry and only a low proportion of patients (4.7%) had Stage IIIB/C disease at study entry. Thirty-four (12.4%) patients presented with stable brain metastasis at baseline: 16 1L patients and 18 2L+ patients.

Table 17: Disease Characteristics (Disease History), VISION Cohorts A + C - SAF-01 Nov 2020 (Combined Set)

	Overall N = 275 (100%)	1L N = 137 (100%)	2L+ N = 138 (100%)
Nicotine consumption, n (%)			
Never used	137 (49.8)	63 (46.0)	74 (53.6)
Regular user	7 (2.5)	6 (4.4)	1 (0.7)
Occasional user	0	0	0
Former user	121 (44.0)	67 (48.9)	54 (39.1)
Missing	10 (3.6)	1 (0.7)	9 (6.5)
Time since initial cancer diagnosis (years) [a, b]			
n (%)	275 (100.0)	137 (100.0)	138 (100.0)
Mean (StD)	1.01 (2.190)	0.70 (2.311)	1.32 (2.025)
Median (Q1, Q3)	0.33 (0.10, 1.20)	0.11 (0.07; 0.41)	0.79 (0.28, 1.52)
Min, max	-0.02, 25.26	-0.02, 25.26	0.01, 15.59
Histopathological classification, n (%)			
Adenocarcinoma	220 (80.0)	109 (79.6)	111 (80.4)
Squamous	27 (9.8)	11 (8.0)	16 (11.6)
Sarcomatoid	7 (2.5)	5 (3.6)	2 (1.4)
Adenosquamous	8 (2.9)	5 (3.6)	3 (2.2)
Large cell	2 (0.7)	2 (1.5)	0
Other	9 (3.3)	4 (2.9)	5 (3.6)
Missing	2 (0.7)	1 (0.7)	1 (0.7)

Source: VISION TLFs 01 February 2021 cutoff, Table 15.1.5.1na, 15.1.5.1nb, 15.1.5.2n, 15.1.5.2nb.

1L=first line of therapy, 2L+=second or later line of therapy, max=maximum, min=minimum, Q1=quartile 1, Q3=quartile 3, SAF=safety analysis set, StD=standard deviation, TLFs=tables, listings, and figures.

a Time since initial cancer diagnosis (years) = (date of informed consent for pre-screening/screening – date of initial cancer diagnosis+1) / 365.25.

b One patient has date of initial cancer diagnosis after pre-screening.

Table 18. Prior Anticancer Therapy, VISION Cohorts A + C – SAF 01 Nov 2020 (combined set)

	Overall N = 275 (100%)
Prior anticancer drug therapy for advanced NSCLC, n (%)	
Yes	138 (50.2)
No	137 (49.8)
Number of prior anticancer drug therapy lines for advanced NSCLC, n (%)	
1	88 (32.0)
2	47 (17.1)
3[a]	3 (1.1)
Prior anticancer therapy for metastatic disease	
n (%)	132 (48.0)

Source: Section 2.7.3, Table 8.

NSCLC=non-small cell lung cancer.

a Three patients were enrolled with 3 prior lines of therapy and are listed in protocol deviations.

- **Numbers analysed**

Table 19: Analysis sets (All lines), based on 01 Feb. 2021 cutoff – VISION study

Cohort A	All subjects in Cohort A who tested positive for METex14 skipping	152 (55%)

	alterations and who received a first dose of tepotinib	
Cohort C SAF-01 Nov 2020	All subjects in Cohort C who tested positive for METex14 skipping alterations and who received a first dose of tepotinib before 01 November 2020	123 (45%)
Cohort A + Cohort C SAF-01 Nov 2020	All subjects in Cohort A and Cohort C who tested positive for METex14 skipping alterations including patients who received their first tepotinib dose before 01 November 2020	275 (100%)

- **Outcomes and estimation**

Table 20: Efficacy results, independent evaluation, VISION study (combined set)

	Overall	1L	2L+
Cohort A SAF, N	**152**	**69**	**83**
ORR [a] n (%) [95% CI] [b]	71 (46.7) [38.6, 55.0]	35 (50.7) [38.4, 63.0]	36 (43.4) [32.5, 54.7]
mDOR, months [c] [95% CI] [d]	15.4 [9.7, 32.7]	32.7 [7.2, ne]	12.4 [9.5, 18.5]
DOR ≥ 6 months, n (% of responders)	53 (74.6)	25 (71.4)	28 (77.8)
mPFS, months [c] [95% CI] [d] Patients with event (PD/Death), n (%)	10.8 [8.3, 12.4] 89 (58.6)	10.3 [8.0, 15.3] 38 (55.1)	11.0 [8.2, 12.7] 51 (61.4)
mOS time [c], months [95% CI] [d] Patients with event, n (%)	19.1 [15.2, 22.1] 88 (57.9)	17.6 [9.9, 29.7] 39 (56.5)	19.7 [15.0, 22.3] 49 (59.0)
Cohort C SAF-01 Nov 2020, N	**123**	**68**	**55**
ORR [a] n (%) [95% CI] [b]	64 (52.0) [42.8, 61.1]	39 (57.4) [44.8, 69.3]	25 (45.5) [32.0, 59.4]
mDOR, months [c] [95% CI] [d]	10.8 [8.3, ne]	ne [8.3, ne]	10.8 [4.2, ne]
DOR ≥ 6 months, n (% of responders)	26 (40.6)	15 (38.5)	11 (44.0)
mPFS, months [c] [95% CI] [d] Patients with event (PD/Death), n (%)	10.4 [7.0, ne] 42 (34.1)	10.4 [7.0, ne] 22 (32.4)	12.1 [6.4, ne] 20 (36.4)
mOS time [c], months [95% CI] [d] Patients with event, n (%)	ne [14.4, ne] 31 (25.2)	14.4 [10.4, ne] 21 (30.9)	ne [ne, ne] 10 (18.2)
Cohorts A + C SAF-01 Nov 2020, N	**275**	**137**	**138**
ORR [a] n (%) [95% CI] [b]	135 (49.1) [43.0, 55.2]	74 (54.0) [45.3, 62.6]	61 (44.2) [35.8, 52.9]
mDOR, months [c] [95% CI] [d]	13.8 [9.9, 19.4]	32.7 [9.0, ne]	11.1 [8.4, 18.5]
DOR ≥ 6 months, n (% of responders)	79 (58.5)	40 (54.1)	39 (63.9)
mPFS, months [c] [95% CI] [d] Patients with event (PD/Death), n (%)	10.8 [8.5, 12.4] 131 (47.6)	10.4 [8.4, 15.3] 60 (43.8)	11.0 [8.2, 12.4] 71 (51.4)
mOS time [c], months [95% CI] [d] Patients with event, n (%)	19.7 [15.6, 22.1] 119 (43.3)	17.6 [13.4, 29.7] 60 (43.8)	19.9 [15.8, 22.3] 59 (42.8)

Source: VISION TLFs 01 February 2021 cutoff, Tables 15.2.1.1ns, 15.2.1.17nsb, 15.2.2.1n, 15.2.2.3nib, 15.2.2.3nsc, 15.2.2.4nso, 15.2.3.1n, 15.2.3.9n, 15.2.4.1n, 15.2.4.4n.

1L=first line of therapy, 2L+=second or later line of therapy, CI=confidence interval, DOR=duration of response, mDOR=median duration of response, mOS=median overall survival, mPFS=median progression-free survival, ne=not estimable, ORR=objective response rate, PD=progressive disease, SAF=safety analysis set, TLFs=tables, listings, and figures.

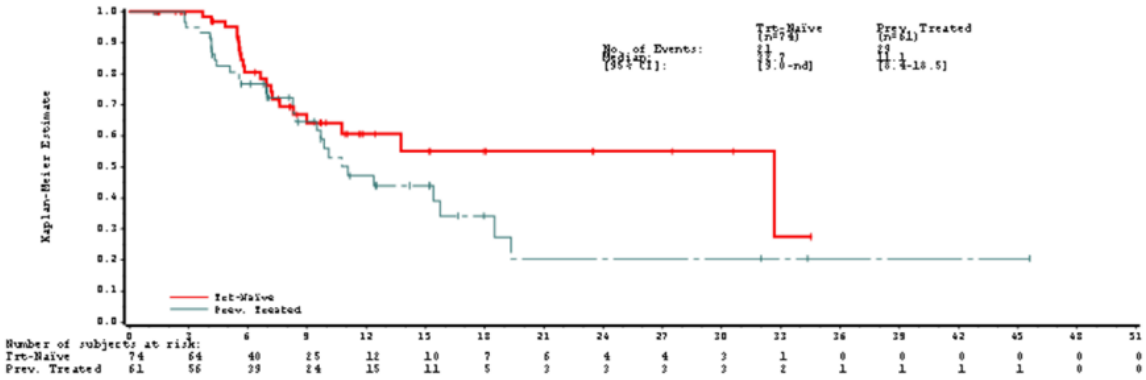
a Confirmed complete response/partial response.

b 95% exact CI using the Clopper-Pearson method.

c Product-limit (Kaplan-Meier) estimates.

d 95% CI for the median using the Brookmeyer and Crowley method.

Duration of response:



Source: Module 2.7.3, Figure 7.
CI=confidence interval, nd=not determined, prev. treated=previously treated, SAF=safety analysis set, trt-naïve=treatment naïve.

Figure 20: Kaplan-Meier curve showing duration of response by prior anticancer drug therapy, independent evaluation, VISION Cohorts A+C SAF-01 Nov 2020

METex14 skipping:

Table 21: Efficacy results, independent evaluation, VISION study, L+, T+, and Combined sets

	L+	T+	L+ and/or T+
Cohort A, SAF N	**99**	**88**	**152**
ORR [a] n (%) [95% CI] [b]	49 (49.5) [39.3, 59.7]	42 (47.7) [37.0, 58.6]	71 (46.7) [38.6, 55.0]
mDOR, months [c] [95% CI] [d]	12.4 [8.4, 19.4]	15.4 [10.1, ne]	15.4 [9.7, 32.7]
DOR ≥ 6 months, n (% of responders)	37 (75.5)	30 (71.4)	53 (74.6)
mPFS, months [c] [95% CI] [d] Patients with event (PD/Death), n (%)	8.6 [6.8, 11.0] 68 (68.7)	12.4 [8.9, 17.1] 46 (52.3)	10.8 [8.3, 12.4] 89 (58.6)
mOS time [c], months [95% CI] [d] Patients with event, n (%)	17.6 [12.0, 21.0] 60 (60.6)	22.3 [17.0, 29.7] 46 (52.3)	19.1 [15.2, 22.1] 88 (57.9)
Cohort C, SAF-01 Nov 2020, N	**60**	**86**	**123**
ORR [a] n (%) [95% CI] [b]	29 (48.3) [35.2, 61.6]	47 (54.7) [43.5, 65.4]	64 (52.0) [42.8, 61.1]
mDOR, months [c] [95% CI] [d]	10.8 [8.3, ne]	ne [8.3, ne]	10.8 [8.3, ne]
DOR ≥ 6 months, n (% of responders)	14 (48.3)	16 (34.0)	26 (40.6)
mPFS, months [c] [95% CI] [d] Patients with event (PD/Death), n (%)	8.4 [5.7, 12.1] 27 (45.0)	ne [6.9, ne] 25 (29.1)	10.4 [7.0, ne] 42 (34.1)
mOS time [c], months [95% CI] [d] Patients with event, n (%)	14.4 [9.5, ne] 23 (38.3)	ne [ne, ne] 13 (15.1)	ne [14.4, ne] 31 (25.2)
Cohorts A + C, SAF-01 Nov 2020, N	**159**	**174**	**275**
ORR [a] n (%) [95% CI] [b]	78 (49.1) [41.1, 57.1]	89 (51.1) [43.5, 58.8]	135 (49.1) [43.0, 55.2]
mDOR, months [c] [95% CI] [d]	11.1 [9.0, 18.5]	15.4 [9.9, 32.7]	13.8 [9.9, 19.4]
DOR ≥ 6 months, n (% of responders)	51 (65.4)	46 (51.7)	79 (58.5)
mPFS, months [c] [95% CI] [d] Patients with event (PD/Death), n (%)	8.5 [6.9, 10.4] 95 (59.7)	12.4 [10.3, 16.8] 71 (40.8)	10.8 [8.5, 12.4] 131 (47.6)
mOS time [c], months [95% CI] [d] Patients with event, n (%)	16.3 [12.1, 20.4] 83 (52.2)	22.3 [19.1, 29.8] 59 (33.9)	19.7 [15.6, 22.1] 119 (43.3)

Source: VISION TLFs 01 February 2021 cutoff, Tables 15.2.1.1ns, 15.2.1.17nsb, 15.2.2.1n, 15.2.2.3nib, 15.2.2.3nsc, 15.2.2.4nso, 15.2.3.1n, 15.2.3.9n, 15.2.4.1n, 15.2.4.4n.

CI = confidence interval, DOR = duration of response, L+ = liquid biopsy positive, mDOR = median duration of response, mOS = median overall survival, mPFS = median progression-free survival, ne = not estimable, ORR = objective response rate, PD = progressive disease, SAF=safety analysis set, T+ = tissue biopsy positive, TLFs=tables, listings, and figures.

a Confirmed complete response/partial response.
b 95% exact CI using the Clopper-Pearson method.
c Product-limit (Kaplan-Meier) estimates.
d 95% CI for the median using the Brookmeyer and Crowley method.

Efficacy outcomes in METex14 skipping 2L+:

Table 22: Efficacy results in 2L+, independent evaluation, VISION study, L+, T+, and Combined sets

	L+	T+	L+ and T+	L+ and/or T+
2L+ Cohorts A + C, SAF-01 Nov 2020, N	**78**	**88**	**29**	**138**
ORR [a] n (%) [95% CI] [b]	34 (43.6) [32.4, 55.3]	42 (47.7) [37.0, 58.6]	15 (51.7) [32.5, 70.6]	61 (44.2) [35.8, 52.9]
mDOR, months [c] [95% CI] [d]	11.1 [8.4, 19.4]	10.1 [8.3, 15.7]	11.1 [4.2, 15.4]	11.1 [8.4, 18.5]

Source: VISION TLFs 01 February 2021 cutoff, Tables 15.2.1.3nc, 15.2.1.17nsb, 15.2.2.4nso, 15.2.2.6nc.

CI = confidence interval, DOR = duration of response, L+ = liquid biopsy positive, mDOR = median duration of response, ne = not estimable, ORR = objective response rate, PD = progressive disease, T+ = tissue biopsy positive,

a Confirmed complete response/partial response.

b 95% exact CI using the Clopper-Pearson method.

c Product-limit (Kaplan-Meier) estimates.

d 95% CI for the median using the Brookmeyer and Crowley method.

Time to response:

The majority of responses to tepotinib occurred early: 121/136 (89.0%) of patients with a BOR of CR or PR were recorded at the first or second tumour assessments, i.e., within the first 3 months of treatment.

Table 23: Time to response, independent evaluation VISION Cohorts A+C, SAF, 01 February 2021 cutoff (Combined set)

	Overall N = 291	1L N =148	2L+ N = 143
Number of subjects with confirmed CR or PR response, n	136	74	62
Time to response (months)			
Mean (StD)	2.2 (2.79)	2.5 (3.65)	1.9 (1.01)
Median	1.4	1.4	1.4
Q1, Q3	1.3, 2.7	1.3, 2.7	1.3, 2.7
5th percentile, 95th percentile	1.2, 5.4	1.3, 6.7	1.2, 4.1
Min, max	1.1, 30.4	1.2, 30.4	1.1, 5.5

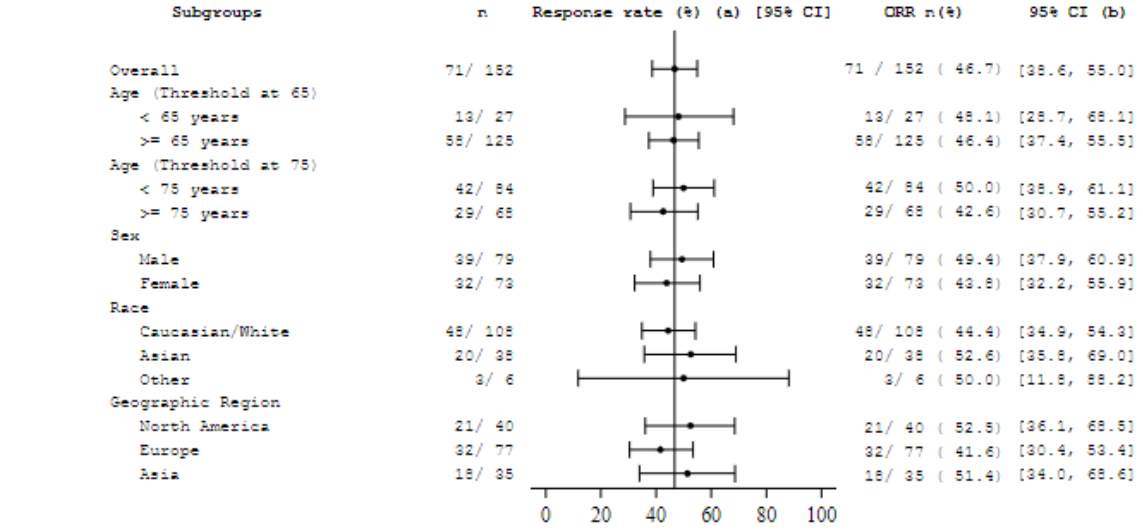
Source: VISION TLFs 01 February 2021 cutoff, Table 15.2.2.24.

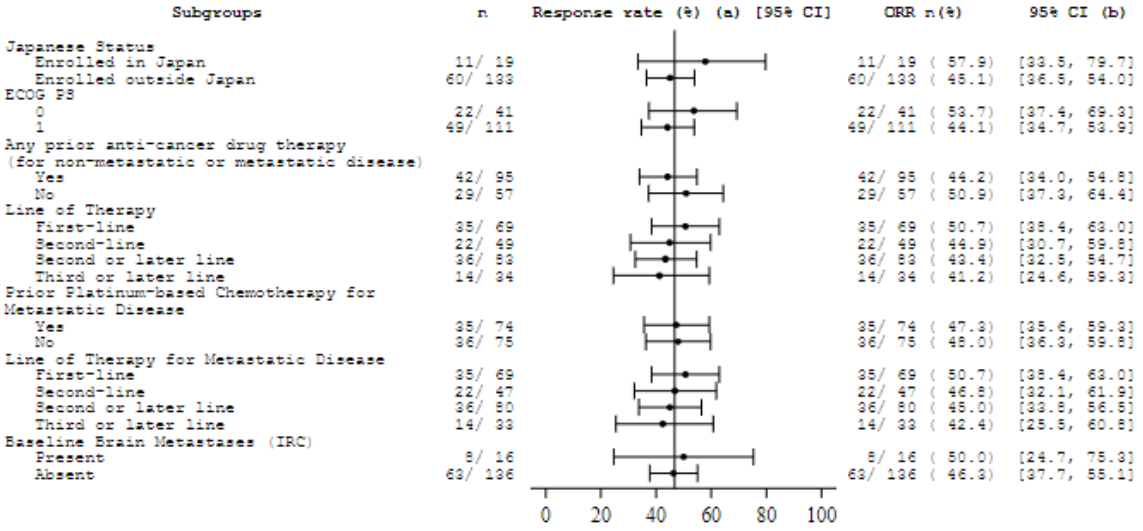
CR = complete response, max = maximum, min = minimum, PR = partial response, Q1 = first quartile, Q3 = third quartile, StD = standard deviation.

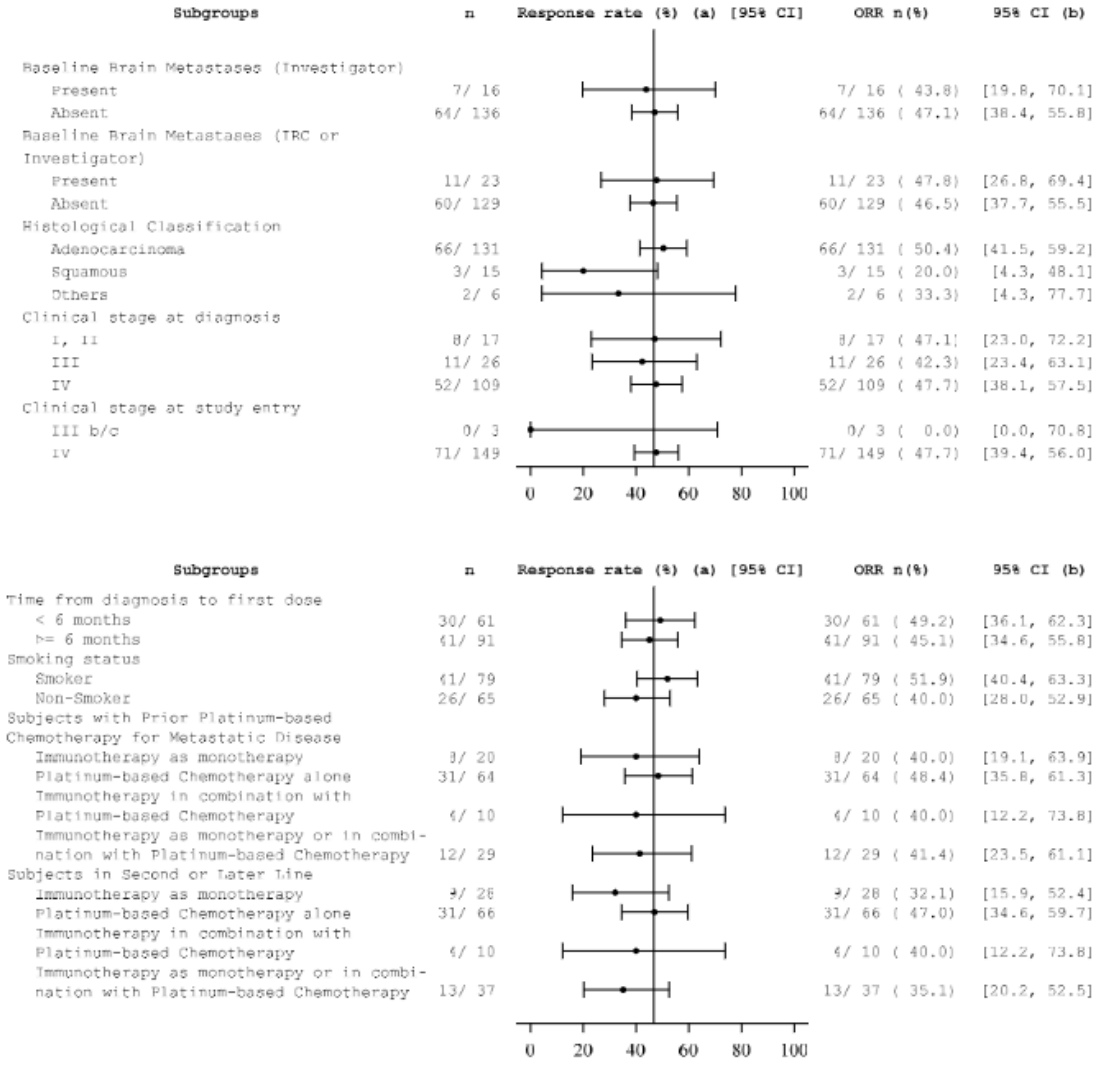
- **Ancillary analyses**

Subgroup analyses:

Figure 21: Forest Plot of objective response, independent evaluation, VISION Cohort A (Combined set)







Source: VISION TLFs 01 February 2021 cutoff, Figure 15.2.1.6nbs.

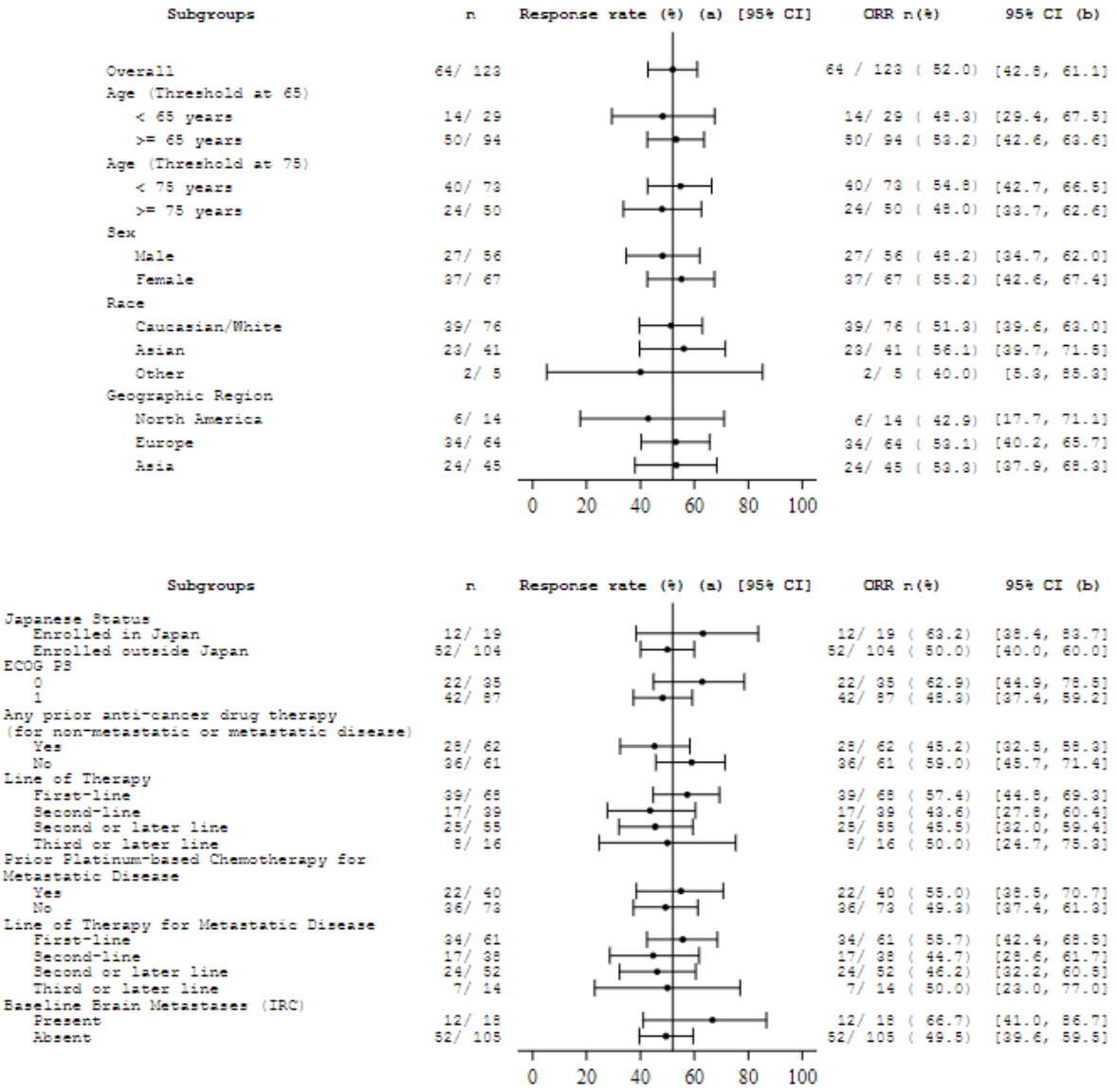
CI=confidence interval, ECOG PS= Eastern Cooperative Oncology Group Performance Status, IRC=independent review committee, ORR=objective response rate, SAF=safety analysis set, TLFs=tables, listings, and figures.

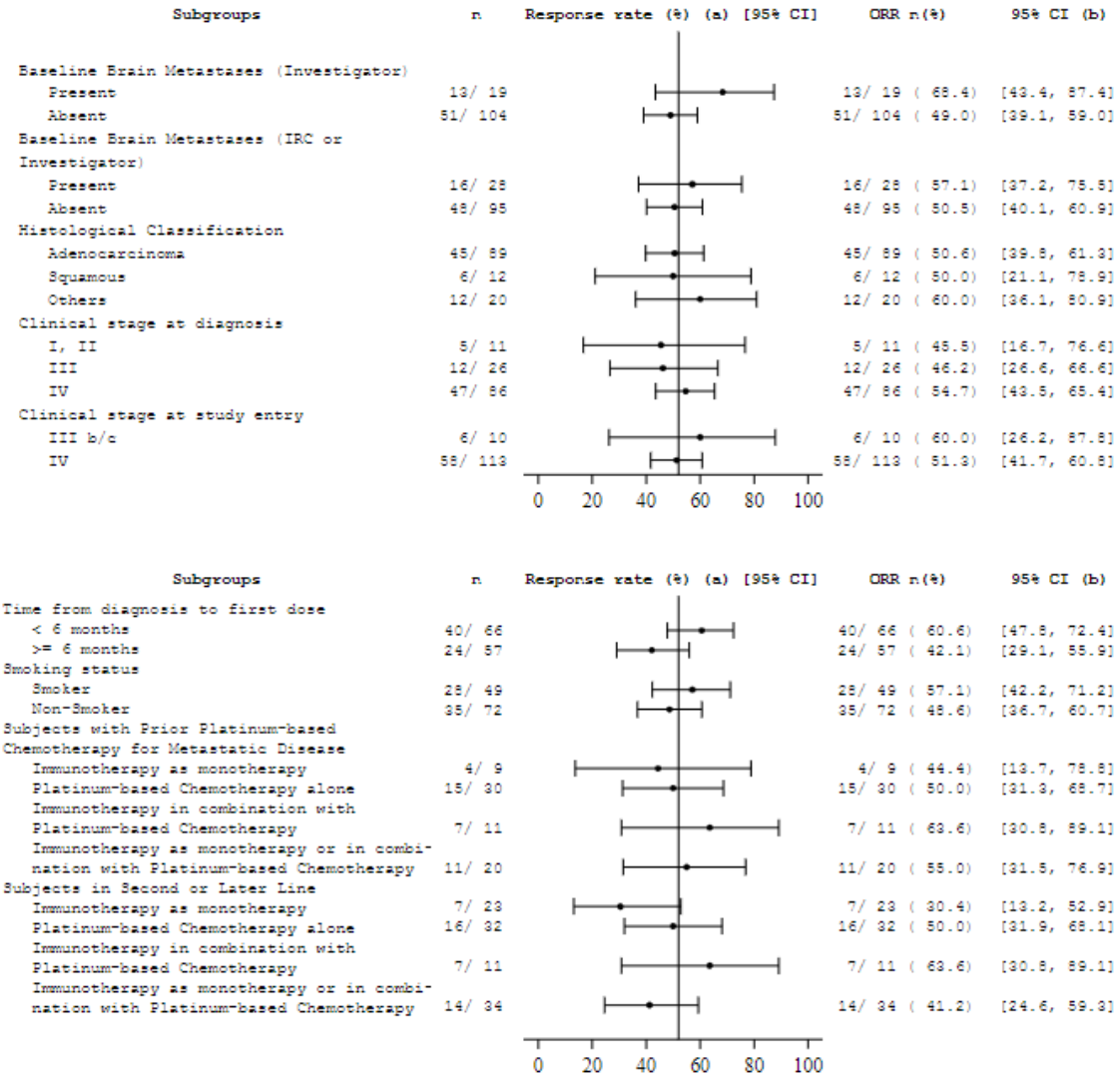
a Number of patients with confirmed complete or partial response / number of patients in subgroup.

b 95% exact CI using the Clopper-Pearson method.

Only prior anti-cancer drug therapies administered for advanced (Stage IIIb/IIIc) or metastatic (IV) diseases are taken into account for the categorization of line of therapy.

Figure 22: Forest Plot of objective response, independent evaluation, VISION Cohort C SAF-01 Nov 2020 (Combined set)





Subsequent therapy:

Table 24: Subsequent anti-cancer drug therapies status by line of therapy, VISION Cohorts A+C SAF-01 Nov 2020, 01 February 2021 cutoff (combined set)

	Overall N = 275	1L N = 137	2L+ N = 138
Tepotinib treatment ongoing	57 (20.7)	36 (26.3)	21 (15.2)
Tepotinib treatment discontinued	218 (79.3)	101 (73.7)	117 (84.8)
Initiated subsequent anticancer therapy	89 (32.4)	38 (27.7)	51 (37.0)
No subsequent anticancer therapy	129 (46.9)	63 (46.0)	66 (47.8)
Died before cutoff	74 (26.9)	42 (30.7)	32 (23.2)
Lost to follow-up before cutoff	3 (1.1)	1 (0.7)	2 (1.4)
Withdrew consent before cutoff	13 (4.7)	4 (2.9)	9 (6.5)
Alive at cutoff with follow up < 3 months [a]	35 (12.7)	13 (9.5)	22 (15.9)
Alive at cutoff with follow up ≥ 3 months [b]	4 (1.5)	3 (2.2)	1 (0.7)

Source: VISION TLFs 01 February 2021 cutoff, Table 15.1.6.6nb

1L = first-line; 2L+ = second or later-line; SAF=safety analysis set, TLFs=tables, listings, and figures.

a Last date known to be alive within 3 months before cut-off date

b Last date known to be alive more than 3 months before cut-off date

In VISION cohorts A + C, 31% of 1L patients died prior to receiving 2L therapy. With an additional 9.5% of patients not having received 2L treatment, but being alive with <3 months of follow-up.

Early mortality:

Table 25: Overall survival, VISION study, Cohort A+C SAF-01 Nov 2020 patient sets

	Overall	1L	2L+
Cohort A, N	152	69	83
Patients with event, n (%)	88 (57.9)	39 (56.5)	49 (59.0)
mOS time [a], months [95% CI] [b]	19.1 [15.2, 22.1]	17.6 [9.9, 29.7]	19.7 [15.0, 22.3]
Subjects at risk/ failed/ survival rates [c], % [95% CI] [d] up to			
3 months	137/ 11/ 93 [87, 96]	63/ 4/ 94 [85, 98]	74/ 7/ 91 [83, 96]
6 months	117/ 29/ 80 [73, 86]	53/ 13/ 81 [69, 88]	64/ 16/ 80 [70, 87]
Cohort C SAF-01 Nov 2020, N	123	68	55
Patients with event, n (%)	31 (25.2)	21 (30.9)	10 (18.2)
mOS time [a], months [95% CI] [b]	ne [14.4, ne]	14.4 [10.4, ne]	ne [ne, ne]
Subjects at risk/ failed/ survival rates [c], % [95% CI] [d] up to			
3 months	115/ 6/ 95 [89, 98]	63/ 5/ 93 [83, 97]	52/ 1/ 98 [87,100]
6 months	100/ 12/ 90 [83, 94]	52/ 10/ 85 [73, 91]	48/ 2/ 96 [86, 99]

Source: VISION TLFs 01 February 2021 cutoff, Tables 15.2.4.1n and 15.2.4.4n.
1L = first-line therapy, 2L+ = second- or later-line therapy, CI = confidence interval, mOS = median overall survival, SAF=safety analysis set, TLFs=tables, listings, and figures.

a Product-limit (Kaplan-Meier) estimates.
b 95% CI for the median calculated using the Brookmeyer and Crowley method.
c Based on Kaplan-Meier estimates.
d 95% confidence interval using the log-log transformation according to Kalbfleisch and Prentice.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the applicant's pivotal study supporting the present marketing authorization application. This summary is based on Cohort A, including data from all patients with confirmed *MET*ex14 skipping alterations.

Table 26. Summary of Efficacy for Clinical Trial MS200095-0022

Title: A Phase II single-arm trial to investigate tepotinib in advanced (locally advanced or metastatic) non-small cell lung cancer with MET exon 14 (*MET*ex14) skipping alterations or MET amplification (VISION)		
Study identifier	MS200095-0022; Referred to as VISION at this point going forward. EudraCT number: 2015-005696-24; NCT number: 02864992	
Design	Phase II, multicenter, multicountry, single-arm, open-label, nonrandomized efficacy and safety study to assess the antitumour activity and tolerability of tepotinib in patients with advanced NSCLC.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	First subject enrolled (signed screening informed consent form): 06 September 2016. Not applicable
Hypothesis	The study aims for an ORR based on an independent review committee (IRC; primary endpoint measure) in the range of 40% to 50%, with a lower limit of the corresponding exact 2-sided 95% CI (according to Clopper-Pearson) to be above 20%.	
Treatments groups	Cohort A (METex14 Skipping Alterations)	Tepotinib 500 mg oral once daily; 152 patients enrolled.
	Cohort C (METex14 Skipping Alterations)	Tepotinib 500 mg oral once daily; 123 patients enrolled.
Endpoints and definitions	Primary endpoint:	
	OR as per IRC	Confirmed complete response (CR) or partial response (PR) determined according to RECIST 1.1; confirmation by a tumour assessment at least 28 days after the tumour assessment initially indicating CR or PR.
	Secondary endpoints:	
	DOR as per IRC	Time from onset of confirmed CR/PR (whichever was first) until progressive disease (PD) or death due to any cause within 84 days of the last tumour assessment, whichever occurred first.

	PFS as per IRC	Time (in months) from the first administration of study treatment to the date of the first documentation of PD or death due to any cause within 84 days of the last tumour assessment, whichever occurred first.		
	OS	Time (in months) from first study treatment administration to the date of death.		
Database lock	01 February 2021 (Data cut-off) including patients who received their first tepotinib dose before 01 November 2020			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Cohort A, ITT: N=152, thereof 69 1L and 83 2L+ patients Cohort C, Safety analysis set (SAF) (first dose before 01 November 2020): N=123, thereof 68 1L and 55 2L+ patients			
Descriptive statistics and estimate variability	Treatment group	**Cohort A + C SAF-01 Nov 2020 (*MET*ex14)**		
		Overall	1L	2L+
	Number of subjects	275	137	138
	Primary Endpoint			
	ORR n (%) [95% CI]	135 (49.1) [43.0, 55.2]	74 (54.0) [45.3, 62.6]	61 (44.2) [35.8, 52.9]
	Secondary Endpoints			
	mDOR (months) by IRC Median [95% CI]	13.8 [9.9, 19.4]	32.7 [9.0, NE]	11.1 [8.4, 18.5]
	mPFS (months) by IRC Median [95% CI] Patients with event n (%)	10.8 [8.5, 12.4] 131 (47.6)	10.4 [8.4, 15.3] 60 (43.8)	11.0 [8.2, 12.4] 71 (51.4)
	mOS (months) Median, [95% CI] Patients with event n (%)	19.7 [15.6, 22.1] 119 (43.3)	17.6 [13.4, 29.7] 60 (43.8)	19.9 [15.8, 22.3] 59 (42.8)
Effect estimate per comparison	Not applicable (single-arm study).			
Notes	1L=First line of therapy, 2L+=Second or later line of therapy, CI=confidence interval, CR=complete response, DOR=duration of response, EudraCT=European Union Drug Regulating Authorities Clinical Trials Database; IRC=independent review committee, ITT=intent to treat, (m) of mDOR, mPFS,mOS=median, METex14=MET exon 14, ne=not estimable, , NCT=National Clinical Trial, NSCLC=Non-small cell lung cancer, PR=partial response; OS=median, OR=objective response, ORR=objective response rate, OS=overall survival, PD=progressive disease, PFS=progression-free survival, RECIST=Response Evaluation Criteria in Solid Tumours.			

2.6.5.3. Clinical studies in special populations

An overview of percentage of patients included in controlled and uncontrolled studies by age group is provided in Table 27.

Table 27: Overview of patients included in controlled and uncontrolled studies by age group

	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	14/89 (15.7%)	4/89 (4.5%)	0/89 (0%)
Non Controlled Trials	197/569 (34.6%)	123/569 (21.6%)	24/569 (4.2%)

Source: VISION SCS 01 February 2021 cutoff

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Prospective testing of MET exon 14 skipping mutations was performed centrally on circulating free DNA (cfDNA) obtained from plasma (liquid biopsy [LBx]) with the use of next-generation sequencing (NGS) panel Guardant360® Test Version 2.10 and ArcherDX MET Variant Test or by evaluating RNA obtained from fresh or archival (formalin-fixed, paraffin-embedded) tumor-biopsy tissue (TBx) with the use of the Oncomine Focus Assay 2.10 and the ArcherDX MET Variant Test.

For circulating free DNA/cfDNA/LBx positive METex14 status was defined as mutations occurring in 12 bp regions centered on the splice donor and acceptor sites.

For tumor tissue RNA/TBx positive METex14 status was defined by detecting a sequence at the Exon 13 to Exon 15 boundary by amplicon NGS. Additionally, a RNA-based reverse transcriptase polymerase chain reaction-based method specific for detecting METex14 skipping alterations from fresh frozen tissue was available to patients in Japan.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

In this submission, the applicant has included 16 Phase I and II clinical studies (the pivotal VISION trial + 1 phase Ib/II tepotinib + gefitinib study in EGFR+NSCLC, 2 phase Ib/II studies in HCC, 2 phase I studies in various advanced solid tumours, 9 phase I studies in non-cancer patients, 1 p II study tepotinib + Osimertinib in EGFR+NSCLC). Accordingly, efficacy data pertinent to the indication derive from the VISION trial.

Due to the rarity of the investigated indication, the mechanism of action of tepotinib supported by scientific evidence, and the lack of satisfactory targeted therapy options for NSCLC harbouring MET alterations, a single-arm design was by the applicant considered appropriate for the pivotal VISION study.

The VISION trial, "A Phase II single-arm trial to investigate tepotinib in advanced (locally advanced or metastatic) non-small cell lung cancer with MET exon 14 (METex14) skipping alterations or MET amplification (VISION)" was initiated as a 2L+ trial in NSCLC patients with MET exon 14 skipping alterations. In effect, due to several protocol changes from amendment 4 and forth, the trial shifted from a 2L+ to a 1L+ trial in a broader population (also MET amplifications, cohort B) and allowed also liquid biopsies for inclusion.

Prospective testing of MET exon 14 skipping mutations was performed centrally on circulating free DNA (cfDNA) obtained from plasma (liquid biopsy [LBx]) with the use of next-generation sequencing (NGS) panel Guardant360® Test Version 2.10 and ArcherDX MET Variant Test or by evaluating RNA obtained from fresh or archival (formalin-fixed, paraffin-embedded) tumor-biopsy tissue (TBx) with the use of the Oncomine Focus Assay 2.10 and the ArcherDX MET Variant Test.

ORR was chosen as primary endpoint, and this is considered a relevant indicator of clinical benefit in a single arm trial, as more direct measures of benefit such as PFS and OS are difficult to interpret without a study-internal control. However, due to study design and that the ORR success criterion is of uncertain relevance, findings are assessed without reference to it.

The study design as well as the powering of the study was discussed within a CHMP scientific advice procedure (EMA/CHMP/SAWP/820655/2015). At that time the sample size estimation approach, the targeted efficacy, and the planning of a pilot phase for sample size adjustment was criticised. Demonstrating that ORR is greater than 10% was not considered sufficient and the applicant was

advised to plan the study to be able to estimate ORR with reasonable precision and also that an impressive response rate would be required for consideration of approval.

The initially targeted sample size was 60 subjects with the aim to show an ORR in the range of 40% to 50% and to demonstrate that the lower limit of the corresponding exact 2-sided 95% CI (Clopper-Pearson) exceeds 20%. During the study, two different primary analysis sets were introduced as was two new cohorts (B and C). While the total expected sample size has been increased, there have however not been any changes made what regards the targeted efficacy in terms of ORR but for the adding of "across lines of therapy". The introduction of two primary analysis sets is claimed to have been to account for potential differences in the detection of METex14 alterations by different methodologies. The aim was to show an ORR of 40-50% in each set and both sets were to include 60 subjects.

Due to the design of Study MS200095-0022 the risk of bias could not be eliminated in initial assessment. Without a concurrent control, the impact of e.g. subject selection on the claimed effect size is difficult to assess and as in any open-label study it will not have been possible to ensure that subjective assessments and decisions were not affected by knowledge of treatment. The use of an Independent Review Committee for tumour assessments is considered necessary and it is acknowledged that METex14 status was determined by a central laboratory. Given the open label study design it is difficult not to interpret the changes made as being data driven. The performance of interim analyses adds to concerns regarding study integrity. Additional concerns in this respect are the introduction of two primary analysis sets that later became three and that there are several data sets defined with different data cut-offs that could be considered to offer several possibilities to claim a positive efficacy study outcome. Overall, there seems not to have been a clear definition of what was to be required for the analysis of cohort A to be considered a success.

Efficacy data and additional analyses

In the initially submitted dataset, the ORR was 45%, with a median DoR of 11 months in 146 patients. Bias in efficacy estimates was a concern, due to the lack of internal control, several protocol amendments and uncertainty in predefinition of the pivotal population as discussed. In view of the demonstrated effects on OS for approved 1L treatment options e.g., combinations of PD-1/PD-L1/CTLA-4 directed therapies and platinum doublets, a line independent indication was considered in need of a justification.

In a requested update, with a 01 February 2021 data cut off following the ITT-principle, data for all 152 (69 1L and 83 2L+) enrolled Cohort A patients receiving at least 1 dose of tepotinib, demonstrate an ORR of 47% (51% 1L, 43% 2L+) with a median DoR of 15 months.

For the expanded confirmatory cohort C (SAF-01 Nov 2020 patient set, 01 February 2021 cut off; n=123 patients, 68 1L and 55 2L+), ORR was 52% (57% 1L, 46% 2L+) with 11 months median DoR.

The updated and independent data corroborate initial findings, and the applicant provides a total of 275 patients with a pooled ORR of 49.1% (95% CI: 43, 55) whereof 138 2L+ patients with an ORR of 44.2% (95% CI: 36, 53). Accordingly, the risk of bias is mitigated.

Although acknowledging a first line ORR of 54%, an impact on time dependent endpoint such as PFS and OS cannot be isolated in SATs. Therefore, the extent to which tepotinib would provide clinical benefit in first line treatment, remains unclear. This was the subject of a SAG oncology consultation (see below). The CHMP considered that, in the absence of studies capable of isolating drug effects on PFS and OS, the activity of the drug in terms of ORR/DoR was not sufficiently high to establish the utility of tepotinib for first line use.

The tissue RNA-based CTAs employed in VISION Cohort A directly demonstrated, for 88 patients, that METex14 skipping has occurred at the gene expression level i.e., that CTAs identified functional METex14 loss by detecting the transcript sequence at the Exon 13 to Exon 15 boundary. In this group of patients, ORR was 48%. Accordingly, relevant efficacy was demonstrated in a group of patients corresponding to the proposed indication in the strict sense.

It further seems clear that a DNA based assay (alone) can identify a group of patients with similar efficacy, and that the proportion of patients with actual loss of exon 14 among those included on the basis of a positive result for the applied LBx assays assay is high.

Additional expert consultation

Input of the SAG-Oncology has been requested. On the meeting of the 3rd of November 2021, the conclusions of the SAG-O were as follows:

1. **The activity of Tepmetko in terms of ORR in the first line treatment of NSCLC with MET exon 14 skipping alteration, appears at least on par with present standard of care options. Further, it has a different safety profile from these agents and is administered orally rather than intravenously. However, all data are derived from single arm trials, which limits the ability to isolate drug effects on time-dependent endpoints. CHMP is seeking the opinion of the SAG-O, whether the ORR and DoR reached with Tepmetko is of such magnitude that clinically relevant efficacy may be considered established, for patients with Met Exon 14 skipping alterations that have not previously been treated for advanced NSCLC**

The SAG agreed that the data submitted for the demonstration of efficacy suffer of a number of shortcomings due to the non-randomized trial submitted, including the lack of reliable comparative data for clinically relevant endpoints like OS, PFS and HRQoL. In the absence of a randomized comparison, the effect on important clinical endpoints is difficult to assess or quantify. The high activity in terms of ORR also suffers of likely selection bias, which may also be the explanation for the similar survival *observed in different lines of treatment. Furthermore, the presented interval estimations do not take* multiplicity into account, and the descriptive analyses of DoR are unreliable due to a number of censored observations.

However, with respect to the claimed 1st line indication, the majority of the SAG agreed that overall, the ORR of 46.7% (95% CI: 38.6%; 55.0%) and 15.4 (95% CI: 9.7; 32.7) months mDOR in cohort A (1st and 2nd line patients; IRC overall population N=152; 1 February 2021 data cut-off) and of 50.7% (95%CI, 38.4, 63.0) and mDOR of 32.7 months (95%CI 7.2, NE) in 1st line patients (cohort A 1L subgroup; N=69; 1 February 2021 data cut-off) is compatible with a likely clinical benefit. Despite the fact that ORR is not considered to be a reliable surrogate for OS/PFS, the magnitude of response is such that a clinical benefit is considered likely, especially if compared (indirectly) to the response rate of available options which is in the order of 20%-40%. Thus, the observed level of activity is considered sufficient to establish clinically relevant efficacy.

In support of this conclusion, there is a sound pharmacodynamic rationale, indirect comparisons of OS, some activity on brain metastases, a likely more patient-friendly option in terms of administration, and a more favourable toxicity profile compared to standard chemo-immunotherapy combinations. Furthermore, non-specific alternative options may be associated with poorer outcomes in this seemingly poorer prognosis population. In this context, the high response rate, the long duration of response, similar results in cohorts A and C and the supportive evidence in this clinical context, point toward a likely clinical benefit.

Unfortunately, the magnitude of such benefit in terms of convincing clinical endpoints like OS, PFS, or HRQoL is difficult to establish although indirect comparisons and activity results support a conclusion of adequate efficacy compared to available treatments.

A minority view considered that ORR is not a good surrogate for OS and it is unreliable to compare ORR/DOR across trials due to patient selection and unclear meaning in terms of clinical endpoints. A randomized clinical trial should have been conducted to establish clinically relevant benefits. The claimed high activity is likely an over-estimation due to patient selection. Taking this into account, the observed 50.7% (95%CI, 38.4, 63.0; unadjusted for multiplicity) in 1st line patients, at best, is indicative of sufficient activity to warrant further investigation in adequately powered randomized trials. There is little evidence (based on small retrospective series) that the established available options are not efficacious in this targeted indication. Thus, tepotinib is associated with substantial questions about efficacy compared to established options that have shown a clinical benefit based on rigorous scientific and regulatory standards. According to this view, tepotinib is associated with substantial uncertainties about efficacy and no clinical benefit can be considered established in 1st line, based on the available data. A 1st line indication would expose patients to the risk of substantial uncertainties in efficacy when established options with a clear effect on OS are available and are the standard of care.

2. **What further investigations, if any, are relevant to further characterise the efficacy and safety of Tepmetko in first- or later line treatment? Particularly, is an RCT deemed feasible in the treatment of first line Met exon 14-altered NSCLC, or in a later treatment line?**

According to the majority view, the available data are sufficient to conclude that tepotinib is associated with a clinical benefit. Unfortunately, the magnitude of such benefit is difficult to establish in the absence of direct comparative data. An RCT post-approval would be considered informative but not necessary, taking into account that the efficacy is not questioned given the high activity and the acceptable safety profile. Furthermore, the feasibility and interest in such a trial is considered questionable given the conclusion of an established clinical benefit and the rarity of the disease.

Thus, additional corroborative data using the RWD approach proposed is considered sufficient to address the likely shortcomings in terms of selection bias and estimation. The objective of such additional data would be to confirm response rate and duration in a broader population that is not highly selected in terms of patient, disease and treatment characteristics (e.g., comorbidities, prior treatments, etc.), using rigorous methodology to assess response and progression-free survival, similar to how this is assessed and adjudicated in clinical trials. Appropriate expectations should be prespecified on what would constitute an effect in the target population that is confirmatory of the high activity observed in the pivotal trial. Additional analyses could try to quantify the effect on OS and PFS although the challenges of external comparisons are acknowledged.

A minority of SAG members disagreed and considered that a RCT is necessary and feasible pre-approval. Even if approved, according to this view, the uncertainties in terms of type and quantity of benefits (PFS, OS, QoL) are such that a randomized trial would be considered feasible and interesting also post-approval. Despite the rarity of the disease, given the promise of an active targeted agent, worldwide recruitment could be highly effective. Feasibility could be enhanced by treatment switching post-PD, based on the claimed high activity in second-line with similar survival, and generally, using early stopping rules for efficacy justified by the claimed high activity to minimise sample size.

Further to the SAG responses, the CHMP acknowledged that according to the SAG-O majority the magnitude of ORR and DOR is such that a clinical benefit is considered likely and that tepotinib was associated with an acceptable safety profile that is consistent with the safety profile of some targeted therapies in this setting.

However, for first-line treatment, CHMP has also considered the limitations of the provided data from a single-arm trial, that selection bias cannot be ruled out, as well as uncertainties regarding long term efficacy outcomes.

The MAH is recommended to conduct and submit the results of two non-interventional studies based on prospectively collected registry data. The planned prospective registry will be able to collect OS data from patients harbouring METex14 NSCLC mutations treated with standard of care or tepotinib. Registry data will be analysed in a non-interventional external control study to VISION, and a comparative effectiveness and safety study on tepotinib versus best available care.

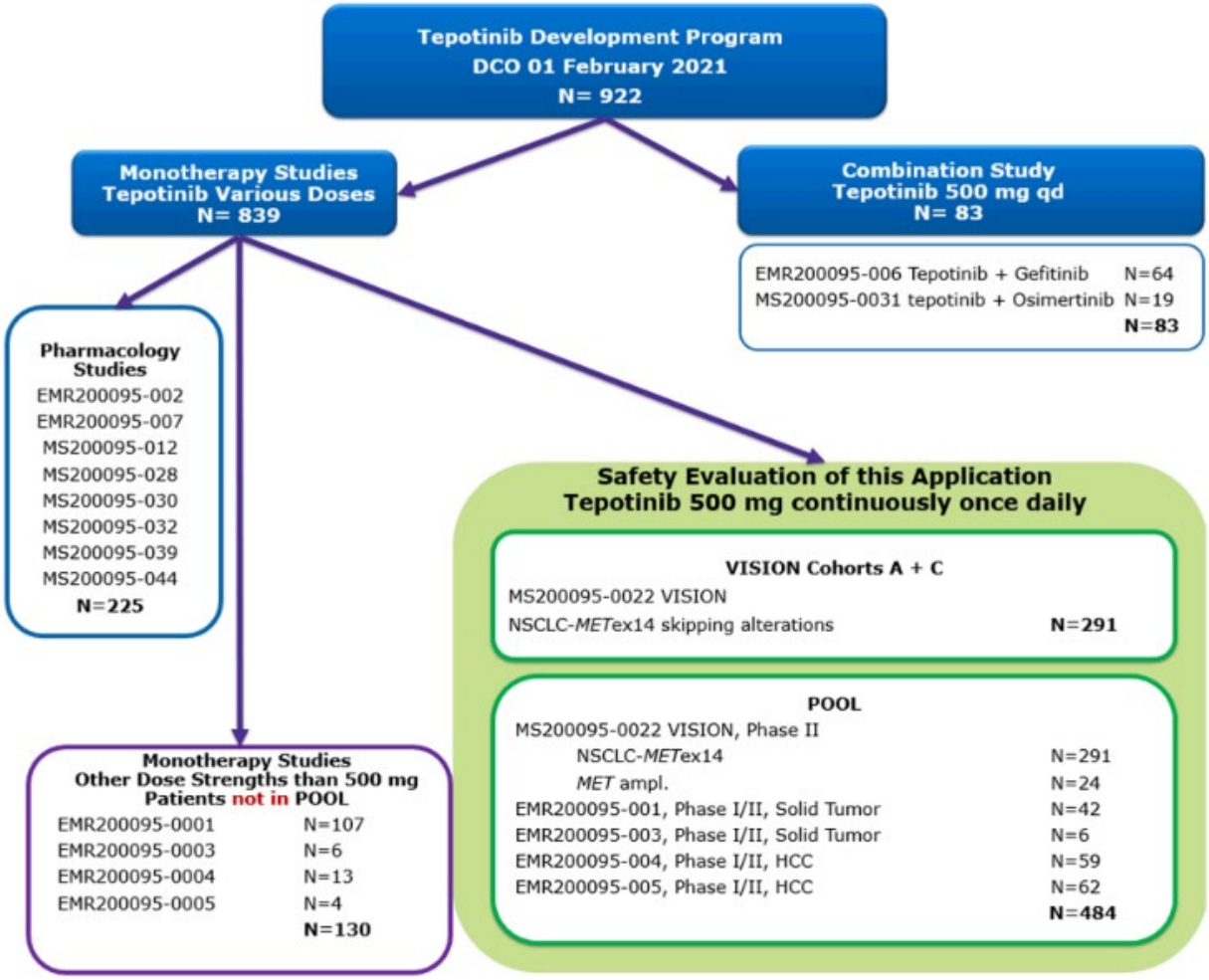
2.6.7. Conclusions on the clinical efficacy

The ORR and response durations for tepotinib are of a magnitude expected to provide benefit to NSCLC patients harbouring METex14 NSCLC mutations that have had at least one line of prior therapy with advanced disease. Clinical benefit is not considered to have been sufficiently established for first line use.

2.6.8. Clinical safety

Safety populations

At the data cut-off (DCO) date of 01 February 2021, the tepotinib clinical development program included 922 participants treated with tepotinib (Figure 23). These included 697 patients with NSCLC, HCC, and solid tumors, 12 participants without cancer (hepatic impairment), and 213 healthy participants. The clinical development program includes monotherapy and combination studies.



Studies included in the pool for safety analyses are shown in the green box.
DCO = Data cutoff; HCC = Hepatocellular carcinoma; *MET* ampl. = *MET* amplification; *MET*ex14 = *MET* exon 14; NSCLC = Non-small cell lung cancer.

Source: SCS, Figure 1, DCO update 01 February 2021

Figure 23. Tepotinib Clinical Development Program (Data Cut-off 01 February 2021)

The VISION study cohorts A and C (NSCLC harbouring METex14 skipping alterations) represent the target population for this application, treated at the proposed dose and schedule. These cohorts are pivotal for the safety evaluation of the METex14 population and the safety profile relevant to this population is presented in the SmPC.

In addition, in order to characterize the safety profile of tepotinib at the recommended dose of 500 mg once daily, data from completed clinical studies for all patients with cancer dosed with tepotinib monotherapy at 500 mg daily were pooled. These analyses are identified as POOL throughout the document. Patients treated at a dose lower or higher than 500 mg daily continuously or intermittently have been excluded from the POOL safety set. Also, patients in the combination study with gefitinib (EMR200095-006) have not been included in the POOL.

The VISION study is still ongoing; other studies constitutive of the POOL were completed by the time of the initially submitted DCO, 01 July 2020.

The safety population in the target population of non-small cell lung cancer (NSCLC) with MET exon 14 (METex14) skipping alterations is relatively small, n = 291.

In the pooled safety population, "POOL", n=484, a total of 315 patients with NSCLC are available, also including those with MET amplification. In addition, 121 patients with hepatocellular carcinoma (HCC) and 48 patients from studies of mixed solid tumours are included. HCC patients constitute 25% of the subjects in the POOL, and NSCLC patients constitute 60%.

Outside the POOL, 69 NSCLC patients were treated with tepotinib in combination with gefitinib (64) or osimertinib (19).

The pivotal VISION study

The pivotal study was performed in NSCLC with MET aberrations, organised in three cohorts:

Cohort A: METex14 skipping, enrolment completed, cohort included in pivotal efficacy data set
Cohort B: MET amplification, enrolment halted following the pre-planned interim analysis
Cohort C: METex14 skipping, enrolment ongoing, cohort partially included in pivotal efficacy data set

At the DCO Feb 2021 the enrolment into Cohort C was ongoing. The last patient was enrolled in the VISION Study into Cohort C on 20 May 2021.

The pivotal safety analysis set for this application includes all 291 subjects enrolled in Cohort A and Cohort C (i.e., pooled METex14 skipping alteration cohorts) who had received at least 1 dose of tepotinib up to the data cut-off date, 01 February 2021.

Patient exposure

Dose – exposure – response

Study EMR 200095-001 (N= 149) was the First-in-Man trial with tepotinib investigating 3 treatment regimens at multiple dose levels and with different formulations in a 3+3 study design:

- Regimen 1 (n=42): 30 mg once daily for 14 days, followed by 7 days with no treatment (21-day cycle). Patients received doses of 30mg – 400 mg (30, 60, 100, 115, 145, 215, 230, 300, and 400 mg cohorts).
- Regimen 2 (n=45): 60 mg once daily 3 times per week (e.g., Days 1, 3, and 5 every week) for 3 weeks (21-day cycle). Patients received doses of 30mg – 315 mg (30, 60, 100, 115, 130, 175, and 315 mg cohorts).
- Regimen 3 (n=62): Continuous once daily treatment in cycles of 21 days without a wash-out period. Patients received doses of 300 mg – 1400 mg (300, 400, 500, 700, 1000 and 1400 mg cohorts).

When comparing cumulative AE frequencies below, please note that the average time on treatment as well as the mean daily dose was considerably lower in the Regimen 2 (49 mg) cohort compared with Regimen 1 (94 mg). In the Regimen 3 cohort, the mean daily dose was considerably higher, 582 mg (Clinical AR/not shown).

The dose span investigated for Regimen 3 was 300-1400 mg; the median daily dose of 500 mg, reflects the large proportion (42/62) of patients receiving the 500 mg dose (Table 29).

Table 28. Overview of Treatment-emergent Adverse Events by Regimen, Study 001

	Tepotinib			
Number of subjects with	Regimen 1 (N = 42)	Regimen 2 (N = 45)	Regimen 3 (N = 62)	Total (N = 149)
TEAEs	41 (97.6%)	45 (100.0%)	59 (95.2%)	145 (97.3%)
TEAEs related to study drug	14 (33.3%)	23 (51.1%)	39 (62.9%)	76 (51.0%)
SAEs	14 (33.3%)	17 (37.8%)	22 (35.5%)	53 (35.6%)
SAEs related to study drug	0 (0.0%)	1 (2.2%)	0 (0.0%)	1 (0.7%)
TEAEs with toxicity grade ≥ 3	17 (40.5%)	19 (42.2%)	32 (51.6%)	68 (45.6%)
TEAEs related to study drug with toxicity grade ≥ 3	1 (2.4%)	3 (6.7%)	9 (14.5%)	13 (8.7%)
TEAEs with toxicity grade ≥ 4	2 (4.8%)	3 (6.7%)	3 (4.8%)	8 (5.4%)
TEAEs related to study drug with toxicity grade ≥ 4	1 (2.4%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
DLTs	1 (2.4%)	3 (6.7%)	2 (3.2%)	6 (4.0%)
TEAEs leading to permanent discontinuation of study drug	3 (7.1%)	4 (8.9%)	13 (21.0%)	20 (13.4%)
Related TEAEs leading to permanent discontinuation of study drug	1 (2.4%)	0 (0.0%)	2 (3.2%)	3 (2.0%)
TEAEs leading to temporary discontinuation of study drug	5 (11.9%)	6 (13.3%)	15 (24.2%)	26 (17.4%)
TEAEs leading to dose reduction of study drug	1 (2.4%)	2 (4.4%)	7 (11.3%)	10 (6.7%)
SAEs leading to hospitalization	14 (33.3%)	17 (37.8%)	22 (35.5%)	53 (35.6%)
TEAEs leading to death	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.7%)
TEAEs related to study drug leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

DLT = dose-limiting toxicity; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Source: Study EMR 200095-001 (Tepotinib First-in-Man trial), CTR, Table 37.

In Study 001, overall, no major differences in AE category frequencies were observed across the three regimens, where very different daily doses and cumulative exposures were achieved and being several times greater in Regimen 3. (Table 28).

Frequencies around 10% higher or more were observed for Regimen 3 compared with the other regimens with regard to the following TEAE categories: treatment-related TEAEs, Grade ≥ 3 TEAEs, treatment-related Grade ≥ 3 TEAEs, and TEAEs leading to permanent, and temporary, treatment discontinuation. A smaller than 10% increase was observed for TEAEs leading to dose reductions.

The TEAE frequencies were however notably similar with regard to all-cause TEAEs and SAEs, treatment-related SAEs, Grade ≥ 4 TEAEs, treatment-related Grade ≥ 4 TEAEs and fatal TEAEs.

Table 29. Overview of TEAEs - Regimen 3 by Dose Level, Study 001

	300 MG (micro) (N = 3)	500 MG (micro) (N = 42)	700 MG (micro) (N = 3)	1000 MG (micro) (N = 7)	1400 MG (micro) (N = 7)	Total (N = 62)
Treatment emergent adverse events (TEAEs)	3 (100.0%)	39 (92.9%)	3 (100.0%)	7 (100.0%)	7 (100.0%)	59 (95.2%)
TEAEs related to study drug	2 (66.7%)	27 (64.3%)	1 (33.3%)	3 (42.9%)	6 (85.7%)	39 (62.9%)
Serious TEAEs (TEAE)	1 (33.3%)	14 (33.3%)	2 (66.7%)	4 (57.1%)	1 (14.3%)	22 (35.5%)
Serious TEAEs related to study drug	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAEs with toxicity grade >=3	2 (66.7%)	22 (52.4%)	2 (66.7%)	4 (57.1%)	2 (28.6%)	32 (51.6%)
TEAEs related to study drug with toxicity grade >= 3	1 (33.3%)	5 (11.9%)	0 (0.0%)	1 (14.3%)	2 (28.6%)	9 (14.5%)
TEAEs with toxicity grade >=4	0 (0.0%)	3 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (4.8%)
TEAEs related to study drug with toxicity grade >= 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dose Limiting Toxicities	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)	2 (3.2%)
TEAEs leading to permanent discontinuation of study drug	1 (33.3%)	9 (21.4%)	1 (33.3%)	1 (14.3%)	1 (14.3%)	13 (21.0%)
Related TEAEs leading to permanent discontinuation of study drug	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	2 (3.2%)
TEAEs leading to temporary discontinuation of study drug	1 (33.3%)	6 (14.3%)	2 (66.7%)	3 (42.9%)	3 (42.9%)	15 (24.2%)
TEAEs leading to dose reduction of study drug	1 (33.3%)	2 (4.8%)	0 (0.0%)	1 (14.3%)	3 (42.9%)	7 (11.3%)
Serious TEAEs leading to hospitalization	1 (33.3%)	14 (33.3%)	2 (66.7%)	4 (57.1%)	1 (14.3%)	22 (35.5%)
TEAEs leading to death	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
TEAEs related to study drug leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Cut-off date: 15FEB2016 (Main Analysis)

Source: Study EMR 200095-001 (Tepotinib First-in-Man trial), CTR, Table 15.3.1.4.

A higher proportion of treatment-related TEAEs (86%) is noted at the 1400 mg dose level compared to lower dose levels. When the 1000 mg and 1400 mg dose levels were pooled, the frequency of treatment-related TEAEs (9/14, 64%) was the same as the 500 mg dose level (64%). SAEs were on a similar level in the pooled 1000-1400 mg group (5/14, 36%) as in the 500 mg (RP2D) group (33%). Grade ≥ 3 TEAEs were not more frequent in the pooled 1000-1400 mg group (6/14, 43%) compared with the 500 mg group (52%), but treatment-related Grade ≥ 3 TEAEs were more frequent in the pooled 1000-1400 mg group (3/14, 21%) compared with the 500 mg group (12%). Similarly, TEAEs leading to permanent discontinuation were not more frequent at the combined two highest dose-levels (2/14) compared to the 500 mg level (2/14, 14% vs 21%, respectively), but treatment-related TEAEs leading to permanent discontinuation were (1/14, 7% vs 2%). TEAEs leading to dose reduction were more frequent at the combined highest dose-levels (4/14, 29%) compared to the 500 mg level (5%). Dose-limiting TEAEs were observed in the two highest dose levels (2/14, 14%), but not at 500 mg (0%), (Table 29).

Table 30. Treatment-emergent Adverse Events in ≥ 10% of Subjects in Total in Regimen3 by SOC and PT – Safety Set (Regimen3 by DL), Study 001

	Tepotinib					
MedDRA System Organ Class Preferred Term	300 MG (N=3)	500 MG (N=42)	700 MG (N=3)	1000 MG (N=7)	1400 MG (N=7)	Total (N=62)
Subjects with any TEAEs	3 (100.0%)	39 (92.9%)	3 (100.0%)	7 (100.0%)	7 (100.0%)	59 (95.2%)
Gastrointestinal Disorders	3 (100.0%)	30 (71.4%)	3 (100.0%)	5 (71.4%)	4 (57.1%)	45 (72.6%)
Constipation	1 (33.3%)	11 (26.2%)	2 (66.7%)	3 (42.9%)	1 (14.3%)	18 (29.0%)
Nausea	1 (33.3%)	11 (26.2%)	2 (66.7%)	1 (14.3%)	0 (0.0%)	15 (24.2%)
Vomiting	0 (0.0%)	9 (21.4%)	1 (33.3%)	2 (28.6%)	1 (14.3%)	13 (21.0%)
Abdominal Pain	1 (33.3%)	6 (14.3%)	2 (66.7%)	1 (14.3%)	1 (14.3%)	11 (17.7%)
Ascites	1 (33.3%)	7 (16.7%)	1 (33.3%)	0 (0.0%)	1 (14.3%)	10 (16.1%)
General Disorders And Administration Site Conditions	2 (66.7%)	32 (76.2%)	2 (66.7%)	2 (28.6%)	5 (71.4%)	43 (69.4%)
Edema Peripheral	1 (33.3%)	15 (35.7%)	2 (66.7%)	2 (28.6%)	4 (57.1%)	24 (38.7%)
Fatigue	1 (33.3%)	16 (38.1%)	0 (0.0%)	1 (14.3%)	2 (28.6%)	20 (32.3%)
Metabolism And Nutrition Disorders	2 (66.7%)	23 (54.8%)	3 (100.0%)	7 (100.0%)	5 (71.4%)	40 (64.5%)
Decreased Appetite	2 (66.7%)	16 (38.1%)	0 (0.0%)	4 (57.1%)	5 (71.4%)	27 (43.5%)
Hypoalbuminemia	1 (33.3%)	6 (14.3%)	1 (33.3%)	1 (14.3%)	2 (28.6%)	11 (17.7%)
Dehydration	0 (0.0%)	6 (14.3%)	2 (66.7%)	2 (28.6%)	0 (0.0%)	10 (16.1%)
Hyponatremia	1 (33.3%)	3 (7.1%)	2 (66.7%)	1 (14.3%)	1 (14.3%)	8 (12.9%)
Investigations	2 (66.7%)	18 (42.9%)	2 (66.7%)	4 (57.1%)	3 (42.9%)	29 (46.8%)
Aspartate Aminotransferase Increased	1 (33.3%)	3 (7.1%)	1 (33.3%)	2 (28.6%)	1 (14.3%)	8 (12.9%)
Transaminases Increased	0 (0.0%)	4 (9.5%)	2 (66.7%)	1 (14.3%)	0 (0.0%)	7 (11.3%)
Respiratory, Thoracic And Mediastinal Disorders	2 (66.7%)	15 (35.7%)	2 (66.7%)	3 (42.9%)	2 (28.6%)	24 (38.7%)
Dyspnea	0 (0.0%)	9 (21.4%)	0 (0.0%)	2 (28.6%)	2 (28.6%)	13 (21.0%)
Pleural Effusion	1 (33.3%)	4 (9.5%)	1 (33.3%)	1 (14.3%)	0 (0.0%)	7 (11.3%)
Nervous System Disorders	1 (33.3%)	15 (35.7%)	1 (33.3%)	4 (57.1%)	1 (14.3%)	22 (35.5%)
Dizziness	1 (33.3%)	3 (7.1%)	1 (33.3%)	1 (14.3%)	1 (14.3%)	7 (11.3%)
Infections And Infestations	1 (33.3%)	14 (33.3%)	0 (0.0%)	2 (28.6%)	2 (28.6%)	19 (30.6%)
Urinary Tract Infection	1 (33.3%)	4 (9.5%)	0 (0.0%)	1 (14.3%)	1 (14.3%)	7 (11.3%)
Blood And Lymphatic System Disorders	1 (33.3%)	10 (23.8%)	1 (33.3%)	2 (28.6%)	0 (0.0%)	14 (22.6%)
Anemia	1 (33.3%)	5 (11.9%)	1 (33.3%)	1 (14.3%)	0 (0.0%)	8 (12.9%)

DL = dose level; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE= treatment-emergent adverse event.

Source: Study EMR 200095-001 (Tepotinib First-in-Man trial), CTR, Table 46.

The First-in-Man dose-finding Study 001, Regimen 3, with continuous dosing explored doses that subsequently were considered supratherapeutic (700-1400 mg daily) as the RP2D 500 mg daily was chosen. As discussed above, the numbers are small and preclude definitive and quantitative conclusions. The reported TEAE frequencies nevertheless suggest an increased risk of peripheral oedema with supratherapeutic dosing. In the 500 mg group the frequency was 36% (15/42), compared with 57% (4/7) in the highest dose group, 1400 mg; 43% (6/14) in patients with 1000-1400 mg; and 47% (8/17) in patients with 700-1400 mg daily.

The frequency of hypoalbuminaemia also appeared to increase with increased dose, but this is based on single patients at each of the higher dose levels. Also pooled dose levels could suggest an increase however, with 14% (6/42) at 500 mg and 24% (4/17) at 700-1400 mg.

Similarly, liver enzymes elevations show a trend of increase with supratherapeutic dosing (Table 30).

Also other TEAEs appear to have increased frequencies at supratherapeutic dosing, e.g. dizziness and urinary tract infection. Given the low numbers and possibility of confounding factors, these trends are difficult to evaluate.

Both peripheral oedemas hypoalbuminaemia show trends of increase with higher dose, but at different frequencies, thus hypoalbuminaemia alone cannot explain the oedema TEAEs.

Exposure in the target population

Table 31. Summary of Exposure to Tepotinib

Characteristic	Tepotinib 500 mg QD – SAF	
	VISION Cohorts A + C (N=291)	POOL (N=484)
Duration of therapy (weeks)		
Mean ± StD	36.2 ± 32.43	28.4 ±2 9.24
Median	27.6	18.9
Q1; Q3	12.3; 48.0	6.7; 36.9
Min; Max	0; 220	0; 220
Total number of cycles received		
Mean ± StD	12.06 ±10.811	9.46 ± 9.746
Median	9.19	6.29
Q1; Q3	4.10; 16.00	2.24; 12.31
Min; Max	0.0; 73.3	0.0; 73.3
Total number of cycles received category, n (%)		
0	9 (3.1)	25 (5.2)
1	15 (5.2)	44 (9.1)
2-3	37 (12.7)	97 (20.0)
4-6	43 (14.8)	85 (17.6)
7-9	56 (19.2)	70 (14.5)
10-12	33 (11.3)	47 (9.7)
≥ 13	98 (33.7)	116 (24.0)
Cumulative dose (mg)		
Mean ± StD	105695.4 ± 92533.43	84587.5 ± 84067.59
Median	85000.0	62500.0
Q1; Q3	42000.0; 149500.0	22500.0; 113500.0
Min; Max	500; 765800	500; 765800
Dose intensity (mg/3 weeks)		
Mean ± StD	9253.6 ± 1790.55	9476.7 ± 1638.31
Median	10343.3	10417.3
Q1; Q3	8076.9; 10500.0	8903.6; 10500.0
Min; Max	1050; 10739	500; 10739
Relative dose intensity (%) category, n (%)		
< 60	23 (7.9)	27 (5.6)
≥ 60 − <80	56 (19.2)	76 (15.7)
≥ 80 − <90	19 (6.5)	37 (7.6)
≥ 90 − <110	193 (66.3)	344 (71.1)
≥ 110	0 (0.0)	0 (0.0)

max=maximum; min=minimum; Q1=25% Quartile; Q3=75% Quartile; QD = (quaque die) once daily; SAF=safety analysis set; StD=standard deviation. DCO 01 February 2021

Duration of therapy (weeks) is calculated as: (date of last dose − date of first dose + 1)/7.

Relative dose intensity (%) is defined as the actual dose intensity divided by the planned dose per cycle. Each cycle is defined by a 3−week period.

The median duration of exposure to tepotinib in the combined Cohorts A +C was 6.3 months (27.6 weeks), which is considered short from a safety assessment perspective, in light of the reported duration of response of 13.8 months (95% CI: 9.9, 19.4) in the pooled pivotal efficacy population

(Cohorts A+C SAF 01 Nov 2020). The median duration of exposure in the POOL was even shorter, 4.3 months (18.9 weeks).

Table 32. Extent of Exposure: All Patients by Patient Years

	Tepotinib 500 mg QD – SAF	
Characteristic	**VISION Cohorts A + C (N=291)**	**POOL (N=484)**
Person−time exposure per 100 PY	2.018	2.634
Number of patients (%) and 100 PEY		
> 0 months	291 (100.0) 2.018	484 (100.0) 2.634
> 3 months	215 (73.9) 1.909	288 (59.5) 2.376
> 6 months	157 (54.0) 1.681	193 (39.9) 2.014
> 9 months	98 (33.7) 1.329	116 (24.0) 1.551
> 12 months	63 (21.6) 1.021	76 (15.7) 1.198
> 15 months	47 (16.2) 0.845	54 (11.2) 0.952
> 18 months	24 (8.2) 0.531	28 (5.8) 0.597
> 24 months	11 (3.8) 0.313	11 (2.3) 0.313
> 30 months	7 (2.4) 0.224	7 (1.4) 0.224
> 36 months	4 (1.4) 0.139	4 (0.8) 0.139
> 42 months	1 (0.3) 0.042	1 (0.2) 0.042
> 48 months	1 (0.3) 0.042	1 (0.2) 0.042
Number of patients 100 PEY in mutually exclusive intervals (%)		
0 − ≤ 3 months	76 (26.1) 0.109	196 (40.5) 0.528
3 − ≤ 6 months	58 (19.9) 0.228	95 (19.6) 0.362
6 − ≤ 9 months	59 (20.3) 0.352	77 (15.9) 0.463
9 − ≤ 12 months	35 (12.0) 0.307	40 (8.3) 0.352
12 −≤ 15 months	16 (5.5) 0.176	22 (4.5) 0.247
15 − ≤ 18 months	23 (7.9) 0.314	26 (5.4) 0.355
18 − ≤ 24 months	13 (4.5) 0.218	17 (3.5) 0.284
24 −≤ 30 months	4 (1.4) 0.089	4 (0.8) 0.089
30 −≤ 36 months	3 (1.0) 0.085	3 (0.6) 0.085
36 −≤ 42 months	3 (1.0) 0.097	3 (0.6) 0.097
42 −≤ 48 months	0 (0.0) 0.000	0 (0.0) 0.000
48 −≤ 54 months	1 (0.3) 0.042	1 (0.2) 0.042

PEY=Person exposure years, calculated by (adding each patient's total treatment duration in days) / 365.25; PY = patient years SAF=safety analysis set.

Duration of therapy (days) is calculated as: (date of last dose − date of first dose + 1).

Source: SCS update, DCO 01 February 2021, Table 4 (Table 12.5.3.1.)

The duration of exposure to tepotinib was over 6 months for 157 (54%) patients and over 12 months for 63 (22%) patients in the Safety analysis set (Cohorts A +C).

Among patients in the POOL (treated at target dose of 500 mg), 193 (40%) had a duration of exposure of over 6 months, and 76 (16%) patients had a duration of exposure of over 12 months.

Dose delays and reductions

Dose delay was defined as at least 2 days between 2 administrations of study drug.

Table 33. Dose Delays and Reductions

Characteristic	Statistics	Tepotinib 500 mg QD – SAF	
		VISION Cohorts A + C (N=291)	POOL (N=484)
Dose delays, n (%)			
Number of patients with dose delays [a]		160 (55.0)	242 (50.0)
Number of patients without dose delays [a]		129 (44.3)	239 (49.4)
Not applicable [a]		2 (0.7)	3 (0.6)
Number of delays per patient, n (%)	1 delay	69 (23.7)	118 (24.4)
	2 delays	29 (10.0)	48 (9.9)
	≥ 3 delays	62 (21.3)	76 (15.7)
Length of maximum delay, n (%)			
	1−2 days	44 (15.1)	74 (15.3)
	3−7 days	27 (9.3)	47 (9.7)
	8−14 days	34 (11.7)	46 (9.5)
	15−21 days	48 (16.5)	66 (13.6)
	> 21 days	7 (2.4)	9 (1.9)
Number of patients with any dose delay due to [b]			
Adverse event		111 (38.1)	156 (32.2)
Missed dose		68 (23.4)	97 (20.0)
Other		43 (14.8)	64 (13.2)
Dose reductions, n (%)			
Number of patients without any dose reduction		191 (65.6)	352 (72.7)
Number of patients with at least one dose reduction		100 (34.4)	132 (27.3)
Number of patients with dose increased back to 500 mg after dose reduction [c]		7 (7.0)	11 (8.3)
Minimum dose level, n (%)			
	100 mg (20%)	0 (0.0)	0 (0.0)
	200 mg (40%)	22 (7.6)	26 (5.4)
	250 mg (50%)	41 (14.1)	41 (8.5)
	300 mg (60%)	37 (12.7)	62 (12.8)
	400 mg (80%)	0 (0.0)	3 (0.6)
	500 mg (100%)	191 (65.6)	352 (72.7)

SAF=safety analysis set.

Dose omission is not considered as dose reduction.

a Delays can be calculated only for patients with at least 2 administrations.

b Patients may have more than 1 reason of delay.

c Percentages use the number of patients with at least one dose reduction as the denominator.

d Total length of treatment on the respective reduced dose.

Source: SCS update, DCO 01 February 2021, Table 4 (Table 12.5.2.1.)

Dose delays were experienced by 55% (n=160) of the patients in the target population VISION Cohorts A + C, and 50% in the POOL. Repeated dose delays occurred in 31% of patients, ≥ 3 delays were observed in 21%, and a significant proportion (89/291, 31%) had delays ≥ 8 days, suggesting tolerability issues (Table 33). Adverse events were reported to be a reason for any dose delay in 111 (38%) A+C cohort patients. For the remaining 43/160 patients the reason for dose delays was documented as "missed dose" or "other", which includes surgery/procedures and administrative reasons and was not due to safety reasons.

Dose reductions were performed in 34% of the patients in VISION Cohorts A + C, and 27% in the POOL, with 7.0% and 8.3%, respectively, subsequently dose escalating back to 500 mg QD. Thus 66-73% remained on the target dose for the whole length treatment (Table 33).

Adverse events

Treatment-emergent adverse events (TEAEs) are defined as events that start within the day of first dose of trial treatment until 30 days after last dose of treatment, or started prior to first dose but worsened during the treatment period.

For grading of severity of adverse events in the pivotal study, the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 was used in the VISION study. In the POOL, the studies used NCI-CTCAE version 4.0 or 4.03 for the grading.

Overview of TEAEs

Table 34. Overview of TEAEs and Exposure-Adjusted TEAE Incidence Rates

	Tepotinib 500 mg QD – SAF					
	VISION Cohorts A + C (N=291)			POOL (N=484)		
Event	Patients with Events n (%)	PY	Incidence Rate per 100 PY	Patients with Events n (%)	PY	Incidence Rate per 100 PY
Any TEAE	287 (98.6)	14.3	2007.8	474 (97.9)	22.0	2159.0
TEAE, NCI-CTCAE Grade ≥ 3	175 (60.1)	134.9	129.7	286 (59.1)	185.1	154.5
Related TEAE	264 (90.7)	30.9	854.4	411 (84.9)	49.1	837.8
Related TEAE, NCI-CTCAE Grade ≥ 3	86 (29.6)	169.3	50.8	136 (28.1)	229.3	59.3
TEAE leading to treatment dose reduction	99 (34.0)	144.6	68.5	126 (26.0)	207.4	60.8
Related TEAE leading to treatment dose reduction	90 (30.9)	149.3	60.3	114 (23.6)	212.8	53.6
TEAE leading to temporary treatment discontinuation	143 (49.1)	127.2	112.4	206 (42.6)	181.2	113.7
Related TEAE leading to temporary treatment discontinuation	114 (39.2)	139.4	81.8	154 (31.8)	199.7	77.1
TEAE leading to permanent treatment discontinuation	69 (23.7)	209.7	32.9	112 (23.1)	282.1	39.7
Related TEAE leading to permanent treatment discontinuation	41 (14.1)	210.8	19.4	55 (11.4)	284.9	19.3
Serious TEAE	138 (47.4)	171.2	80.6	224 (46.3)	233.1	96.1
Related serious TEAE	41 (14.1)	204.4	20.1	58 (12.0)	277.2	20.9
TEAE leading to death	36 (12.4)	222.9	16.1	60 (12.4)	298.3	20.1
Related TEAE leading to death	2 (0.7)	223.5	0.9	4 (0.8)	299.4	1.3

Source: SCS DCO 01 February 2021, Table 12.6.1.2.1.

NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; PY=patient years; SAF=safety analysis set; TEAE=treatment-emergent adverse event.

Exposure adjusted incidence rate is calculated as number of patients experiencing AEs divided by the sum of the individual time of all patients in the safety analysis set from start of treatment to first onset of AE or to end of treatment period for patients without AE.

Incidence rates give the number of AEs expected in 100 patients within 1 year of treatment.

The Exposure-Adjusted TEAE Incidence Rates (EAIRs) were also overall similar in the VISION cohorts A+C and the POOL (data not shown).

TEAEs by liquid or tissue biopsy (L+ or T+) subgroups in VISION study

Across the subsets of liquid biopsy positive (L+) and tissue biopsy positive (T+) patients, the TEAE frequencies across categories were largely consistent, considering the smaller numbers of patients. (Source: CSR, Table 15.3.1.2, DCO 01 July 2020).

All-cause, all-grade TEAEs

In VISION Cohorts A + C, the most frequently (in ≥ 20% of patients) reported PTs were peripheral oedema, nausea, diarrhoea, blood creatinine increased, dyspnoea and hypoalbuminemia. (Table 35)

Table 35. TEAEs by SOC and PT (≥ 10% of Patients by PT)

SOC PT	Tepotinib 500 mg QD – SAF VISION Cohorts A + C (N=291) n (%)	Tepotinib 500 mg QD – SAF POOL (N=484) n (%)
Patients with at least one TEAE	287 (98.6)	474 (97.9)
General disorders and administration site conditions	249 (85.6)	400 (82.6)
Oedema peripheral	191 (65.6)	286 (59.1)
Fatigue	45 (15.5)	91 (18.8)
Asthenia	37 (12.7)	59 (12.2)
Pyrexia	27 (9.3)	52 (10.7)
Gastrointestinal disorders	187 (64.3)	336 (69.4)
Nausea	88 (30.2)	126 (26.0)
Diarrhoea	81 (27.8)	132 (27.3)
Constipation	46 (15.8)	89 (18.4)
Vomiting	41 (14.1)	69 (14.3)
Abdominal pain	24 (8.2)	61 (12.6)
Investigations	153 (52.6)	243 (50.2)
Blood creatinine increased	76 (26.1)	102 (21.1)
Alanine aminotransferase increased	37 (12.7)	57 (11.8)
Aspartate aminotransferase increased	24 (8.2)	50 (10.3)
Respiratory, thoracic and mediastinal disorders	144 (49.5)	192 (39.7)
Dyspnoea	60 (20.6)	81 (16.7)
Cough	42 (14.4)	50 (10.3)
Pleural effusion	38 (13.1)	53 (11.0)
Metabolism and nutrition disorders	140 (48.1)	241 (49.8)
Hypoalbuminaemia	81 (27.8)	122 (25.2)
Decreased appetite	48 (16.5)	97 (20.0)
Skin and subcutaneous tissue disorders	126 (43.3)	174 (36.0)
Alopecia	34 (11.7)	36 (7.4)
Infections and infestations	117 (40.2)	174 (36.0)
Pneumonia	29 (10.0)	37 (7.6)
Musculoskeletal and connective tissue disorders	87 (29.9)	142 (29.3)
Back pain	32 (11.0)	42 (8.7)
Arthralgia	30 (10.3)	39 (8.1)
Blood and lymphatic system disorders	42 (14.2)	75 (15.5)
Anemia	31 (10.7)	52 (10.7)

Source: SCS DCO 01 February 2021, Table 12.6.2.1.1.

PT=preferred term; SAF=safety analysis set; SOC=System Organ Class; TEAE= treatment-emergent adverse event.

Note: TEAEs meeting the threshold in either VISION or POOL have been included.

Table 36. VISION Cohorts A + C TEAEs by category, SOC and PT (SAF, N = 291)

Primary System Organ Class Preferred Term	All TEAEs ≥ 10% n (%)	Related TEAEs ≥ 5% n (%)	All Grade >=3 TEAEs ≥ 2% n (%)	Related Grade >=3 TEAEs ≥ 1% n (%)
Subjects with at least one Event	287 (98.6)	264 (90.7)	175 (60.1)	86 (29.6)
General disorders and administration site conditions	249 (85.6)	214 (73.5)	65 (22.3)	39 (13.4)
Oedema peripheral	191 (65.6)	175 (60.1)	31 (10.7)	29 (10.0)
Fatigue	45 (15.5)	25 (8.6)	3 (1.0)	3 (1.0)
Asthenia	37 (12.7)	17 (5.8)	3 (1.0)	1 (0.3)
Oedema	27 (9.3)	24 (8.2)	1 (0.3)	1 (0.3)
Generalised oedema	17 (5.8)	15 (5.2)	6 (2.1)	5 (1.7)
Disease progression	13 (4.5)	0	13 (4.5)	0
General physical health deterioration	11 (3.8)	0	9 (3.1)	0
Gastrointestinal disorders	187 (64.3)	128 (44.0)	16 (5.5)	5 (1.7)
Nausea	88 (30.2)	66 (22.7)	3 (1.0)	1 (0.3)
Diarrhoea	81 (27.8)	62 (21.3)	1 (0.3)	1 (0.3)
Constipation	46 (15.8)	15 (5.2)	0	0
Vomiting	41 (14.1)	19 (6.5)	3 (1.0)	1 (0.3)
Abdominal pain upper	26 (8.9)	16 (5.5)	0	0
Investigations	153 (52.6)	115 (39.5)	45 (15.5)	24 (8.2)
Blood creatinine increased	76 (26.1)	57 (19.6)	2 (0.7)	1 (0.3)
Alanine aminotransferase increased	37 (12.7)	28 (9.6)	8 (2.7)	5 (1.7)
Amylase increased	27 (9.3)	22 (7.6)	10 (3.4)	6 (2.1)
Aspartate aminotransferase increased	24 (8.2)	19 (6.5)	4 (1.4)	4 (1.4)
Lipase increased	24 (8.2)	21 (7.2)	11 (3.8)	9 (3.1)
Respiratory, thoracic and mediastinal disorders	144 (49.5)	42 (14.4)	34 (11.7)	13 (4.5)
Dyspnoea	60 (20.6)	11 (3.8)	7 (2.4)	2 (0.7)
Cough	42 (14.4)	1 (0.3)	1 (0.3)	0
Pleural effusion	38 (13.1)	19 (6.5)	12 (4.1)	8 (2.7)
Pulmonary embolism	11 (3.8)	1 (0.3)	7 (2.4)	1 (0.3)
Metabolism and nutrition disorders	140 (48.1)	77 (26.5)	35 (12.0)	14 (4.8)
Hypoalbuminaemia	81 (27.8)	55 (18.9)	17 (5.8)	9 (3.1)
Decreased appetite	48 (16.5)	24 (8.2)	4 (1.4)	1 (0.3)
Hyponatraemia	15 (5.2)	6 (2.1)	10 (3.4)	4 (1.4)
Skin and subcutaneous tissue disorders	126 (43.3)	90 (30.9)	3 (1.0)	1 (0.3)
Alopecia	34 (11.7)	27 (9.3)	0	0
Rash	26 (8.9)	16 (5.5)	1 (0.3)	0
Infections and infestations	117 (40.2)	18 (6.2)	28 (9.6)	3 (1.0)
Pneumonia	29 (10.0)	2 (0.7)	11 (3.8)	0
Musculoskeletal and connective tissue disorders	87 (29.9)	10 (3.4)	10 (3.4)	0
Back pain	32 (11.0)	0	2 (0.7)	0
Arthralgia	30 (10.3)	2 (0.7)	3 (1.0)	0
Renal and urinary disorders	63 (21.6)	33 (11.3)	15 (5.2)	9 (3.1)
Chronic kidney disease	13 (4.5)	10 (3.4)	5 (1.7)	3 (1.0)
Renal impairment	9 (3.1)	6 (2.1)	3 (1.0)	3 (1.0)
Blood and lymphatic system disorders	42 (14.4)	16 (5.5)	11 (3.8)	4 (1.4)
Anaemia	31 (10.7)	10 (3.4)	9 (3.1)	3 (1.0)

PT=preferred term; SAF=safety analysis set; SOC=System Organ Class; TEAE= treatment-emergent adverse event. Notes: Events are coded using MedDRA version 23.1 TEAEs meeting the threshold in any column have been included.

Source: Response to questions, Question 6, Table 4. (DCO 01 February 2021)

Table 37. POOL, TEAEs by category, SOC and PT (SAF, N=484)

Primary System Organ Class Preferred Term	All TEAEs ≥ 10% n (%)	Related TEAEs ≥ 5% n (%)	All Grade >=3 TEAEs ≥ 2% n (%)	Related Grade >=3 TEAEs ≥ 1% n (%)
Subjects with at least one Event	474 (97.9)	411 (84.9)	286 (59.1)	136 (28.1)
General disorders and administration site conditions	400 (82.6)	310 (64.0)	109 (22.5)	53 (11.0)
Oedema peripheral	286 (59.1)	233 (48.1)	40 (8.3)	37 (7.6)
Fatigue	91 (18.8)	57 (11.8)	12 (2.5)	7 (1.4)
Asthenia	59 (12.2)	31 (6.4)	8 (1.7)	1 (0.2)
Pyrexia	52 (10.7)	7 (1.4)	0	0
Oedema	38 (7.9)	29 (6.0)	1 (0.2)	1 (0.2)
Disease progression	32 (6.6)	1 (0.2)	32 (6.6)	1 (0.2)
Generalised oedema	25 (5.2)	20 (4.1)	8 (1.7)	7 (1.4)
General physical health deterioration	13 (2.7)	0	11 (2.3)	0
Gastrointestinal disorders	336 (69.4)	201 (41.5)	51 (10.5)	14 (2.9)
Diarrhoea	132 (27.3)	96 (19.8)	6 (1.2)	4 (0.8)
Nausea	126 (26.0)	87 (18.0)	6 (1.2)	1 (0.2)
Constipation	89 (18.4)	24 (5.0)	2 (0.4)	0
Vomiting	69 (14.3)	32 (6.6)	7 (1.4)	2 (0.4)
Abdominal pain	61 (12.6)	15 (3.1)	9 (1.9)	0
Ascites	46 (9.5)	10 (2.1)	11 (2.3)	4 (0.8)
Investigations	243 (50.2)	164 (33.9)	84 (17.4)	44 (9.1)
Blood creatinine increased	102 (21.1)	71 (14.7)	4 (0.8)	2 (0.4)
Alanine aminotransferase increased	57 (11.8)	37 (7.6)	14 (2.9)	8 (1.7)
Aspartate aminotransferase increased	50 (10.3)	27 (5.6)	15 (3.1)	8 (1.7)
Lipase increased	39 (8.1)	32 (6.6)	23 (4.8)	18 (3.7)
Amylase increased	35 (7.2)	29 (6.0)	13 (2.7)	8 (1.7)
Metabolism and nutrition disorders	241 (49.8)	120 (24.8)	69 (14.3)	23 (4.8)
Hypoalbuminaemia	122 (25.2)	69 (14.3)	22 (4.5)	11 (2.3)
Decreased appetite	97 (20.0)	47 (9.7)	8 (1.7)	1 (0.2)
Hyponatraemia	29 (6.0)	10 (2.1)	23 (4.8)	7 (1.4)
Respiratory, thoracic and mediastinal disorders	192 (39.7)	48 (9.9)	45 (9.3)	13 (2.7)
Dyspnoea	81 (16.7)	13 (2.7)	10 (2.1)	2 (0.4)
Pleural effusion	53 (11.0)	20 (4.1)	13 (2.7)	8 (1.7)
Cough	50 (10.3)	1 (0.2)	1 (0.2)	0
Infections and infestations	174 (36.0)	25 (5.2)	44 (9.1)	3 (0.6)
Pneumonia	37 (7.6)	2 (0.4)	14 (2.9)	0
Skin and subcutaneous tissue disorders	174 (36.0)	125 (25.8)	6 (1.2)	4 (0.8)
Rash	43 (8.9)	26 (5.4)	1 (0.2)	0
Alopecia	36 (7.4)	28 (5.8)	0	0
Blood and lymphatic system disorders	75 (15.5)	27 (5.6)	19 (3.9)	5 (1.0)
Anaemia	52 (10.7)	15 (3.1)	13 (2.7)	3 (0.6)

PT=preferred term; SAF=safety analysis set; SOC=System Organ Class; TEAE= treatment-emergent adverse event. Notes: Events are coded using MedDRA version 23.1. TEAEs meeting the threshold in any column have been included.

Source: Response to questions, Question 6, Table 5. (DCO 01 February 2021)

Treatment-related TEAEs

In VISION Cohorts A + C most patients (91%) had treatment-related TEAEs based on Investigator assessment (Table 36). Consistent with the most common SOCs overall, the most common treatment-related SOCs were General disorders and administration site conditions and Gastrointestinal disorders.

Peripheral oedema was the most common treatment-related TEAE in VISION Cohorts A + C (60%, Table 36) and the POOL (48%, Table 37), followed by nausea, diarrhoea, blood creatinine increased, and hypoalbuminaemia in the VISION A+C.

The frequencies of common treatment-related TEAEs reflects the all-cause frequencies. Causality assessment of individual AEs by the investigator will be affected by the general knowledge of the drug's safety profile.

Grade ≥ 3 adverse events

In VISION Cohorts A + C, NCI-CTCAE Grade ≥ 3 TEAEs occurred most frequently (≥5%) for PTs peripheral oedema (11%) and hypoalbuminaemia (5.8%). (Table 36).

In VISION Cohorts A + C, 13 patients (4.5%) had on-treatment Grade 4 events (not shown). Two patients each had ALT increased, amylase increased, and lipase increased. All others were single events in 1 (0.3%) patient each. These events were chest pain, generalized oedema, general physical health deterioration, AST increased, platelet count decreased, neutrophil count decreased, dyspnoea, pleural effusion, infective cholecystitis, bacterial pneumonia, metastases to spine, neuralgia, cardiac tamponade and acute myocardial infarction.

In the POOL, Grade ≥ 3 events reported for ≥ 5% of patients were peripheral oedema (8.3%), and disease progression (6.6%) (Table 37)

Unlike all-grade TEAE frequencies, gastrointestinal Grade ≥ 3 TEAEs were not prominent.

On-treatment Grade 4 events were reported in the POOL by 24 (5%) patients (not shown). Events experienced by more than 1 patient were lipase increased (5 patients), ALT increased, amylase increased, dyspnoea, disease progression, hyponatremia, and hepatic failure (2 patients each).

Thirty-six (12%) patients died due to a TEAE (Grade 5) in VISION Cohorts A + C, and 59 (12%) patients died in the POOL (not shown).

To which degree a certain TEAE may be assumed to be attributable to the underlying disease is difficult to determine given the single-arm study design, since also investigators' causality assessments are affected by the current knowledge of the drug's safety profile. The generally slightly lower frequencies of Respiratory SOC TEAEs (all cause, Grade ≥ 3, related) in the POOL (with 315/484 =65% being NSCLC patients) compared to the VISION cohorts (100% NSCLC) may suggest a certain degree of respiratory SOC AEs being attributable to the underlying disease.

Grade ≥ 3 treatment-related adverse events

Approximately 30% of patients in VISION Cohorts A + C (30%) and in the POOL (28%) experienced treatment-related Grade > 3 TEAEs. The pattern of affected SOCs was similar in VISION (Table 36) and the POOL (Table 37).

Peripheral oedema was the most frequently experienced treatment-related Grade ≥ 3 TEAE in both VISION Cohorts A + C (10%) and the POOL (7.6%), followed by lipase increased (3.1%), hypoalbuminemia (3.1%), pleural effusion (2.7%), ALT increased (1.7%), and amylase increased (2.1%) in VISION Cohorts A + C.

Treatment-related Grade > 4 TEAEs were experienced in 3.5% of patients in VISION Cohorts A + C and in 3.3% of patients in the POOL (not shown).

TEAEs by exposure

Table 38. VISION Cohorts A+ C – Treatment Emergent Adverse Events by Exposure, SOC and PT (Cut-off ≥ 10%) – (SAF, N=291)

	All Subjects (N=291)		Subjects with Exposure ≥6 Months (N=157)		Subjects with Exposure ≥12 Months (N=63)	
Primary System Organ Class Preferred Term	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Subjects with at least one event	287 (98.6)	175 (60.1)	157 (100.0)	98 (62.4)	63 (100.0)	42 (66.7)
General disorders and administration site disorders	**249 (85.6)**	**65 (22.3)**	**150 (95.5)**	**33 (21.0)**	**62 (98.4)**	**17 (27.0)**
Oedema peripheral*	191 (65.6)	31 (10.7)	128 (81.5)	20 (12.7)	56 (88.9)	12 (19.0)
Fatigue	45 (15.5)	3 (1.0)	29 (18.5)	3 (1.9)	12 (19.0)	0
Asthenia	37 (12.7)	3 (1.0)	23 (14.6)	0	13 (20.6)	0
Gastrointestinal Disorders	**187 (64.3)**	**16 (5.5)**	**107 (68.2)**	**10 (6.4)**	**48 (76.2)**	**6 (9.5)**
Nausea	88 (30.2)	3 (1.0)	50 (31.8)	1 (0.6)	21 (33.3)	1 (1.6)
Diarrhoea*	81 (27.8)	1 (0.3)	51 (32.5)	1 (0.6)	24 (38.1)	1 (1.6)
Constipation	46 (15.8)	0	31 (19.7)	0	13 (20.6)	0
Vomiting	41 (14.1)	3 (1.0)	26 (16.6)	2 (1.3)	9 (14.3)	1 (1.6)
Investigations	**153 (52.6)**	**45 (15.5)**	**87 (55.4)**	**28 (17.8)**	**46 (73.0)**	**15 (23.8)**
Blood creatinine increased*	76 (26.1)	2 (0.7)	48 (30.6)	2 (1.3)	25 (39.7)	1 (1.6)
Alanine aminotransferase increased*	37 (12.7)	8 (2.7)	14 (8.9)	2 (1.3)	6 (9.5)	1 (1.6)
Respiratory, thoracic and mediastinal disorders	**144 (49.5)**	**34 (11.7)**	**84 (53.5)**	**18 (11.5)**	**39 (61.9)**	**9 (14.3)**
Dyspnoea	60 (20.6)	7 (2.4)	34 (21.7)	5 (3.2)	15 (23.8)	3 (4.8)
Cough	42 (14.4)	1 (0.3)	31 (19.7)	1 (0.6)	13 (20.6)	1 (1.6)
Pleural effusion	38 (13.1)	12 (4.1)	23 (14.6)	8 (5.1)	12 (19.0)	3 (4.8)
Metabolism and nutrition disorders	**140 (48.1)**	**35 (12.0)**	**85 (54.1)**	**19 (12.1)**	**38 (60.3)**	**8 (2.7)**
Hypoalbuminaemia*	81 (27.8)	17 (5.8)	53 (33.8)	8 (5.1)	24 (38.1)	4 (6.3)
Decreased appetite	48 (16.5)	4 (1.4)	28 (17.8)	2 (1.3)	11 (17.5)	0
Skin and subcutaneous tissue disorders	**126 (43.3)**	**3 (1.0)**	**85 (54.1)**	**0**	**38 (60.3)**	**0**
Alopecia	34 (11.7)	0	26 (16.6)	0	13 (20.6)	0
Infections and infestations	**117 (40.2)**	**28 (9.6)**	**79 (50.3)**	**18 (11.5)**	**35 (55.6)**	**5 (7.9)**
Pneumonia	29 (10.0)	11 (3.8)	20 (12.7)	6 (3.8)	13 (20.6)	3 (4.8)
Musculoskeletal and connective tissue disorders	**87 (29.9)**	**10 (3.4)**	**60 (38.2)**	**8 (5.1)**	**25 (39.7)**	**3 (4.8)**
Back pain	32 (11.0)	2 (0.7)	21 (13.4)	1 (0.6)	13 (20.6)	0
Arthralgia	30 (10.3)	3 (1.0)	22 (14.0)	2 (1.3)	10 (15.9)	0
Blood and lymphatic system disorders	**42 (14.4)**	**11 (3.8)**	**19 (12.1)**	**3 (1.9)**	**9 (14.3)**	**2 (3.2)**
Anaemia	31 (10.7)	9 (3.1)	12 (7.6)	2 (1.3)	5 (7.9)	1 (1.6)

PT = preferred term; SAF = safety analysis set; SOC = System Organ Class; TEAE = treatment-emergent adverse event. Notes: Cohort A and Cohort C combined. * Denotes an ADR according to the applicant.

Source: Response to questions, Question 6, Table 5. (DCO 01 February 2021)

Adverse events of special interest

Adverse events of special interest (AESI) related to laboratory aberrations are discussed under

Oedema

Includes PTs: Face oedema, Oedema, Oedema peripheral, Localised oedema, Oedema genital, Periorbital oedema, Scrotal oedema, Peripheral swelling, Abdominal wall oedema, Generalised oedema.

In VISION Cohorts A + C, peripheral oedema was the most frequently reported TEAE (191; 66%), followed by oedema (27; 9.3%) and generalized oedema (17; 5.8%; Table 39). Oedema events were mainly of low grade (Grade 1 to 2). Thirty-six (12.4%) patients had Grade 3 oedema TEAEs, and one patient had a Grade 4 event.

Most of the events were non-serious; 5.2% of patients in VISION Cohorts A + C had a serious oedema TEAE. Less than half of patients with generalized oedema had a Grade 3 or serious event (6/17 patients for both criteria). In all but 1 patient the severe or serious Generalized oedema events, respectively, were considered treatment-related by the Investigator.

Median time to onset was 9.0 weeks for any grade oedema and 18.6 weeks for Grade ≥ 3 oedema, suggestive of a potential worsening with time exposure.

Thirty-nine (17.3%) patients with oedema fully recovered (Table 39). Median time to resolution was 69 weeks.

The number of reported events of oedema (420 in 225 patients) and the high proportion of patients with oedema events ongoing (64%) suggest that usually > 1 episode of oedema is experienced per patient. In some patients, oedema may last a long time, but oedema events infrequently led to permanent treatment discontinuation (7.2%). Temporary treatment discontinuation and dose reduction due to oedema were more frequent (26.5% and 20.6%, respectively), (Table 39).

Most frequently peripheral oedema led to temporary treatment discontinuation and dose reductions (19% and 15%, respectively). Generalised oedema events led to a dose reduction in 2.7% of patients, to temporary treatment discontinuation in 3.8% and to permanent discontinuation in 0.7%.

Table 39. Oedema by Composite Term and Preferred Term

Composite Term / Preferred Term	Tepotinib 500 mg qd – SAF: VISION Cohorts A + C (N=291) n (%)	95% CI	POOL (N=484) n (%)	95% CI
Any NCI-CTCAE Grade				
Oedema	225 (77.3)	[72.1; 82.0]	333 (68.8)	[64.5; 72.9]
Oedema peripheral	191 (65.6)	[59.9; 71.1]	286 (59.1)	[54.6; 63.5]
Oedema	27 (9.3)	[6.2; 13.2]	38 (7.9)	[5.6; 10.6]
Generalised oedema	17 (5.8)	[3.4; 9.2]	25 (5.2)	[3.4; 7.5]
Localised oedema	13 (4.5)	[2.4; 7.5]	19 (3.9)	[2.4; 6.1]
Face oedema	7 (2.4)	[1.0; 4.9]	9 (1.9)	[0.9; 3.5]
Oedema genital	6 (2.1)	[0.8; 4.4]	6 (1.2)	[0.5; 2.7]
Periorbital oedema	3 (1.0)	[0.2; 3.0]	4 (0.8)	[0.2; 2.1]
Scrotal oedema	3 (1.0)	[0.2; 3.0]	4 (0.8)	[0.2; 2.1]
Peripheral swelling	1 (0.3)	[0.0; 1.9]	2 (0.4)	[0.1; 1.5]
NCI-CTCAE Grade ≥3 [a]				
Oedema	37 (12.7)	[9.1; 17.1]	47 (9.7)	[7.2; 12.7]
Oedema peripheral	31 (10.7)	[7.4; 14.8]	40 (8.3)	[6.0; 11.1]
Generalised oedema	6 (2.1)	[0.8; 4.4]	8 (1.7)	[0.7; 3.2]
Oedema genital	3 (1.0)	[0.2; 3.0]	3 (0.6)	[0.1; 1.8]
Localised oedema	1 (0.3)	[0.0; 1.9]	2 (0.4)	[0.1; 1.5]
Dose Modification (Any NCI-CTCAE Grade)				
Permanent Discontinuation caused by TEAE	21 (7.2)	NA	28 (5.8)	NA
Dose Modification caused by TEAE				
Temporary Discontinuation	77 (26.5)	NA	92 (19.0)	NA
Dose Reduction	60 (20.6)	NA	70 (14.5)	NA
Time to Resolution (days) [b]				
Number of Events [c]	420	NA	579	NA
Median	485	NA	344	NA
Min;Max	1; 1349+	NA	1; 1349+	NA
Outcome				
Patients with all events resolved	39 (17.3)	NA	65 (19.5)	NA
Patients with any event ongoing	186 (82.7)	NA	268 (80.5)	NA

CI=confidence interval; NA=not applicable; NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; SAF=safety analysis set; TEAE=treatment-emergent adverse event.

95% CI for incidence proportion according to Clopper-Pearson.

a 1 patient had a Grade 4 NCI-CTCAE event of edema.

b Time to resolution using Kaplan−Meier. '+' Indicates censored observation.

c All events (resolved as well as ongoing). A patient may have several episodes of edema.

Source: SCS update, DCO 01 February 2021, Table 26 (Tables 12.6.25.2.1.1, 12.6.25.2.3.1, 12.6.26.2.2.1.1, and 12.6.26.2.2.2.1.)

In VISION Cohorts A + C, 148 of 225 (66%) patients with oedema received at least one diuretic. Furosemide was used most frequently; it was given to 132 of 225 patients (59%) with oedema; note that furosemide was not necessarily administered in connection to the TEAE of oedema.

In the POOL, data were consistent to VISION Cohorts A + C.

Pleural effusion

Table 40. Pleural Effusion

	Tepotinib 500 mg qd – SAF			
	VISION Cohorts A + C (N=291)		POOL (N=484)	
Preferred Term	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Any NCI-CTCAE Grade				
Pleural effusion	38 (13.1)	[9.4; 17.5]	53 (11.0)	[8.3;14.1]
NCI-CTCAE Grade ≥ 3				
Pleural effusion	12 (4.1)	2.1;7.1]	13 (2.7)	[1.4;4.5]
Dose Modification (Any NCI-CTCAE Grade)				
Permanent Discontinuation caused by TEAE	5 (1.7)	NA	5 (1.0)	NA
Dose Modification caused by TEAE				
Temporary Discontinuation	11 (3.8)	NA	12 (2.5)	NA
Dose Reduction	7 (2.4)	NA	7 (1.4)	NA
Time to Resolution (days) [a]				
Number of events [b]	45	NA	60	NA
Median	393.0	NA	393.0	NA
Min;Max	4; 770+	NA	4; 770+	NA
Outcome				
Patients with all events resolved	14 (4.8)	NA	16 (3.3)	NA
Patients with any event ongoing	24 (8.2)	NA	37 (7.6)	NA

Source: SCS DCO 01Feb2021 Tables 12.6.25.2.1.1, 12.6.25.2.3.1, and 12.6.26.2.10.1.1.

CI=confidence interval; NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; NA=not applicable; SAF=safety analysis set; TEAE=treatment-emergent adverse event.

95% CI for incidence proportion according to Clopper-Pearson.

a Time to resolution using Kaplan−Meier. '+' Indicates censored observation.

b All events (resolved as well as ongoing). A patient may have several episodes of the AE of clinical interest.

Source: SCS update, DCO 01 February 2021, Table 35 (Tables 12.6.25.2.1.1, 12.6.25.2.3.1, and 12.6.26.2.10.1.1.)

Fluid Retention

Fluid retention is a broad term which describes the accumulation of excess fluids in body tissues or cavities and includes oedema, ascites, and pleural effusion, among others. To ensure a comprehensive search, the clinical database was explored using the search criteria: SMQ: Haemodynamic oedema, effusions and fluid overload – narrow.

The most frequently reported events were oedema peripheral followed by pleural effusion (Table 41).

Median time to onset of any grade and Grade 3 fluid retention was 8.9 weeks and 18.4 weeks, respectively. In VISION Cohorts A + C, fluid retention resolved in 41 of the 231 patients affected (not shown).

Table 41. Fluid Retention

	Tepotinib 500 mg qd – SAF			
Composite Term	VISION Cohorts A + C (N=291)		POOL (N=484)	
Preferred Term	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Any NCI-CTCAE Grade				
Fluid Retention	231 (79.4)	[74.3;83.9]	360 (74.4)	[70.2;78.2]
Ascites	4 (1.4)	[0.4;3.5]	46 (9.5)	[7.0;12.5]

Composite Term	Tepotinib 500 mg qd – SAF			
	VISION Cohorts A + C (N=291)		POOL (N=484)	
Preferred Term	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Generalised oedema	17 (5.8)	[3.4;9.2]	25 (5.2)	[3.4;7.5]
Joint swelling	1 (0.3)	[0.0;1.9]	3 (0.6)	[0.1;1.8]
Localised oedema	13 (4.5)	[2.4;7.5]	19 (3.9)	[2.4;6.1]
Lymphoedema	0	[0.0;1.3]	2 (0.4)	[0.1;1.5]
Oedema	27 (9.3)	[6.2;13.2]	38 (7.9)	[5.6;10.6]
Oedema peripheral	191 (65.6)	[59.9;71.1]	286 (59.1)	[54.6;63.5]
Pericardial effusion	2 (0.7)	[0.1;2.5]	2 (0.4)	[0.1;1.5]
Peripheral swelling	1 (0.3)	[0.0;1.9]	2 (0.4)	[0.1;1.5]
Pleural effusion	38 (13.1)	[9.4;17.5]	53 (11.0)	[8.3;14.1]
Pulmonary oedema	0	[0.0;1.3]	1 (0.2)	[0.0;1.1]
NCI-CTCAE Grade ≥ 3				
Fluid Retention	45 (15.5)	[11.5;20.1]	63 (13.0)	[10.1;16.3]
Ascites	1 (0.3)	[0.0;1.9]	11 (2.3)	[1.1;4.0]
Generalised oedema	6 (2.1)	[0.8;4.4]	8 (1.7)	[0.7;3.2]
Localised oedema	1 (0.3)	[0.0;1.9]	2 (0.4)	[0.1;1.5]
Oedema	1 (0.3)	[0.0;1.9]	1 (0.2)	[0.0;1.1]
Oedema peripheral	31 (10.7)	[7.4;14.8]	40 (8.3)	[6.0;11.1]
Pleural effusion	12 (4.1)	[2.1;7.1]	13 (2.7)	[1.4;4.5]
Dose Modification (Any NCI-CTCAE Grade)				
Permanent Discontinuation caused by TEAE	24 (8.2)	NA	36 (7.4)	NA
Dose Modification caused by TEAE				
Temporary Discontinuation	79 (27.1)	NA	100 (20.7)	NA
Dose Reduction	61 (21.0)	NA	73 (15.1)	NA
Time to Resolution (days) [a]				
Number of events [b]	453	NA	676	NA
Median	485.0	NA	344.0	NA
Min;Max	1; 1349+	NA	1; 1349+	NA
Outcome				
Patients with all events resolved	41 (14.1)	NA	66 (13.6)	NA
Patients with any event ongoing	190 (65.3)	NA	294 (60.7)	NA

Source: SCS DCO 01FEB2021 Tables 12.6.25.2.1.1, , 12.6.25.2.3.1, and 12.6.26.2.15.1.1.

CI=confidence interval; NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; NA=not applicable; SAF=safety analysis set; TEAE=treatment-emergent adverse event.

95% CI for incidence proportion according to Clopper-Pearson.

a Time to resolution using Kaplan−Meier. '+' Indicates censored observation.

b All events (resolved as well as ongoing). A patient may have several episodes of the AE of clinical interest.

Source: SCS update, DCO 01 February 2021, Table 37 (Tables 12.6.25.2.1.1, 12.6.25.2.3.1, and 12.6.26.2.15.1.1.)

Ascites

In VISION Cohorts A + C, ascites was infrequently reported (4 patients, 1.6%). One event was serious. The serious event started on Day 439 and was due to peritoneal carcinosis. One patient had a Grade 1 event, two patients had a Grade 2 event (1 of them with baseline history of tissue swelling, the other was the serious event). One patient had a Grade 3 event and was associated with a baseline history of hepatic cirrhosis. No events were treatment related. None led to temporary discontinuation, none led to dose reduction, and none led to permanent discontinuation.

Interstitial Lung Disease

Interstitial lung disease (ILD) is an important identified risk of tepotinib in patients with NSCLC.

Up to the 01 February 2021, the distribution of patients is as follows (Table 42 and **Error! Reference source not found.**):

- In VISION Cohorts A + C, ILD-like events were reported in 11/291 (3.8%) patients.
- In the POOL, ILD-like event was reported in 13/484 (2.7%) patients, including 1/24 (4.2%) from VISION Cohort B and 1/42 (2.4%) from Study EMR200095-001.
- In addition, an ILD-like event was reported in 1/64 (1.6%) from Study EMR200095-006 (not included in the POOL).

Table 42. ILD-like Events: integrated assessment

MedDRA PTs	VISION Cohorts A + C (N=291) n (%)	POOL (N=484) n (%)
All	8 (2.7)	10 (2.1)
Acute respiratory failure	1 (0.3)	1 (0.2)
Interstitial Lung Disease	4 (1.4)	4 (0.8)
Pneumonitis	3 (1.0)	3 (0.6)
Pulmonary fibrosis	0	1 (0.2)
Radiation pneumonitis	0	1 (0.2) [a]

Source: SCS DCO 01 February 2021, Table 12.6.25.2.6.1; refer to Independent Panel Review Report and see Appendix 9.2.

a No conclusive assessment could be made for Patient [redacted] from Study EMR200095-001 because no scans were available.

Table 43: Overview of TEAEs Categories of ILD-like Events: integrated assessment

TEAE Category	Tepotinib 500 mg qd: VISION Cohorts A + C (N=291) n (%)	Tepotinib 500 mg qd: POOL (N=484) n (%)
All	8 (2.7)	10 (2.1)
Related	8 (2.7)	8 (1.7)
NCI-CTCAE Grade ≥ 3	1 (0.3) [a]	1 (0.2)
Serious TEAEs	4 (1.4) [b]	4 (0.8)
TEAE leading to death	1 (0.3) [a]	1 (0.2)
Related TEAE leading to death	1 (0.3) [a]	1 (0.2)
Resolved	1 (0.3) [c]	1 (0.2)
Ongoing	7 (2.4) [d]	9 (1.9) [e]
Temporary discontinuation of study therapy	3 (1.0) [f]	3 (0.6)
Permanent discontinuation of study therapy	5 (1.7) [g]	5 (1.0)

Source: SCS DCO 01 February 2021, Table 12.6.25.1.3.1.

ILD=interstitial lung disease; NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; TEAE=treatment-emergent adverse event.

For patient listings see Appendix 9.1.; refer to SCS DCO 01 February 2021, Listing 12.6.25.3.1.1 and Listing 12.6.25.3.1b.1.

ILD-like TEAEs reported in VISION cohorts A+C were 11 (3.8%) including 6 pneumonitis, 4 ILD and 1 respiratory failure. Three (3) cases were deemed to have other more likely causes by an independent

panel assessment, reactivated tuberculosis, reaction to pleurodesis and small infiltrate which resolved on therapy, respectively.

Hepatobiliary toxicity

Based on the repeat-dose toxicity studies in rats and dogs, the liver/hepatobiliary system was identified as target organ of toxicity (see Non-Clinical section).

In VISION Cohorts A + C, 41% of patients in VISION Cohorts A + C reported an event in the hepatobiliary toxicity SMQ (Table 44). Hypoalbuminemia, ALT/AST increase and ALP increase are the most frequent TEAEs (≥ 5%).

Median time to first onset for ALT and/or AST increase of any grade reported as an adverse event by investigators was 6.1 weeks and the median time to resolution was 4.9 weeks. 82% of patients recovered from all events. Only one patient permanently discontinued treatment due to hepatobiliary toxicity event.

In the POOL, data were inconsistent with VISION Cohorts A + C.

Table 44: Hepatobiliary Toxicity in ≥ 2% of Patients

	Tepotinib 500 mg qd – SAF			
Composite Term	**VISION Cohorts A + C (N=291)**		**POOL (N=484)**	
Preferred Term	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Any NCI-CTCAE Grade				
Hepatobiliary toxicity	120 (41.2)	[35.5;47.1]	218 (45.0)	[40.5;49.6]
Hypoalbuminaemia	81 (27.8)	[22.8;33.4]	122 (25.2)	[21.4;29.3]
ALT increased	37 (12.7)	[9.1;17.1]	57 (11.8)	[9.0;15.0]
Ascites	4 (1.4)	[0.4;3.5]	46 (9.5)	[7.0;12.5]
AST increased	24 (8.2)	[5.4;12.0]	50 (10.3)	[7.8;13.4]
Blood ALP increased	25 (8.6)	[5.6;12.4]	40 (8.3)	[6.0;11.1]
Blood bilirubin increased	4 (1.4)	[0.4;3.5]	18 (3.7)	[2.2;5.8]
γ-GT increased	19 (6.5)	[4.0;10.0]	25 (5.2)	[3.4;7.5]
NCI-CTCAE Grade ≥ 3				
Hepatobiliary toxicity	35 (12.0)	[8.5;16.3]	75 (15.5)	[12.4;19.0]
ALT increased	8 (2.7)	[1.2;5.3]	14 (2.9)	[1.6;4.8]
AST increased	4 (1.4)	[0.4;3.5]	15 (3.1)	[1.7;5.1]
Hypoalbuminaemia	17 (5.8)	[3.4;9.2]	22 (4.5)	[2.9;6.8]
Ascites	1 (0.3)	[0.0;1.9]	11 (2.3)	[1.1;4.0]
Dose Modification (Any NCI-CTCAE Grade)				
Permanent Discontinuation caused by TEAE	1 (0.3)	NA	15 (3.1)	NA
Dose Modification caused by TEAE				
Temporary Discontinuation	13 (4.5)	NA	33 (6.8)	NA
Dose Reduction	6 (2.1)	NA	13 (2.7)	NA
Time to Resolution (days) [a]				
Number of events [b]	242	NA	479	NA
Median	58.0	NA	71.0	NA
Min;Max	1; 1089+	NA	1+; 1089+	NA
Outcome				
Patients with all events resolved	43 (14.8)	NA	63 (13.0)	NA
Patients with any event ongoing	77 (26.5)	NA	155 (32.0)	NA

ALT= alanine aminotransferase; AST= aspartate aminotransferase; ALP=alkaline Phosphatase; γ-GT= gamma−glutamyl transferase; CI=confidence interval; NA=not applicable; NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; SAF=safety analysis set; TEAE= treatment-emergent adverse event

Only PTs reported in VISION Cohorts A + C are included.

Events meeting the threshold in either VISION or POOL have been included.

95% CI for incidence proportion according to Clopper-Pearson.

a Time to resolution using Kaplan−Meier. '+' Indicates censored observation.

b All events (resolved as well as ongoing). A patient may have several episodes of the AE of clinical interest.

Source: SCS update, DCO 01 February 2021, Table 38 (Tables 12.6.25.2.1.1, 12.6.25.2.3.1, 12.6.26.2.12.1.1.)

Drug induced liver injury - Hy's Law Criteria

Drug-induced liver injury was explored by searching for concurrent occurrence increases of ALT or AST (≥ 3×ULN) and total bilirubin (≥ 2×ULN) and with ALP (< 2×ULN or missing).

In VISION Cohorts A + C, 1 patient met Hy's law criteria and had fatal acute hepatic failure. A previously liver-healthy 77-year-old male with adenocarcinoma of the lung, without liver metastasis and apparently without other risk factors or confounders, experienced initially asymptomatic Grade 4 elevation of ALT and Grade 3 elevation of AST on D22 of tepotinib treatment, with subsequent

worsening fulfilling Hy's law criteria and resulting in fatal acute hepatic failure. (See also section Serious adverse events and deaths.)

In the POOL, 9 additional patients met laboratory Hy's Law criteria. All 9 patients suffered from hepatocellular cancer; in 7 of these cases, concomitant liver cirrhosis and/or viral hepatitis are additional alternative explanations for the observed liver parameter increases. The presence of an alternative explanation for the biochemical parameters means that the criteria for Hy's law are not met in the HCC cases.

Renal Toxicity

In order to have a comprehensive assessment of renal toxicity, the SMQs of Acute renal failure (narrow scope) and Chronic kidney disease (narrow scope) were analysed.

Acute Renal Failure

Patients experiencing acute renal failure were analysed using MedDRA SMQ Renal failure acute, narrow scope (Table 45).

In VISION Cohorts A + C, acute renal failure events were reported in 32 (11.0%) patients, Grade ≥ 3 acute renal failure events were reported in 9 (3.1%) patients, and no Grade 4 events were reported. Serious events were reported in 6 (2.1%) patients, with acute kidney injury [AKI] (4 [1.4%] patients) being the only event reported in more than 1 patient. Dose modifications were infrequent and no patient permanently discontinued treatment.

In VISION Cohorts A + C, 5 of the 9 patients who experienced a Grade ≥ 3 events were older than 80 years. Time to onset for Grade 3 events ranged from 5.6 to 18.4 weeks. Events for 6 of the 9 patients with Grade 3 events were considered treatment related by the Investigator. Five of the 9 patients recovered.

Of the patients who experienced a severe event, most of the patients had concurrent TEAEs of peripheral/generalised oedema and or low levels of albumin (Grade 1 or 2). Few patients had a medical history of renal failure. None of these 9 patients had severe hyperkalaemia reported as an adverse event.

The acute renal failure-type events were mainly nonserious. The Investigator determined that 5 serious cases were related to tepotinib. Four of the 5 patients with treatment-related serious events recovered.

Dosage was reduced in 3 (1.0%) patients and temporarily discontinued in 9 (3.1%) patients. Events resolved in 16 (5.5%) patients. In the POOL, data were consistent with VISION Cohorts A + C.

Table 45. Acute Renal Failure

Composite Term / Preferred Term	Tepotinib 500 mg qd – SAF: VISION Cohorts A + C (N=291) n (%)	95% CI	POOL (N=484) n (%)	95% CI
Any Grade				
Renal failure acute	32 (11.0)	[7.6;15.2]	47 (9.7)	[7.2;12.7]
Acute kidney injury	9 (3.1)	[1.4;5.8]	17 (3.5)	[2.1;5.6]
Azotaemia	4 (1.4)	[0.4;3.5]	4 (0.8)	[0.2;2.1]
Renal failure	12 (4.1)	[2.1;7.1]	17 (3.5)	[2.1;5.6]
Renal impairment	9 (3.1)	[1.4;5.8]	12 (2.5)	[1.3;4.3]
NCI-CTCAE Grade ≥ 3				
Renal failure acute	9 (3.1)	[1.4;5.8]	11 (2.3)	[1.1;4.0]
Acute kidney injury	3 (1.0)	[0.2;3.0]	4 (0.8)	[0.2;2.1]
Renal failure	4 (1.4)	[0.4;3.5]	5 (1.0)	[0.3;2.4]
Renal impairment	3 (1.0)	[0.2;3.0]	3 (0.6)	[0.1;1.8]
Dose Modification (Any NCI-CTCAE Grade)				
Permanent Discontinuation caused by TEAE	0	NA	0	NA
Dose Modification caused by TEAE				
Temporary Discontinuation	9 (3.1)	NA	11 (2.3)	NA
Dose Reduction	3 (1.0)	NA	5 (1.0)	NA
Time to Resolution (days) [a]	40		57	
Number of events [b]	22 (55.0)	NA	28 (49.1)	NA
Median	317	NA	317	NA
Min;Max	17; 734	NA	17; 734	NA
Outcome				
Patients with all events resolved	16 (5.5)	NA	21(4.3)	NA
Patients with any event ongoing	16 (4.3)	NA	26 (5.4)	NA

95% CI for incidence proportion according to Clopper-Pearson.

CI=confidence interval; NA=not applicable; NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; SAF=safety analysis set.

a Time to resolution using Kaplan−Meier. '+' Indicates censored observation.

b All events (resolved as well as ongoing). A patient may have several episodes of the AE of clinical interest.

Source: Updated SCS, DCO 01 February 2021, Table 42 (Tables 12.6.25.2.1.1, 12.6.25.2.3.1, 12.6.26.2.13.1.1.)

Chronic Renal Failure

As renal failure is a PT under both MedDRA SMQs of acute renal failure and chronic renal failure with narrow scope and was described in the previous section, the PT chronic kidney disease will primarily be discussed in detail in this section.

In VISION Cohorts A + C, the PT chronic kidney disease was reported in 13 (4.5%) patients. One patient in VISION Cohorts A + C had a serious event. Four patients had dose reductions, 7 patients had temporary dose interruptions, and no patient permanently discontinued treatment. Events resolved in 11 out of the 13 patients. Five (1.7%) patients had Grade 3 events, of which 3 (1.0%) were assessed as treatment related by the Investigator. Four of these 5 patients recovered.

In the POOL, data were overall consistent with VISION Cohorts A + C.

Diarrhoea

Diarrhoea is an identified risk of tepotinib.

In VISION Cohorts A + C, diarrhoea was very common (28%), nonserious, mostly non-severe, and frequently considered treatment related. One (0.3%) patient experienced a Grade 3 event which was the most severe reported grade. No event was serious. Diarrhoea did not lead to dose reduction, it infrequently led to temporary discontinuation (5 patients, 1.7%, all were treatment related), or permanent treatment discontinuation (1 patient, 0.3% which was related to treatment).

Median time to onset of any grade and Grade ≥ 3 diarrhoea was 2.4 weeks and 25.6 weeks, respectively. Diarrhoea resolved in 70 of 81patients with a median time to resolution of 11 days.

In the POOL, data were consistent to VISION Cohorts A + C. Diarrhoea was very common (27%), nonserious, mostly non-severe, and frequently considered treatment related. Diarrhoea infrequently led to dose modifications or temporary discontinuation (6 patients, 1.2%) and permeant discontinuation (1 patient, 0.2%).

Nausea

Nausea is an identified risk of tepotinib.

In VISION Cohorts A + C, nausea was very commonly reported (30%), mostly not severe and nonserious, and frequently considered treatment related. Three (1.0%) patients had a Grade 3 event. One (0.3%) patient had a serious event. Nausea infrequently led to permanent study drug discontinuation (0.7%), temporary discontinuation (2.7%), or a dose reduction (1.0%). Median time to onset of any grade and Grade ≥ 3 nausea was 6.5 weeks and 9.6 weeks, respectively. Nausea resolved in 66 of 88 patients with a median time to resolution of 41 days.

In the POOL, data were consistent to VISION Cohorts A + C. Nausea was very commonly reported (26.0%), mostly not severe and nonserious, and frequently considered treatment relate). Grade 3 events were experienced by 1.2% of patients in the POOL and 0.8% patients had a serious event. Events infrequently led to permanent study drug discontinuation (0.6%), temporary discontinuation (2.1%), or a dose reduction (0.8%). Nausea resolved in 86 of 126 patients with a median time to resolution of 35 days.

Vomiting

Vomiting is an identified risk of tepotinib.

In VISION Cohorts A + C, vomiting was very commonly (14.1%) reported. Events were mostly not severe and nonserious and considered treatment-related in less than a half of patients. Three (1.0%) patients had Grade 3 events, which were also the most severe grade reported. Two (0.7%) patients had a serious event. Vomiting did not lead to dose reduction or permeant treatment discontinuation; 4 (1.4%) patients temporarily interrupted treatment due to vomiting. Median time to onset of any grade vomiting was 7.0 weeks. Vomiting resolved in the majority of patients (38 of 41 patients) with a median time to resolution of 2 days.

In the POOL, data was consistent to VISION Cohorts A + C. Vomiting was very common (14.3%). Events were mostly not severe and nonserious, and infrequently considered treatment-related. Four (0.8%) patients had a serious event. Vomiting infrequently led to permanent study drug discontinuation (0.2%), temporary discontinuation (1.0%), or a dose reduction (0.2%). Vomiting resolved in 38 of 41 patients with a median time to resolution of 2 days.

Cardiac disorders

During treatment with tepotinib, 34 (7.0%) patients in the POOL experienced TEAEs associated with Cardiac disorders. Severe and serious events were mainly reported from VISION Cohort A + C.

In VISION Cohorts A + C, during treatment with tepotinib 27 (9.3%) patients experienced TEAEs associated with Cardiac disorders. The most frequently reported TEAEs were atrial fibrillation (7 [2.4%]), cardiac failure (4 [1.4%]), and tachycardia (4 [1.4%]). Three patients (1.0%) had treatment related TEAEs. Of these three patients, one (0.3%) experienced a treatment-related TEAE of tachycardia, one (0.3%) experienced treatment-related TEAE of pericardial effusion and one (0.3%) had treatment-related TEAE of sinus tachycardia. Ten (3.4%) patients experienced Grade ≥ 3 events, with cardiac failure in 3 (1.0%) patients being the only event reported in more than 1 patient; none were related to treatment. Serious events occurred in 10 (3.4%) patients, with cardiac failure (3 [1.0%] patients) being the only event reported in more than 1 patient; none were related to treatment. All 3 patients had risk factors or medical history that provide an explanation for the occurrence of the events.

The data does not suggest a causal relationship between cardiac disorders and tepotinib, with the exception of QT prolongation.

Nervous System Disorders

In VISION Cohorts A + C, TEAEs in the Nervous System Disorders SOC were reported for 91 (31%) patients. The most frequent (> 5%) neurologic TEAEs in VISION Cohorts A + C included dizziness (6.5%) and headache (5.2%).

One patient with brain metastasis experienced an event of encephalopathy.

Twenty-eight patients (9.6%) had treatment-related TEAEs; dysgeusia (3.8%) was the most frequent.

Thirteen (4.5%) patients had Grade ≥ 3 events. Cerebrovascular accident (4 patients; 1.4%) and spinal cord compression (2 patients, 0.7%) were the only events reported in more than 1 patient. The events were considered not to be related to treatment. All four patients with cerebrovascular accidents had a medical history contributing to this event. The 2 patients with spinal cord compression had vertebral bone metastases. In the POOL, data were consistent with VISION Cohort A + C.

2.6.8.1. Serious adverse event/deaths/other significant events

Deaths

Data for deaths by primary cause are taken from the Death page of the study CRF (which include deaths beyond 30 days after last treatment, and deaths not considered as TEAEs leading to death). In the ongoing VISION Study, reporting of deaths continued after treatment discontinuation during the survival follow-up period.

Disease progression was the most frequent cause of death in VISION Cohorts A + C (30.6%) and the POOL (38.6%; see Table 46).

Primary causes of death

Table 46. Primary Cause of Death

Primary cause of death	Tepotinib 500 mg QD – SAF VISION Cohorts A + C (N=291) n (%)	Tepotinib 500 mg QD – SAF POOL (N=484) n (%)
All deaths	**119 (40.9)**	**251 (51.9)**
Disease Progression	89 (30.6)	187 (38.6)
Related AE	2 (0.7)	4 (0.8)
Unrelated AE	19 (6.5)	26 (5.4)
Other	0 (0.0)	1 (0.2)
Unknown	9 (3.1)	33 (6.8)
Deaths up to 30 days of last dose	**39 (13.4)**	**75 (15.5)**
Disease Progression	19 (6.5)	45 (9.3)
Related AE	2 (0.7)	4 (0.8)
Unrelated AE	16 (5.5)	21 (4.3)
Unknown	2 (0.7)	5 (1.0)
Deaths up to 60 days of first dose	**11 (3.8)**	**33 (6.8)**
Disease Progression	5 (1.7)	18 (3.7)
Related AE	1 (0.3)	2 (0.4)
Unrelated AE	5 (1.7)	10 (2.1)
Unknown	0 (0.0)	3 (0.6)

AE=adverse event; SAF=safety analysis set.

Source: Updated SCS, DCO 01 February 2021, Table 16 (Table 12.6.19.1.1 and Listing 12.6.21.1)

TEAEs with an outcome of death

Table 47. TEAEs Leading to Death by SOC and PT

SOC PT	Tepotinib 500 mg QD – SAF VISION Cohorts A + C (N=291) n (%)	Tepotinib 500 mg QD – SAF POOL (N=484) n (%)
Patients with at least one TEAE leading to death	**36 (12.4)**	**60 (12.4)**
General disorders and administration site conditions	16 (5.5)	28 (5.8)
Disease progression	10 (3.4)	21 (4.3)
General physical health deterioration	4 (1.4)	5 (1.0)
Death	2 (0.7)	2 (0.4)
Infections and infestations	7 (2.4)	11 (2.3)
Pneumonia	2 (0.7)	3 (0.6)
Bacterial infection	1 (0.3)	1 (0.2)
COVID-19 pneumonia	1 (0.3)	1 (0.2)
Respiratory tract infection	1 (0.3)	1 (0.2)
Sepsis	2 (0.7)	3 (0.6)
Septic shock	0 (0.0)	1 (0.2)
Systemic infection	0 (0.0)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	5 (1.7)	8 (1.7)
Dyspnoea	0 (0.0)	1 (0.2)
Acute respiratory failure	1 (0.3)	1 (0.2)
Pneumonia aspiration	1 (0.3)	1 (0.2)
Pulmonary embolism	1 (0.3)	1 (0.2)
Pulmonary haemorrhage	1 (0.3)	1 (0.2)

SOC PT	Tepotinib 500 mg QD – SAF VISION Cohorts A + C (N=291) n (%)	 POOL (N=484) n (%)
Respiratory failure	1 (0.3)	2 (0.4)
Cardiac disorders	3 (1.0)	3 (0.6)
Cardiac arrest	1 (0.3)	1 (0.2)
Cardiac failure	1 (0.3)	1 (0.2)
Cardio−respiratory arrest	1 (0.3)	1 (0.2)
Gastrointestinal disorders	1 (0.3)	3 (0.6)
Ileus	1 (0.3)	1 (0.2)
Gastrointestinal haemorrhage	0 (0.0)	1 (0.2)
Upper gastrointestinal haemorrhage	0 (0.0)	1 (0.2)
Injury, poisoning and procedural complications	1 (0.3)	1 (0.2)
Spinal fracture	1 (0.3)	1 (0.2)
Metabolism and nutrition disorders	1 (0.3)	1 (0.2)
Dehydration	1 (0.3)	1 (0.2)
Electrolyte imbalance	1 (0.3)	1 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.3)	1 (0.2)
Neoplasm progression	1 (0.3)	1 (0.2)
Hepatobiliary disorders	0 (0.0)	2 (0.4)
Hepatic failure	0 (0.0)	2 (0.4)
Psychatric disorders	1 (0.3)	1 (0.2)
Assisted suicide	1 (0.3)	1 (0.2)
Nervous system disorders	2 (0.7)	4 (0.8)
Cerebrovascular accident	1 (0.3)	1 (0.2)
Parkinson's disease	1 (0.3)	1 (0.2)
Coma	0 (0.0)	1 (0.2)
Hypoglycaemic coma	0 (0.0)	1 (0.2)

PT=preferred term; SAF=safety analysis set; SOC=System Organ Class; TEAE= treatment-emergent adverse event.

Source: Updated SCS, DCO 01 February 2021, Table 17 (Table 12.6.17.1.)

In VISION Cohorts A + C, TEAEs leading to death in more than 1 patient were disease progression (10 patients, 3.4%), general physical health deterioration (4 patients, 1.4%), death, pneumonia and sepsis in each 2 patients (0.7%; Table 47).

In the POOL, disease progression was the most common TEAE leading to death. Hepatic failure was recorded as the cause of death in 2 patients with HCC in the POOL.

Treatment-related TEAEs leading to death

At the DCO, 4 patients in the POOL, including 2 patients from VISION had a treatment-related TEAE with an outcome of death. An additional narrative was provided for a patient with a TEAE with an outcome of death considered treatment-related by the Sponsor, which occurred after the patient's withdrawal of consent and thereby not included in the study statistics and no investigator assessment of causality was made.

Of these 5 cases with fatal TEAEs, 3 were considered possibly treatment-related, based on the investigator and/or Sponsor assessment, and is agreed by the agency. All 3 were male patients from the VISION study METexon14 skipping NSCLC cohorts. Treatment was discontinued on the day of onset in all cases except the third one where it was discontinued on the day before onset. The cases included one case of acute respiratory failure and dyspnoea with radiological signs of diffuse alveolar damage (DAD)/acute respiratory distress syndrome, potentially representing drug-induced interstitial lung disease, a massive allergic reaction, or an atypical pneumonia; another case of dyspnoea due to

respiratory failure (initially reported as generalised oedema with pulmonary oedema occurring in another hospital, but this was not confirmed); and one case of acute hepatic failure, beginning on Day 22 of tepotinib treatment and fulfilling Hy's law criteria for drug-induced liver injury in a previously liver-healthy individual apparently without risk factors and with major alternative aetiologies excluded. See RMP section.

Two TEAEs considered treatment-related by the Investigator were not considered treatment-related by the sponsor, Upper gastrointestinal haemorrhage in a patient with HCC, pre-existing liver cirrhosis, and hepatitis B; and Hypoglycemic coma in a patient with advanced HCC, type I diabetes mellitus, chronic renal failure, hypertension, chronic hepatitis C, hepatic cirrhosis, and concomitant medication with 3 different insulin products.

Serious adverse events (SAEs)

One or more serious TEAE (SAE) were experienced by 138 (47%) patients in VISION Cohorts A + C, and 224 (46%) patients in the POOL, (Table 48).

In VISION, the most frequent SAEs were pleural effusion (6.2%), disease progression (4.5%), pneumonia (4.1%), dyspnoea (3.4%), and general physical health deterioration (3.4%). Pleural effusion, pneumonia, and dyspnoea are commonly observed TEAEs in patients with NSCLC.

In the POOL, disease progression was the most common SAE (6.4%). Ascites occurred almost exclusively in the POOL (2.3%) and in patients with HCC in studies EMR200095-004 and EMR200095-005 and can be explained by the underlying HCC disease in these studies.

Table 48. Serious TEAEs and Treatment-related Serious TEAEs by SOC and PT (≥ 2% of Patients by PT)

SOC PT	Tepotinib 500 mg QD – SAF VISION Cohorts A + C (N=291) n (%)	Tepotinib 500 mg QD – SAF POOL (N=484) n (%)
Any Serious TEAEs		
Patients with at least one serious TEAE	**138 (47.4)**	**224 (46.3)**
General disorders and administration site conditions	48 (16.5)	76 (15.7)
Disease progression	13 (4.5)	31 (6.4)
General physical health deterioration	10 (3.4)	12 (2.5)
Oedema peripheral	9 (3.1)	15 (3.1)
Generalised oedema	6 (2.1)	8 (1.7)
Respiratory, thoracic and mediastinal disorders	41 (14.1)	49 (10.1)
Pleural effusion	18 (6.2)	18 (3.7)
Dyspnoea	10 (3.4)	13 (2.7)
Pulmonary embolism	6 (2.1)	6 (1.2)
Infections and infestations	32 (11.0)	47 (9.7)
Pneumonia	12 (4.1)	15 (3.1)
Gastrointestinal disorders	10 (3.4)	38 (7.9)
Ascites	1 (0.3)	11 (2.3)
Treatment-related Serious TEAEs		
Patients with at least one treatment-related serious TEAE	41 (14.1)	58 (12.0)
Respiratory, thoracic and mediastinal disorders	17 (5.8)	18 (3.7)
Pleural effusion	10 (3.4)	10 (2.1)
General disorders and administration site conditions	17 (5.8)	24 (5.0)
Oedema peripheral	8 (2.7)	13 (2.7)

PT=preferred term; SAF=safety analysis set; SOC=System Organ Class; TEAE=treatment-emergent adverse event. TEAEs meeting the 2% threshold in either VISION or POOL have been included.

Source: Updated SCS, DCO 01 February 2021, Table 18 (Table 12.6.15.1 and SCS Table 12.6.16.1)

The all-cause and treatment-related SAE frequencies, respectively, were consistent between the VISION cohort A+C and the POOL, with the exception of Respiratory, thoracic and mediastinal disorders SOC being overrepresented in the lung cancer population of VISION, and PT Ascites being almost exclusively seen in the POOL, i.e. outside VISION, exception in one patient.

PTs pleural effusion (2-3%), peripheral oedema (2.7%) were the most commonly reported SAEs that were considered treatment-related by investigators in the two safety populations.

2.6.8.2. Laboratory findings

Laboratory values have been graded according to NCI-CTCAE version 4.03 for the SCS.

Haematology

Table 49. Haematology - Summary by Worst On-treatment NCI-CTCAE Toxicity Grade

Parameter Worst Grade On-Treatment	VISION Cohorts A + C - SAF (N=291) n (%)	POOL (N=484) n (%)
Hemoglobin (g/L) Low		
Any Grade >=1	210 (72.2)	359 (74.2)
Any Grade >=3	8 (2.7)	13 (2.7)
Lymphocytes (10^9/L) Low		
Any Grade >=0	245 (84.2)	423 (87.4)
Any Grade >=1	167 (57.4)	285 (58.9)
Any Grade >=3	34 (11.7)	62 (12.8)
Neutrophils (10^9/L) Low		
Any Grade >=0	267 (91.8)	446 (92.1)
Any Grade >=1	47 (16.2)	77 (15.9)
Any Grade >=3	3 (1.0)	6 (1.2)
Platelets (10^9/L) Low		
Any Grade >=1	67 (23.0)	150 (31.0)
Any Grade >=3	0 (0.0)	1 (0.2)
Leukocytes (10^9/L) Low		
Any Grade >=1	69 (23.7)	132 (27.3)
Any Grade >=3	4 (1.4)	4 (0.8)

NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; SAF=safety analysis set.

N1 - the number of subjects with non−missing Baseline NCI−CTCAE toxicity grade and at least one laboratory assessment during the on−treatment period. It is used as a denominator for the percentage of subjects with NCI−CTCAE toxicity grades. Only new onset abnormalities or abnormalities worsening from Baseline are considered.

Source: Updated SCS, DCO 01 February 2021, Table 44 (Table 12.7.2.1.1. and 12.7.2.2.1)

Low grade reductions in haematology laboratory values were frequent, while only lymphocytes had reductions to Grade≥ 3 in more than 5% of patients.

It is notable that approximately one-half of patients had normal lymphocyte count at Baseline (163/291 in VISION Cohorts A + C) and 274/484 in the POOL, thus low lymphocyte count was very common at Baseline (30.9% patients in VISION Cohorts A + C had low lymphocytes Grade ≥1).

Lymphocytes low were recorded in 57% and 59%, respectively; with grade ≥ 3 at 11.7% in in VISION Cohorts A + C and 12.8% in the POOL; Table 49).

On-treatment Grade 4 low lymphocytes were documented in 5 (1.7%) patients in VISION Cohorts A + C and 7 (1.4%) patients in the POOL.

Haemoglobin low was recorded in 72% and 74% of patients in the VISION cohorts A+C and the POOL, respectively; with grade ≥ 3 at 2.7% in both safety populations.

Platelets low were recorded in 23% and 31%, respectively; with grade ≥ 3 at/near 0% in both safety populations (1 patient in POOL).

Leukocytes low were recorded in 24% and 27%, respectively; with grade ≥ 3 at 1% in both safety populations.

Biochemistry and related adverse events

On-treatment biochemistry parameters of Grade ≥ 3 with an incidence of ≥ 5% in either VISION Cohorts A + C or the POOL were low creatinine clearance (12% and 10%, respectively), low albumin (8.2% and 7.9%, respectively), low sodium (9.3% and 10.3%, respectively), high AST (3.1% and 7.2%, respectively), high lipase (5.2% and 6.6%, respectively), high Gamma-Glutamyl Transferase (GGT) (6.5% and 14.7%, respectively) and high glucose (3.4% and 7.4%, respectively). (Table 50, Table 51).

Table 50. Biochemistry LOW - Summary by Worst On-treatment NCI-CTCAE Toxicity Grade

	Tepotinib 500 mg qd – SAF	
Parameter	**VISION Cohorts A + C (N=291) n (%)**	**POOL (N=484) n (%)**
Creatinine clearance		
Grade >= 1	273 (93.8)	442 (91.3)
Grade >= 3	35 (12.0)	49 (10.1)
Albumin (g/L)		
Grade >= 1	254 (87.3)	419 (86.6)
Grade >= 3	24 (8.2)	38 (7.9)
Corr. Serum Calcium (mmol/L)		
Grade >= 1	57 (19.6)	84 (17.4)
Grade >= 3	2 (0.7)	2 (0.4)
Glucose (mmol/L)		
Grade >= 1	21 (7.2)	44 (9.1)
Grade >= 3	1 (0.3)	1 (0.2)
Potassium (mmol/L)		
Grade >= 1	66 (22.7)	88 (18.2)
Grade >= 3	6 (2.1)	9 (1.9)
Magnesium (mmol/L) Low		
Grade >= 1	51 (17.5)	74 (15.3)
Grade >= 3	0 (0.0)	1 (0.2)
Sodium		
Grade >= 1	113 (38.8)	202 (41.7)
Grade >= 3	27 (9.3)	50 (10.3)

NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; SAF=safety analysis set. N is the number of subjects with non−missing Baseline NCI−CTCAE toxicity grade and at least one laboratory assessment during the on−treatment period. It is used as a denominator for the percentage of subjects with NCI−CTCAE toxicity grades.

Source: Updated SCS, DCO 01 February 2021, Table 47 (Table 12.7.7.1.1.)

Table 51. Biochemistry HIGH- Summary by Worst On-treatment NCI-CTCAE Toxicity Grade

Parameter	Tepotinib 500 mg qd – SAF	
	VISION Cohorts A + C (N=291) n (%)	POOL (N=484) n (%)
Alanine Aminotransferase (U/L)		
Grade >= 1	129 (44.3)	267 (55.2)
Grade >= 3	12 (4.1)	23 (4.8)
Alkaline phosphatase (U/L)		
Grade >= 1	189 (64.9)	338 (69.8)
Grade >= 3	6 (2.1)	23 (4.8)
Aspartate Aminotransferase (U/L) (mmol/L)		
Grade >= 1	108 (37.1)	262 (54.1)
Grade >= 3	9 (3.1)	35 (7.2)
Total Bilirubin (umol/L)		
Grade >= 1	16 (5.5)	95 (19.6)
Grade >= 3	1 (0.3)	15 (3.1)
Creatinine (umol/L)		
Grade >= 1	183 (62.9)	287 (59.3)
Grade >= 3	1 (0.3)	3 (0.6)
Gamma Glutamyl Transferase (U/L)		
Grade >= 1	116 (39.9)	241 (49.8)
Grade >= 33	19 (6.5)	71 (14.7)
Corr. Serum calcium (mmol/L)		
Grade >= 1	23 (7.9)	49 (10.1)
Grade >= 33	1 (0.3)	3 (0.6)
Glucose (mmol/L)		
Grade >= 1	10 (3.4)	36 (7.4)
Grade >= 3	10 (3.4)	36 (7.4)
Potassium (mmol/L)		
Grade >= 1	76 (26.1)	133 (27.5)
Grade >= 3	4 (1.4)	7 (1.4)
Lipase (U/L)		
Grade >= 1	57 (19.6)	104 (21.5)
Grade >= 3	15 (5.2)	32 (6.6)
Amylase (U/L)		
Grade >= 1	80 (27.5)	130 (26.9)
Grade >= 3	13 (4.5)	17 (3.5)

Source: SCS DCO 01 February 2021 Table 12.7.7.2.1

Source: Updated SCS, DCO 01 February 2021, Table 48 (Table 12.7.7.2.1)

Hyponatraemia and hypo-and hyperkalaemia

The frequent aberrations with regard to sodium and potassium might be related to use of diuretics due to oedema. Such laboratory aberrations are frequent among hospitalized patients in general.

Hyponatraemia is common in cancer patient population and is a well-recognized comorbidity in lung cancer patients. It is often multifactorial, common causes include diuretic use, gastrointestinal losses, syndrome of inappropriate antidiuretic hormone secretion.

Thorough review of individual data for 27 patients who experienced any ≥ 2-grade shift from Baseline or had a Grade 3 TEAE of hyponatremia showed that in 25 of 27 patients there were clear alternative explanations for events or observations, such as concurrent AEs or relevant concomitant medication.

A detailed review of the available data for patients who experienced ≥2-grade shift in decreased potassium (6 patients) showed that there were alternative explanations for the observations in all 6 patients such as concurrent AEs or relevant concomitant medication.

A detailed review of the available data for patients who experienced ≥2-grade shift in elevated potassium or a Grade 3 hyperkalaemia showed that there were alternative explanations for events or observations in 12 of 18 patients e.g. concurrent AEs or relevant concomitant medication, including 2 patients with 3-grade shifts. In 6 patients no associated confounders were reported, however, potassium levels showed only a single peak and did not indicate a sustained elevation.

Amylase, lipase

Increase in pancreatic enzymes have been reported with other TKIs or MET inhibitors and may represent a TKI class effect (Pezzilli 2011; brigatinib EU SmPC; capmatinib US PI).

In VISION Cohorts A + C, Amylase and/or Lipase increased was reported in 37 (13%) patients. TEAEs were mainly of a low severity (Grades 1 and 2). Severe Amylase and/or Lipase increased (Grade 3) were documented in 18 (6.2%) of patients. There were two Grade 4 events of amylase and lipase, each.

Amylase increases occurred in 27 patients (9.3%). Lipase increases occurred in 24 patients (8.2%). Serious TEAE of lipase increased occurred in 2 (0.7%) patients and there were no serious amylase increases. All increases of amylase and lipase reported as an adverse event by investigators were asymptomatic. No patient experienced a pancreatitis. 3.1% of patients temporarily discontinued treatment and there were no permanent treatment discontinuation or dose reduction. Median time to onset of any grade in lipase/amylase increase was 12 weeks and median time to resolution was 5.9 weeks. 65% of the patients recovered from all events.

ALT and/or AST increase

PTs: Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Transaminases increased, Transaminases abnormal, Hypertransaminasaemia, AST/ALT ratio abnormal

ALT and/or AST increases are identified risks for tepotinib.

ALT and AST elevations captured as a laboratory abnormality by routine laboratory collection during study is shown above (Table 51).

Laboratory values of ALT high occurred frequently in both safety populations; the higher incidences in the POOL (55%) compared to VISION cohorts A+C (44%) may be attributed to the 25% proportion of patients with HCC in the POOL. Grade ≥3 ALT aberrations were less than 5% in both populations.

Laboratory values of AST high occurred frequently in both safety populations with higher incidences in the POOL (54%) compared to VISION cohorts A+C (37%). Grade ≥3 AST aberrations occurred in 7.2% of patients in the POOL and 3.1% in VISION cohorts A+C.

With regard to liver function laboratory values, the data from the VISION study is considered more reflective of the true tepotinib safety profile due to confounding of the HCC disease in the POOL.

ALT and AST TEAEs

ALT and AST elevations were also captured as TEAE by investigators.

In VISION Cohorts A + C, events of ALT and/or AST increase (composite term) were very common (39 patients, 13.4%). ALT increased was the most frequent TEAE (37 patients, 12.7%). The events were mainly nonserious and of low grade (Grade 1 or 2). ALT and/or AST increase led to permanent study drug discontinuation only in 1 (0.3%) patient, and infrequently led to temporary discontinuation or dose reduction. Events resolved in 32 of 39 patients. Nine (3.1%) patients had Grade ≥ 3 events. Of these, 2 (0.7%) patients had ALT and/or AST increases of Grade 4. Two (0.7%) patients reduced their tepotinib dose and 9 (3.1%) temporarily discontinued tepotinib due to transaminases elevation. One (0.3%) patient permanently discontinued treatment due to ALT elevation.

The median time to first onset was 6.1 weeks for any grade of ALT and/or AST increase and 7.9 weeks for Grade ≥ 3 events. ALT and/or AST increase events resolved in most patients (32/39). At the event level, 60 of 72 reported events resolved, and 50 of those 72 events resolved on-treatment. Median time to resolution for the ALT/AST increase events was 34 days.

AST and ALT increase occur frequently also for the approved multikinase inhibitors that include MET, crizotinib and cabozantinib, and may be a class effect. These reactions appear manageable with no need of further characterisation. See also Hepatobiliary toxicity above.

Alkaline phosphatase

Blood ALP increased is an identified risk (adverse drug reaction) for tepotinib.

ALP elevations captured as a laboratory abnormality by routine laboratory collection during study is shown above (Table 51). Alkaline phosphatase (ALP) was increased in 65% of patients in VISION Cohorts A + C, with Grade ≥ 3 in 2.1%.

ALP TEAEs

ALP elevations were also captured as TEAE by investigators.

In VISION Cohorts A + C, blood ALP increased was reported in 25 (8.6%) patients. No event was serious. No event led to a dose reduction, temporary treatment discontinuation, or permanent treatment discontinuation.

Only one (0.3%) patient had a severe (Grade 3) event of ALP increase. This patient had multiple confounding factors for ALP elevation, however. The observed ALP increase was not associated with cholestasis.

Median time to first onset for ALP increase of any grade was 4.4 weeks and the median time to resolution was 11 weeks. 67% of the events resolved. In the POOL, data were consistent with VISION Cohorts A + C, with blood ALP increased was reported in 40 (8.3%) patients.

Other liver function tests

Other liver function tests were similarly elevated (Table 51). In VISION cohorts A+C, Gamma glutamyl transferase (GGT) was increased in 40% of patients (24% had a shift from baseline), with Grade ≥3 in 6.5%. Total bilirubin was increased in 5.5% (4% had a shift from baseline), with only 1 patient (0.3%) having a Grade ≥3 aberration. Alternative explanations for the laboratory abnormalities were present in most cases of GGT shifts and for nearly half of bilirubin shifts from baseline.

Creatinine increased

PTs: Hypercreatininaemia, Blood creatinine increased, Blood creatinine abnormal

Creatinine increase is an identified risk of tepotinib. Patients with mild or moderate renal impairment could enrol into VISION Study. In earlier studies only patients with mild renal impairment could enrol into the studies.

Creatinine increase and creatinine clearance decrease captured as laboratory abnormalities are shown above (Table 50, Table 51).

The frequency of elevated creatinine laboratory values was high (63% and 59% in VISION A+C and POOL, respectively). However, less than 1% (0.3% and 0.6%) were grade ≥ 3. (Table 51) The laboratory creatinine clearance was low in 94% and 91%, respectively. (Table 50)

One patient who experienced a Grade 3 event had concomitant elevation of blood urea nitrogen (BUN). Median time to onset of creatinine increase in VISION Cohorts A + C reported as an adverse event by investigators was 3.1 weeks. The median time to resolution was 78 days. 61% of patients recovered from all events.

In the POOL creatinine increase occurred in 22% of patients.

Creatinine increase events infrequently led to treatment discontinuation (<1% in VISION and POOL) or required dose interruption (5.8% in VISION Cohorts A + C) or reduction (3% in both populations).

Hypoalbuminemia

PTs: Blood albumin abnormal, Blood albumin decreased, Hypoalbuminaemia

Laboratory values of albumin low was recorded in 87% of patients in VISION cohorts A+C as well as in the POOL. Grade ≥3 low albumin laboratory values were 8% in both populations (Table 50).

In VISION Cohorts A + C, hypoalbuminemia was very common (83 patients, 28.5%) and was mainly nonserious and non-severe (Grade 1 to 2). Seventeen patients (5.8%) had Grade 3 hypoalbuminemia. There were no Grade ≥ 4 events. One (0.3%) patient had a serious Grade 3 hypoalbuminemia; the event was ongoing at DCO. The PT hypoalbuminemia was the most frequent PT (81; 28%).

Median time to onset of any grade and Grade ≥ 3 hypoalbuminemia reported as an adverse event by investigators was 9.4 weeks and 19.0 weeks, respectively. Hypoalbuminemia seemed to be long-lasting but did not lead to permanent treatment discontinuation. Dose reductions (3 patients, 1.0%) and temporary discontinuations (4 patients, 1.4%) were infrequent. Hypoalbuminemia resolved in 22 of 83 patients; a median time to resolution could not be estimated.

Proteinuria has been infrequently observed (2 patients, 0.7%) in the VISION Study. Both events were low to moderate grade (Grade 1 and 2), nonserious and did not lead to dose modifications or treatment discontinuation. In the POOL, 5 (1.0%) patients treated with tepotinib experienced proteinuria. Similar to VISION, the events were low to moderate (Grade 1 and 2), nonserious and did not lead to dose modifications or treatment discontinuations. Systematic collection of data for proteinuria was limited to screening, Day 1 Cycle 1, end of treatment, and the safety follow-up visit. The review of proteinuria data (dipstick) on patients who reported hypoalbuminemia during tepotinib treatment did not show evidence of drug induced proteinuria or that hypoalbuminemia is due to drug-induced proteinuria.

Among the 225 (77%) patients who had oedema events in VISION Cohorts A + C, 209 (72%) had Grade ≥1 low albumin levels on-treatment including 58 (20%) patients with Grade 1 low albumin, 130 (45%) patients with Grade 2 low albumin and 21 (7.2%) patients with Grade 3 low albumin. Among the 66 (23%) patients without oedema, 45 (15.5%) had low albumin level Grade ≥ 1 on-treatment

including 18 (6.2%) patients with Grade 1 low albumin, 24 (8.2%) patients with Grade 2 low albumin and 3 (1.0%) patients with Grade 3 low albumin.

Vital signs and ECG

No specific pattern in change of blood pressure (BP) was observed in patients treated with tepotinib, although there was variability in both systolic and diastolic BP.

No significant change in weight was observed in patients treated with tepotinib and no significant change in body mass index (BMI) was observed in patients treated with tepotinib.

ECG - QTc

Table 52. Summary of On-treatment QT Prolongation Findings

	Tepotinib 500 mg qd -- SAF	
QT Prolongation Findings	**VISION Cohorts A + C (N=291) n (%)**	**POOL (N=484) n (%)**
Any on-treatment QTcF > 500 ms	6 (2.1)	12 (2.5)
On-treatment QTcF > 500 ms (Baseline ≤ 450 ms)	3 (1.0)	4 (0.8) [a]
On-treatment QTcF > 500 ms (Baseline > 450 ms - ≤ 480 ms)	0	1 (0.2) [b]
On-treatment QTcF > 500 ms (Baseline > 480 ms - ≤ 500 ms)	0	1 (0.2) [c]
On-treatment QTcF > 500 ms (Baseline > 500 ms)	2 (0.7) [d]	5 (1.0) [d]
On-treatment QTcF > 500 ms (Baseline unknown)	1 (0.3)	1 (0.2)
On-treatment QTcF prolonged by > 60 ms	15 (5.2)	20 (4.1)
On−treatment QTcF > 500 ms and prolonged by > 60 ms	3 (1.0)	4 (0.8)

SAF=safety analysis set. Footnotes are derived from a review of the patient level data.

a All also had an on-treatment shift of > 60 ms.

b 1 patient had relevant concurrent events and concomitant medication that provided a clear alternative cause.

c 1 patient had Baseline QTcF of > 480 ms and a single on-treatment reading that was > 500 ms.

d No on-treatment worsening.

Source: Updated SCS, DCO 01 February 2021, Table 51 (Listing 12.8.2.3.1 and Tables 12.8.2.1.2.1, 12.8.2.1.1.1, and 12.8.2.1.3.1.)

A broad search for TEAEs belonging to the medical concept QT prolongation was performed (as specified by ICH E14 guideline:

SMQ: Torsade de pointes/QT prolongation – broad; PTs: Seizure, Tonic convulsion, Clonic convulsion, Generalised tonic−clonic seizure

Table 53. Overview of TEAEs Related to QTc Prolongation

Primary System Organ Class Preferred Term	Tepotinib 500 mg qd – SAF VISION Cohorts A + C (N=291) n (%)	Tepotinib 500 mg qd – SAF POOL (N=484) n (%)
Patients with at least one event	14 (4.8)	21 (4.3)
Investigations		
Electrocardiogram QT Prolonged	8 (2.7)	12 (2.5)
Nervous system disorders		
Syncope	2 (0.7)	4 (0.8)
Generalized tonic−clonic seizure	0	1 (0.2)
Loss of consciousness	1 (0.3)	1 (0.2)
Seizure	1 (0.3)	1 (0.2)
Cardiac disorders		
Cardiac arrest	1 (0.3)	1 (0.2)
Cardio-respiratory arrest	1 (0.3)	1 (0.2)
Long QT syndrome	1 (0.3)	1 (0.2)

Source: Updated SCS, DCO 01 February 2021, Table 52 (Table 12.6.25.2.1.1.)

On-treatment ECG recordings with QTc-F prolongation were observed in the pivotal study and in the pooled safety population at 500 mg (POOL) at similar frequencies (Table 52).

A QTcF > 500 ms was recorded in 2.1% of patients in the VISION Cohorts A + C and 2.5% in the POOL.

A QTcF increase of at least 60 ms from baseline was observed in 5.2% of patients in VISION cohorts A+C and 4.1% in the POOL.

Combination of QTcF > 500 ms and prolonged by > 60 ms was reported in 1.0% (3 patients) and 0.8% (4 patients) in VISION Cohorts A + C and POOL, respectively.

Medical concept QT prolongation TEAEs, which includes TEAEs related to QTc prolongation, also showed similar frequencies in the two populations (Table 53).

TEAEs of QTc prolongation without conclusive alternative explanations for these QTc effects were reported in 4 patients in VISION cohorts A+C; 2 of the patients had more than one episode.

One patient in the POOL (from Study EMR200095-004), with normal electrolyte values, experienced Grade 3 QT prolonged on Day 125, with subsequent positive dechallenge and rechallenge. Thus, the AE improved to Grade 2 during temporary discontinuation of tepotinib and worsened to Grade 3 again, 5 days after restarting tepotinib. The prolonged QT interval resolved 1 day after permanent discontinuation of tepotinib and the event was considered treatment-related by the Investigator.

2.6.8.3. Adverse drug reactions

According to the SmPC guideline 2009 (revision 2), the safety information in the EU product information should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SmPC. A single table (or structured listing) should list all

adverse reactions with their respective frequency category. Adverse reactions described in the table below reflect exposure to tepotinib in 484 patients with various solid tumours enrolled in five open-label studies, in which patients received tepotinib as a single agent at a dose of 450 mg once daily. The frequencies of adverse reactions are based on all-cause adverse event frequencies identified in 291 patients exposed to tepotinib at the recommended dose in the target indication, whereas frequencies for changes in laboratory parameters are based on worsening from baseline by at least 1 grade and shifts to ≥ grade 3. Median duration of treatment was 27.6 weeks (range 0 to 220).

Frequencies presented may not be fully attributable to tepotinib alone but may contain contributions from the underlying disease or from other medicinal products used concomitantly.

The severity of adverse reactions was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE), defining grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening and grade 5 = death.

The following list of adverse drug reactions (ADRs) is currently included in the SmPC:

Table 54: **Adverse reactions in patients with NSCLC harbouring *MET*ex14 skipping alterations (VISION)**

System organ class/Adverse reaction	**Tepmetko N=291**		
	Frequency category	**All grades %**	**Grade ≥ 3 %**
Metabolism and nutrition disorders			
Decrease in albumin *	Very common	76	7.9
Cardiac disorders			
QT prolongation *	Common	2.1	
Respiratory, thoracic and mediastinal disorders			
ILD-like reactions [a]*	Common	2.7	0.3
Gastrointestinal disorders			
Nausea	Very common	30	1.0
Diarrhoea	Very common	28	0.3
Increase in amylase *	Very common	23	4.5
Increase in lipase *	Very common	18	4.5
Vomiting	Very common	14	1.0
Hepatobiliary disorders			
Increase in alkaline phosphatase (ALP) *	Very common	48	1.7
Increase in alanine aminotransferase (ALT) *	Very common	43	4.1
Increase in aspartate aminotransferase (AST) *	Very common	34	3.1
Renal and urinary disorders			
Increase in creatinine *	Very common	55	0.3
General disorders and administration site conditions			
Oedema [b]*	Very common	77	13

* Additional information on the respective adverse reaction is provided below.
a includes terms interstitial lung disease, pneumonitis, acute respiratory failure
b includes terms oedema peripheral, oedema, generalised oedema, oedema genital, face oedema, localised oedema, periorbital oedema, peripheral swelling, scrotal oedema

2.6.8.4. Safety in special populations

Table 55: Treated Subjects by Subgroup

Characteristic	Statistics	Tepotinib 500 mg 001-003-004-005-0022 METamp [3] (N=193) n (%)	0022 METex14 [2] (N=291) n (%)	Pooled (N=484) n (%)
Sex	Male	154 (79.8)	143 (49.1)	297 (61.4)
	Female	39 (20.2)	148 (50.9)	187 (38.6)
Age (years) Category	< 65	112 (58.0)	64 (22.0)	176 (36.4)
	>= 65-<75	64 (33.2)	107 (36.8)	171 (35.3)
	>= 75-<85	17 (8.8)	96 (33.0)	113 (23.3)
	>= 85	0 (0.0)	24 (8.2)	24 (5.0)
Race	Asian	76 (39.4)	88 (30.2)	164 (33.9)
	White	89 (46.1)	191 (65.6)	280 (57.9)
	Other	4 (2.1)	4 (1.4)	8 (1.7)
	Unknown	24 (12.4)	8 (2.7)	32 (6.6)
BMI (kg/m**2)	Underweight: < 18.5	13 (6.7)	16 (5.5)	29 (6.0)
	Normal: >= 18.5 - <25	103 (53.4)	165 (56.7)	268 (55.4)
	Overweight: >= 25 - <30	51 (26.4)	82 (28.2)	133 (27.5)
	Obese: >= 30	21 (10.9)	22 (7.6)	43 (8.9)
	Missing	5 (2.6)	6 (2.1)	11 (2.3)
ECOG	0	74 (38.3)	77 (26.5)	151 (31.2)
	>=1	119 (61.7)	214 (73.5)	333 (68.8)
Renal impairment	Normal	NA	62 (21.3)	NA
	Mild	NA	136 (46.7)	NA
	Moderate	NA	87 (29.9)	NA
	Severe	NA	0 (0.0)	NA
	Missing	NA	6 (2.1)	NA
History of Hypertension	Yes	NA	144 (49.5)	NA
	No	NA	147 (50.5)	NA
	Missing	NA	0 (0.0)	NA
Nicotine Consumption	Smoker	NA	138 (47.4)	NA
	Non-Smoker	NA	143 (49.1)	NA
	Missing	NA	10 (3.4)	NA

Source: Updated SCS, DCO 01 February 2021, Table 12.1.2.1

Sex

In VISION Cohorts A + C, the proportion of males (123, 48.2%) and females (132, 51.8%) was similar.

Serious TEAEs were reported in similar proportions in males (48.8%) and females (41.7%).

Differences between sexes in frequencies of ≥10% or a doubling in events by PT or medical concepts has been noted for the following:

Nausea:	Male: 30 (21.0%);	Female: 58 (39.2%)
Diarrhoea:	Male: 31 (21.7%);	Female: 50 (33.8%)
Vomiting:	Male: 13 (9.1%);	Female: 28 (18.9%)
Hypoalbuminaemia:	Male: 50 (35.0%);	Female: 33 (22.3%)
Generalized oedema:	Male: 12 (8.4%);	Female: 5 (3.4%)
Pain:	Male: 7 (4.9%)	Female: 1 (0.7%)
Alopecia:	Male: 7 (4.9%);	Female: 27 (18.2%)

In the POOL, there were more men (297, 61%) than women (187, 39%). The POOL was consistent with VISION Cohorts A + C regarding serious and serious related TEAEs. Consistent with VISION Cohorts A + C, in the POOL, nausea was more frequent in female patients (37.4%) than in male patients (18.9%). No other similar difference was observed with other events.

Age

Of the 291 patients in VISION Cohorts A + C who received 500 mg tepotinib once daily continuously, 78% were 65 years or older, and 8% were 85 years or older.

TEAE frequencies for selected TEAEs of interest in elderly patients is shown in Table 56.

Table 56: Selected TEAEs in elderly patients, VISION Cohorts A+C

Preferred Term	VISION Cohorts A + C (N=291) n (%)			
	Age < 65 years	Age 65 - < 75 years	Age 75 - < 84 years	Age ≥85+ years
Patients	**64 (22.0)**	**107 (36.8)**	**96 (33.0)**	**24 (8.2)**
Patients with at least one TEAE	62 (96.9)	107 (100.0)	94 (97.9)	24 (100.0)
Patients with Serious TEAEs	22 (34.4)	49 (45.8)	51 (53.1)	16 (66.7)
Fatal	4 (6.3)	10 (9.3)	17 (17.7)	5 (20.8)
Hospitalization / prolong existing hospitalization	21 (32.8)	45 (42.1)	44 (45.8)	13 (54.2)
Life-threatening	0	0	4 (4.2)	0
Disability/incapacity	0	0	0	0
Other (medically significant)	2 (3.1)	5 (4.7)	2 (2.1)	2 (8.3)
AE leading to drop-out (study discontinuation)	3 (4.7)	3 (2.8)	15 (15.6)	3 (12.5)
Psychiatric disorders	6 (9.4)	18 (16.8)	11 (11.5)	3 (12.5)
Nervous system disorders	21 (32.8)	38 (35.5)	27 (28.1)	5 (20.8)
Central nervous system vascular disorders (SMQ)	2 (3.1)	4 (3.7)	2 (2.1)	1 (4.2)
Cerebrovascular accident	1 (1.6)	1 (0.9)	1 (1.0)	1 (4.2)
Cerebral infarction	0	2 (1.9)	0	0
Haemorrhage intracranial	0	1 (0.9)	0	0
Subdural haematoma	0	0	1 (1.0)	0
Subdural haemorrhage	1 (1.6)	0	0	0
Accidents and injuries (SMQ)	7 (10.9)	16 (15.0)	13 (13.5)	6 (25.0)
Fall	2 (3.1)	6 (5.6)	6 (6.3)	3 (12.5)
Cardiac disorders	3 (4.7)	6 (5.6)	14 (14.6)	4 (16.7)
Cardiac arrythmias (atrial fibrillations)	3 (4.7)	5 (4.7)	9 (9.4)	2 (8.3)
Heart failures	0	0	2 (2.1)	2 (8.3)
Vascular disorders	10 (15.6)	13 (12.1)	14 (14.6)	2 (8.3)
Infections and infestations	21 (32.8)	50 (46.7)	37 (38.5)	9 (37.5)
Anticholinergic syndrome	0	1 (0.9)	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	11 (17.2)	24 (22.4)	13 (13.5)	6 (25.0)
Other AE appearing more frequently in older patients				
Fracture	4 (6.3)	10 (9.3)	3 (3.1)	3 (12.5)

Source: Updated SCS, DCO 01 February 2021, Table 54 (Table 12.6.27.1.2.1, 12.1.2.1, 12.9.1.1, 12.9.1.2, 12.9.1.3, 12.9.1.4, 12.9.1.5, 12.9.2.1, 12.9.3.1, 12.9.5.1, 12.9.6.1, and 12.9.4.1)

Trends of increased frequencies of serious adverse events and TEAEs leading to discontinuation, accidents and injuries, and cardiac disorders with increased age are noted, as may be expected due to age-related comorbidity and frailty, which may also cause increased sensitivity to adverse reactions. Causality assessment is generally difficult due to the single-arm study design.

Ethnicity/Race

In VISION Cohorts A + C, most patients were White (191 (65.6%) and 88 (30.2%) patients were Asian. Race was unknown in 8 (2.7%) patients, and in 4 (1.4%) patients, race was "other"

The proportion of TEAE categories reported were generally consistent between Asian and White patients. (Source: Updated SCS, DCO 01 February 2021, Table 12.6.27.1.3.1, not shown)

Differences between White and Asian patients in frequencies of ≥ 10% or a doubling in events by PT or medical concepts were however noted for the following:

Asian > White:

Creatinine increased (medical concept):	Asian: 34 (38.6%);	White: 44 (23.0%)
Blood creatinine increased:	Asian: 34 (38.6%);	White: 41 (21.5%)
Diarrhoea:	Asian: 32 (36.4%);	White: 48 (25.1)
ALT and/or AST increase (composite term)	Asian: 19 (21.6%);	White: 20 (10.5%)
GGT increased	Asian: 13 (14.8%);	White: 6 (3.1%)

In Asian patients a small numerical imbalance was observed for electrocardiogram QT prolonged (5; 5.7%) when comparing to White patients (4; 2.1% [3 patients with Electrocardiogram QT prolonged and 1 patient with Long QT syndrome]). Similarly, decreases in white blood cell count, lymphocyte count and platelet count were slightly more frequent in Asian patients (6.8%, 3.4% and 5.7%) than in White patients (1.0%, 0%, 1.0%).

White > Asian:

Oedema (medical concept):	Asian: 56 (63.6%);	White: 159 (83.2%)
Nausea:	Asian: 13 (14.8%);	White: 72 (37.7%)
Dyspnoea:	Asian: 4 (4.5%);	White: 56 (29.3%)
Cough	Asian: 7 (8.0%);	White: 32 (16.8%)
Pleural effusion:	Asian: 7 (8.0%);	White: 31 (16.2%)

In White patients a small numerical imbalance was observed for pulmonary embolism (9; 4.7%) when comparing to Asian patients (1; 1.1%). Also, in White patients hypokalaemia, weight decreased and protein total decreased were slightly more frequent (6.8%, 5.2% and 4.7%) than in Asian patients (3.4%, 2.3% and 1.1%)

In the POOL, 280 (57.9%) patients were White and 164 (33.9%) patients were Asian. Race was unknown in 32 (6.6%) patients and 8 (1.7%) patients' race was "other".

Reported TEAE proportions were generally consistent between Asian and White patients with a ≥10% cut off or doubling incidence.

In summary, notable differences in AE frequencies between Asian and White patients were observed. Whether these represent true differences in toxicity by ethnic group or reflect other circumstances is not possible to know, but no mechanisms have been proposed.

ECOG Status

In VISION Cohorts A + C, most patients had an ECOG status ≥ 1 at Baseline (77 [26.5%] patients had ECOG status 0 and 214 [73.5%] patients had ECOG ≥ 1. Inclusion criteria for this study allowed patients with ECOG status 0 or 1.

The proportion of patients reporting TEAEs were generally consistent between patients in both groups, except for the serious TEAEs which were more frequent in patients with ECOG status ≥ 1 (108; 50.5%

patients) than in patients with ECOG status 0 (30; 39% patients). Among patients with ECOG ≥ 1 no events or medical concepts have been identified with TEAEs frequency ≥ 10% higher than that in patients with ECOG status 0. A small numerical imbalance in ECOG ≥ 1 group was observed for anaemia, hypotension, conjunctivitis and pulmonary embolism (13.1%, 6.5%, 5.1% and 4.7% patients, respectively) when compared to ECOG 0 group (3.9%, 2.6%, 0% and 1.3% patients, respectively).

In the POOL, most patients had an ECOG status ≥ 1 at baseline (303 [67.6%] patients had ECOG status ≥ 1 and 145 [32.4%] patients had ECOG 0).

The proportion of patients reporting TEAEs were generally consistent between patients in patients with ECOG performance status 0 and 1. Higher incidences were reported in patients with ECOG status ≥1 compared with ECOG 0 for Grade ≥ 3, serious, and fatal events.

Body Mass Index

Body mass index (BMI) in kilograms per square meter was defined as underweight (< 18.5), normal (≥ 18.5 to < 25), overweight (≥ 25 to < 30), and obese (≥ 30).

In VISION Cohorts A + C, patient numbers in these categories were as follows: Underweight: 16 (5.5%) patients; Normal: 165 (56.7%) patients; Overweight: 82 (28.2%) patients; Obese: 22 (7.6%) patients; BMI missing: 6 (2.1%) patients.

In VISION Cohorts A + C, differences among weight categories (notably Obese and Underweight compared to normal weight) in event frequency of ≥ 20% or a doubling in frequency for events by PT have been noted for arthralgia and fall, with increasing incidence in heavier patients, and for oedema (see below).

Oedema (medical concept):

Underweight:	10 (62.5%) patients
Normal:	120 (72.7%) patients
Overweight:	70 (85.4%) patients
Obese:	21 (95.5%) patients

Associations with weight category were also observed for frequencies of Fall and Renal failure, acute and chronic, (medical concept).

In the POOL, there was no obvious association of BMI with TEAEs, included medical concepts, or event categories.

Renal Function Based on GFR

Renal function based on eGFR at baseline (mL/min/1.73 m2) was defined as: normal (eGFR ≥ 90), mild (eGFR ≥ 60 and < 90), moderate (eGFR ≥ 30 and < 60), and severe (eGFR < 30). Of note, creatinine increase is an ADR for tepotinib and does not always reflect a true renal injury. GFR has been estimated based on creatinine values in tepotinib studies.

In VISION Cohorts A + C, patient numbers in these categories were as follows:

Normal renal function: 62 (21.3%) patients
Mild renal impairment: 136 (46.7%) patients
Moderate renal impairment: 87 (29.9%) patients
Severe: 0

Missing: 6 (2.1%) patients

As expected, a trend for higher reporting rates of creatinine increased (medical concept) was observed with increasing severity of renal impairment. Increased creatinine was more often reported in patients with moderate renal impairment (41.4%), compared to the two other groups (12.9% and 25.0%, respectively).

2.6.8.5. Immunological events

A TEAE of PT Drug hypersensitivity was reported in 1 patient (0.7%) in VISION cohorts A + C, and 1 (i.e., the same) patients (0.3%) in the POOL. In addition, the PT Hypersensitivity was reported in 2 patients in both VISION A+C (1.4%) and POOL (1.1%). There was 1 treatment-related TEAE in the Immune system SOC, PT Hypersensitivity, the same patient in VISION A+C (0.3%) and POOL (0.2%). There was no indication of hypersensitivity reactions being an ADR of tepotinib.

2.6.8.6. Safety related to drug-drug interactions and other interactions

See assessment above in the section on **Dose – exposure – response**, with regard to safety using supratherapeutic dosing in Study 001, of potential relevance to situations with increased exposure, such us drug-drug interactions.

2.6.8.7. Discontinuation due to adverse events

Permanent treatment discontinuations due to TEAEs occurred in 69 patients (24%) in VISION Cohort A + C and in 112 patients (23%) in the POOL.

Permanent treatment discontinuations due to treatment-related TEAEs occurred in 41 patients (14%) in VISION Cohort A + C and in 51 patients (11%) in the POOL (Table 34).

Table 57: TEAEs Leading to Permanent Treatment Discontinuation by SOC and PT (≥ 1% of Patients by PT)

	Tepotinib 500 mg QD – SAF	
SOC **PT**	**VISION Cohorts A + C (N=291) n (%)**	**POOL (N=484) n (%)**
Any TEAEs		
Patients with at least 1 TEAE leading to permanent treatment discontinuation	**69 (23.7)**	**112 (23.1)**
General disorders and administration site conditions	30 (10.3)	47 (9.7)
Oedema peripheral	13 (4.5)	20 (4.1)
Disease progression	4 (1.4)	9 (1.9)
General physical health deterioration	4 (1.4)	5 (1.0)
Oedema	3 (1.0)	3 (0.6)
Respiratory, thoracic and mediastinal disorders	17 (5.8)	19 (3.9)
Pleural effusion	5 (1.7)	5 (1.0)
Interstitial lung disease	3 (1.0)	3 (0.6)
Pneumonitis	3 (1.0)	3 (0.6)
Gastrointestinal disorders	4 (1.4)	15 (3.1)
Ascites	0 (0.0)	6 (1.2)
Reproductive system and breast disorders	4 (1.4)	4 (0.8)

SOC PT	Tepotinib 500 mg QD – SAF VISION Cohorts A + C (N=291) n (%)	 POOL (N=484) n (%)
Oedema genital	3 (1.0)	3 (0.6)
Treatment-related TEAEs		
Patients with at least 1 TEAE leading to permanent treatment discontinuation	41 (14.1)	55 (11.4)
General disorders and administration site conditions	21 (7.2)	29 (6.0)
Oedema peripheral	13 (4.5)	20 (4.1)
Oedema	3 (1.0)	3 (0.6)
Respiratory, thoracic and mediastinal disorders	13 (4.5)	13 (2.7)
Interstitial lung disease	3 (1.0)	3 (0.6)
Pleural effusion	3 (1.0)	3 (0.6)
Pneumonitis	3 (1.0)	3 (0.6)

SAF=safety analysis set; TEAE=treatment-emergent adverse event.

Source: Updated SCS, DCO 01 February 2021, Table 19 (Tables 12.6.13.1 and 12.6.14.1.)

Adverse Events Leading to Dose Interruption

Per protocol, temporary discontinuation of treatment (i.e., dose interruption) was allowed for up to 21 days. TEAEs that led to temporary treatment discontinuation affected 143 patients (49 %) in VISION Cohorts A + C and 206 patients (43%) in the POOL. The most common adverse reactions leading to temporary discontinuation in ≥ 2% of patients are peripheral oedema (18.6%), increase in creatinine (5.8%), generalised oedema (3.8%), oedema (3.8%), increase in ALT (2.7%), nausea (2.7%) and increase in amylase (2.1%).

Adverse Events Leading to Dose Reduction

TEAEs that required a dose reduction were experienced by 99 patients (34%) in VISION Cohorts A + C and in 126 patients (26%) in the POOL. The most common adverse reactions leading to dose reduction in ≥ 2% of patients are peripheral oedema (15.1%), increase in creatinine (3.1%), generalised oedema (2.7%) and oedema (2.4%).

2.6.8.8. Post marketing experience

Tepotinib received its first marketing approval in Japan on 25 March 2020 and is currently authorized in 2 countries (Japan and the US). Tepotinib is currently available to patients in Japan only via a post-marketing noninterventional study (MS200095-0045). In the US, tepotinib became available to patients on 04 February 2021. Cumulatively, 52,920 tablets have been sold in both countries. In the post-marketing setting in Japan, an estimated 216 patients have been treated cumulatively until 24 March 2021.

Cumulatively, up to 24 March 2021, **ILD** has been reported in 9 patients in the post-marketing setting. All 9 cases were received from Japan and the patients had received tepotinib for the treatment of NSCLC. Drug-induced ILD tends to be more frequently reported in Japanese patients. This observation has been particularly prominent since the approval of EGFR inhibitors in treatment of NSCLC.

Seven events (in 6 cases) of **pleural effusion** consisting of the PTs Pleural effusion (5 events), Malignant pleural effusion (1 event), and Infectious pleural effusion (1 event) have been received. Two of the 7 events were considered related to tepotinib by the reporting physician. In all cases, the

progressive nature of the underlying cancer disease and infection in the case of infectious pleural effusion contributed to the event. There is insufficient evidence to confirm a causal association with tepotinib treatment.

No events of relevance for **QT interval prolongation** or **severe hepatotoxicity** have been received from post-marketing sources.

Overall, the post-marketing data in this period do not alter the known safety profile of tepotinib.

2.6.9. Discussion on clinical safety

Introduction

Tepotinib is a selective MET inhibitor and shares some safety issues with previously EU approved products that inhibit MET as part of their mechanism of action, XALKORI (crizotinib), Cometriq and CABOMETYX (both cabozantinib). Such common adverse reactions may represent class effects and include oedema and liver enzyme elevations (observed for both approved substances), and hypoalbuminaemia (observed for cabozantinib). These events also constitute adverse drug reactions (ADRs) for FDA-approved MET inhibitor TABRECTA (capmatinib). Non-clinical studies have identified the liver/hepatobiliary system as target organ of tepotinib toxicity. In addition, elevated pancreatic enzymes are identified reactions of capmatinib and is suggested by the applicant to potentially be a class effect. Furthermore, interstitial lung disease (ILD) is a labelled reaction for both crizotinib and capmatinib, noting that these drugs are both indicated for treatment of lung cancer, unlike cabozantinib, which does not share this ADR.

Safety data base

The tepotinib clinical development program included 922 participants treated with tepotinib at different doses and regimens, of whom 315 were NSCLC patients included in the Phase 2 VISION monotherapy study, 291 of whom represent the sought indication of non-small cell lung cancer (NSCLC) with MET exon 14 (METex14) skipping alterations. The safety population in the target population is considered relatively small.

The pooled safety population ("POOL") consists of 484 patients who received treatment at the intended dose and regimen for approval, monotherapy tepotinib 500 mg (450 mg free base) daily. The POOL includes a total of 315 (65%) patients with NSCLC, including those with MET amplification. In addition, 121 (25%) patients with hepatocellular carcinoma (HCC) and 48 patients from studies of mixed advanced late line solid tumours are included.

Study design

The single-arm design of the main (pivotal for approval) study hampers causality assessment. The investigators' causality assessments will be affected by the current knowledge (or lack thereof) of the drug's safety profile.

Exposure

The median duration of exposure to tepotinib in the pivotal safety population of VISION cohorts A + C was 6.3 months. This is considered short from a safety assessment perspective, in light of the reported median duration of response of over 13 months in the ITT population of Cohort A. The median duration of exposure in the POOL was 4.3 months. Only 76 patients in the POOL (including 63 patients from VISION) had a tepotinib exposure longer than 12 months. Further analyses to better delineate the safety profile in responding patients showed that the frequencies of many AEs clearly increased with exposure time, as may generally be expected. For some, such as oedema, a pattern that may suggest

cumulative toxicity was observed. Others showed only a weak increase that may be more related to the longer observation period itself allowing more events to be captured. (Table 38)

Safety findings

The TEAE frequencies in the POOL were mostly very similar to VISION cohorts A+C, as may be expected given the large proportion of lung cancer patients from VISION (65%). A few exceptions were noted that are likely reflective of the underlying disease of HCC in 25% of the POOL. These TEAEs concerned liver function laboratory aberrations and TEAEs, and ascites.

The Exposure-Adjusted TEAE Incidence Rates (EAIRs) were also overall similar in the VISION cohorts A+C and the POOL. Given the high degree of consistency in safety between the pivotal safety population, VISION cohorts A+C, and the POOL, the focus of this discussion will be on the former.

Two different data cut-offs (DCOs) have been submitted during review, 01 July 2020 and 01 February 2021. Data from the latter DCO is presented below.

VISION cohorts A and C

In VISION cohorts A+C, 49% of patients had TEAEs leading to dose interruption (temporary discontinuation), 34% had TEAE leading to dose reduction, 24% had TEAE leading to permanent treatment discontinuation, while 14% had a TEAE considered to be study drug-related leading to permanent treatment discontinuation. The pattern of common dosing adjustments and discontinuations due to adverse events reflects the degree of experienced tolerability but also laboratory abnormalities requiring dosing adjustments.

Apart from disease progression, the TEAEs causing permanent treatment discontinuation were peripheral oedema and pleural effusion.

In VISION Cohorts A+C, the most common adverse reactions in ≥ 20% of exposed to tepotinib at the recommended dose in the target indication are oedema (77.3% of patients), mainly peripheral oedema (65.6%), nausea (30.2%), hypoalbuminaemia (28.5%), diarrhoea (27.8%) and increase in creatinine (27.1%).

The most commonly observed (in ≥2% of patients) NCI CTCTAE Grade ≥ 3 TEAEs, apart from disease progression and general physical health deterioration, were peripheral oedema (11%), hypoalbuminaemia (5.8%), pleural effusion (4.1%), pneumonia (3.8%), lipase increased (3.8%), amylase increased (3.4%), hyponatraemia (3.4%), anaemia (all 3.1%), ALT increased (2.7%), dyspnoea (2.4%), pulmonary embolism (2.4%), and generalised oedema (2.1%). It is noted that, unlike the all-grade TEAE frequencies, gastrointestinal TEAEs were not prominent among Grade ≥ 3 TEAEs.

The most common serious adverse reactions in ≥ 1% of patients are peripheral oedema (3.1%), generalised oedema (2.1%) and ILD (1.4%).

TEAEs leading to death were observed in 12% of patients in both VISION cohorts A +C and the POOL. Five patients in the POOL (3 patients in VISION and 2 patients in other studies) had TEAEs leading to death that were considered treatment-related. Two cases in VISION cohort A are noted of interest, one with acute hepatic failure fulfilling Hy's law for drug- induced liver injury, and one with ILD or an ILD-like reaction.

Specific reactions

Oedema (77%) occur early during treatment (median time to onset 9 weeks) and, apparently, at low exposures. Severe oedema events were common (9.5%) and peripheral oedema was the most common cause for permanent treatment discontinuation (7.2%). Resolution rates were low (13%) and

time to resolution long (485 days in VISION A+C, 344 days in POOL). A pattern of cumulative toxicity was noted for oedema.
As noted in the PK section, in model-based analysis, tepotinib exposure did not have a significant impact on the hazard of first occurrence of peripheral oedema. Advanced age was associated with an increase in the risk of developing oedema independent of exposure.
In view of possible risk minimisation, the applicant analysed in a response to question, groups of patients with grade 2 and grade 3 oedema, respectively, and found that prior dose reduction did not seem to prevent grade 3 oedema reactions and concluded that an earlier dose reduction was unlikely to would enhance risk minimization. Subgroup analysis did not reveal likely meaningful risk factors for oedema. In addition, a review of the individual patient data did not indicate that severe oedema coincided with lowest albumin values on-treatment, nor was there any apparent link with sodium levels. Therefore, no further risk minimisation was considered possible.

Further characterisation is warranted with regard to the mechanism for oedemas, their resolution and of severe cases. Oedema events have been reported for several MET inhibitors across several indications. Moreover, based on in vitro data, expression of MET in vascular and lymphatic endothelial tissue could provide a mechanism for MET inhibition to cause oedema. HGF also increases expression of angiogenic mediators, including VEGF and its receptor, in endothelial cells and that both ligands act synergistically (Shojaei 2010; You 2008; Hack 2014). Other selective MET inhibitors in development were associated with oedema events, suggesting a class effect.
A treatment-related fatal AE of dyspnoea was due to respiratory failure, initially reported as generalised oedema with pulmonary oedema occurring in another hospital, but this was not confirmed. The limited experience of this type of drug reaction in general and of tepotinib in particular, the common frequency of both severe and serious events of oedema, and the lack of possible preventive measures suggest that additional information to further characterise these events is still needed, thus severe oedema will be followed as an Important identified risk in the RMP.

The applicant considered pleural effusion (13%) an Important potential risk of tepotinib. The causality assessment is hampered due to the single-arm trial (SAT), as pleural effusion is a common comorbidity in patients with NSCLC. Pleural effusion was observed at similar frequencies in both safety populations and could hypothetically be due to a similar mechanism as oedema. In the 13 cases from the POOL not coming from the VISION study, confounding factors were identified in all cases, including baseline pleural effusion or lung metastasis, lymph vascular invasion, concomitant ascites and or liver cirrhosis in HCC patients; and the events were considered unrelated to study drug by the investigator in 12/13. Pleural effusion is presently not considered an ADR but is an important potential risk of tepotinib.

Interstitial lung disease or ILD-like events (including also acute respiratory failure, pneumonitis disease) was reported in 11 patients (3.8%) in VISION A+C. Adjudication was performed by an expert panel where 3 cases were discarded due to other more likely causes. Thus, the ILD frequency is 2.7% (8/291) in the ADR list in the SmPC. ILD is included as an Important identified risk in the RMP. Patients should be monitored for pulmonary symptoms indicative for ILD-like reactions. Tepotinib should be withheld and patients should be promptly investigated for alternative diagnosis or specific aetiology of interstitial lung disease. Tepotinib must be permanently discontinued if interstitial lung disease is confirmed and the patient be treated appropriately (see section 4.4 of the SmPC).

QT interval prolongation
A concentration-dependent increase in QTc interval was observed in the concentration-QTc analysis. At the recommended dose, no large mean increases in QTc (i.e. > 20 ms) were detected in patients with various solid tumours. The QTc effect of tepotinib at supratherapeutic exposures has not been evaluated. One patient in the POOL had normal electrolyte values and positive dechallenge and rechallenge. TEAEs of QTc prolongation were furthermore reported in 4 patients in VISION cohorts A+C without clear alternative explanations for these QTc effects; 2 of the patients had more than one

episode. QTc-prolongation is therefore considered an established ADR of tepotinib and included as an Important identified risk in the RMP. In patients at risk of developing QTc prolongation, including patients with known electrolyte disturbances or taking concomitant medicinal products known to have QTc prolongation effects, monitoring is recommended as clinically indicated (e.g. ECG, electrolytes).

Gastrointestinal toxicity TEAEs were among the most commonly reported in VISION cohorts A+C with nausea (30%), diarrhoea (28%) and vomiting (14%). Median time to onset of diarrhoea was 2.4 weeks, for nausea 6.5 weeks and for vomiting 7.0 weeks. These TEAEs were severe (grade ≥3) in less than 0.3% of patients for diarrhoea and 1.0% for nausea and vomiting. They were the cause for permanent treatment discontinuation in single cases (2 nausea, 1 diarrhoea, 0 vomiting), caused temporary discontinuation in 2.7% of patients for nausea, 1.7% for diarrhoea and 1.4% for vomiting, and dose reduction in single cases (3 nausea, 0 diarrhoea, 0 vomiting). Thus, despite the high frequency of gastrointestinal toxicity, it does not appear to impact importantly on tolerability.

Hepatotoxicity, including transaminase elevations, is a well-known reaction to MET-inhibitors and the liver/hepatobiliary system was identified as target organ of toxicity of tepotinib in non-clinical studies.

Increase in ALT and/or AST have been reported in patients who received tepotinib monotherapy at the recommended dose regimen. At this point, a causal relationship between tepotinib and GGT increase or bilirubin increase is not clearly established despite a handful of cases with no obvious confounding factor. Further data is thus awaited in the context of routine pharmacovigilance, before the possible conclusion of an ADR. Severe hepatotoxicity will be followed as an Important potential risk, and causality for these events may be captured in cases that may arise.

A case of acute hepatic failure occurred in the pivotal study beginning on Day 22 of tepotinib treatment in a liver-healthy individual apparently without confounding factors and fulfilling Hy's law criteria for drug-induced liver injury. Nine additional patients in the POOL met Hy's Law laboratory criteria but had confounding causes, including the disease under treatment – hepatocellular carcinoma. Due to the single case and remaining uncertainties of causality, severe hepatotoxicity has been included in the RMP as an Important potential risk. Liver enzymes (ALT and AST) and bilirubin should be monitored prior to the start of Tepmetko treatment and thereafter as clinically indicated. If grade 3 or higher increases (ALT and/or AST greater than 5 times ULN) occur, dose adjustment or discontinuation is recommended (see sections 4.2, 4.4 and 4.8 of the SmPC).

Hepatobiliary toxicity TEAEs, as defined by SMQ: Drug related hepatic disorders - comprehensive search, occurred in 41% of patients in VISION cohorts A+C. This included hypoalbuminaemia (28%) as the most frequent PT, which may likely not represent hepatic toxicity when it comes to MET-inhibitors.

Decreased albumin laboratory values were recorded in 87% of patients, with grade ≥ 3 low albumin values in 8.2%. Any grade hypoalbuminaemia was reported as TEAE in 28%. There were no indications that hypoalbuminemia is secondary to renal loss of albumin or to liver dysfunction. Low albumin correlated with increased risk of oedema but did not fully explain it. The underlying mechanism of albumin decreases under treatment with MET inhibitors is not fully understood. Hypoalbuminemia has been reported for other MET inhibitors (Wu 2018; Spigel 2017) and may represent a potential class effect. Hypoalbuminemia is an identified risk of tepotinib.

High creatinine laboratory values were recorded in 63% of patients and were reported as TEAE in 27%. The short median time to onset of 3.1 weeks and the low frequency (less than 1%) of grade ≥ 3 elevations are consistent with inhibition of the renal transporters OCT2 or MATE being the main cause for these events rather than renal injury. Other abnormal renal function test parameters may likely be secondary to rise in serum creatinine and to impairment of hemodynamic stability due to oedema and hypoalbuminaemia, rather than suggesting an intrinsic direct toxicity of tepotinib on renal function.

Subgroups

Elderly patients (≥ 65 years of age) constituted 78% of the VISION cohorts A+C. A large proportion, 41%, of patients treated with tepotinib in VISION cohorts A+C were ≥ 75 years old, while only 8% (24 patients) were ≥ 85 years old. The occurrence of grade ≥ 3 events increased with age. Treatment-related serious events were more frequent in patients aged ≥ 75 years and < 85 years (19.8%) or those aged ≥ 85 years (20.8%) when compared to those younger than 65 years (7.8%), although this comparison is limited by the small sample size in patients aged ≥ 85 years (see section 4.8 of the SmPC).

Safety and efficacy of tepotinib in paediatric patients below 18 years of age have not been established. No data are available.

Notable differences in AE frequencies between Asian and White patients were observed. Whether these represent true differences in toxicity by ethnic group or reflect other circumstances cannot be determined based on the currently presented data, but no mechanisms have been proposed.

An apparent impact of body mass index (BMI) on the occurrence of oedema was noted: underweight (BMI< 18.5): 62.5%, normal (BMI ≥ 18.5 to < 25): 73%, overweight (BMI ≥ 25 to < 30): 85%, and obese (BMI ≥ 30): 95.5%.

The applicant presented TEAE overviews for the subsets of liquid biopsy positive (L+) and tissue biopsy positive (T+) patients in the VISION study. There seem to be no mechanistic reason to assume differential safety profiles depending T+ or L+ detection method, and there was no indication of any important differences across TEAEs categories.

There are no clinical data on the use of tepotinib in pregnant women. Studies in animals have shown teratogenicity. Based on the mechanism of action and findings in animals tepotinib can cause foetal harm when administered to pregnant women. Tepotinib should not be used during pregnancy, unless the clinical condition of the woman requires treatment with tepotinib. Women of childbearing potential or male patients with female partners of childbearing potential should be advised of the potential risk to a foetus (see sections 4.6 and 5.3 of the SmPC)

There are no data regarding the secretion of tepotinib or its metabolites in human milk or its effects on the breast-fed child or milk production. Breast-feeding should be discontinued during treatment with tepotinib and for at least 1 week after the last dose.

Tepotinib has been investigated at doses up to 1 261 mg, but experience with doses higher than the recommended therapeutic dose is limited.

The symptoms of overdose are expected to be in the range of known adverse reactions. There is no specific antidote for tepotinib. Treatment of overdose is directed to symptoms (see sections 4.7 and 4.8 of the SmPC).

Tepotinib contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional expert consultations

Input of the SAG-Oncology has been requested. On the meeting of the 3rd of November 2021, the conclusions of the SAG-O were as follows:

1. **Is the observed safety profile of Tepmetko acceptable for use in first line NSCLC**

The SAG agreed that tepotinib was associated with an acceptable safety profile that is consistent with the safety profile of some targeted therapies in this setting. A number of toxicities, including oedema, will require careful management and minimisation measures to be optimised.

2.6.10. Conclusions on the clinical safety

The tepotinib safety profile is dominated by MET inhibitor class effects and other toxicity commonly observed with TKI treatment. Oedema is the most prominent toxicity of tepotinib, observed in 77% of patients, including severe reactions and with peripheral oedema being the most frequent cause for permanent treatment discontinuations. Similar to approved tyrosine kinase inhibitors, a large proportion of patients experienced gastrointestinal symptoms with short time to onset, mostly mild-moderate. These did not seem to impact on tolerability as understood from dosing interruptions, reductions, and permanent discontinuations to any important extent, however. Dosing adjustments due to TEAEs and permanent discontinuations due to TEAEs were frequent, however, reflecting tolerability and laboratory abnormalities.

Severe, single cases with fatal reactions involving ILD/ILD-like reaction and hepatotoxicity also impact on the B/R balance to some degree.

2.7. Risk Management Plan

Safety concerns

Table 58. Summary of the Safety Concerns

Summary of the safety concerns	
Important identified risks	Interstitial lung disease QT interval prolongation Severe oedema
Important potential risks	Pleural effusion Severe hepatotoxicity
Missing information	None

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient to characterise the safety concerns.

Risk minimisation measures

Table 59. Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Routine risk minimization activities
Interstitial lung disease (Important identified risk)	Routine risk communication: • *SmPC Sections 4.2,4.4, and 4.8* • *Package leaflet (PL) Sections 2 and 4*

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: • *Advice to withhold or discontinue tepotinib if patients develop pulmonary symptoms indicative of ILD-like reactions in SmPC Section 4.2.* • *Recommendation to monitor for pulmonary symptoms indicative of ILD-like reactions, to promptly investigate, to treat patients and to permanently discontinue tepotinib if ILD is confirmed in SmPC Section 4.4.* Other routine risk minimization measures beyond the Product Information: • *Legal status: subject to medical prescription*
QT interval prolongation (Important identified risk)	Routine risk communication: • *SmPC Section 4.4 and 4.8* • *Package leaflet Sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: • *Recommendation for monitoring (e.g., ECG, electrolytes) in patients at risk of developing QTc prolongation in SmPC Section 4.4.* Other routine risk minimization measures beyond the Product Information: *Legal status: subject to medical prescription*
Severe Oedema (Important identified risk)	Routine risk communication: • *SmPC Section 4.8* • *Package leaflet Section 4* Routine risk minimization activities recommending specific clinical measures to address the risk: • *Advice to reduce the dose, interrupt or discontinue tepotinib treatment if patients develop grade 3 events or higher in SmPC Section 4.2.* Other routine risk minimization measures beyond the Product Information: *Legal status: subject to medical prescription*
Pleural effusion (Important potential risk)	Routine risk communication: • *None.* Routine risk minimization activities recommending specific clinical measures to address the risk: • *None.* Other routine risk minimization measures beyond the Product Information: *Legal status: subject to medical prescription*

Safety concern	Routine risk minimization activities
Severe hepatotoxicity (Important potential risk)	Routine risk communication: • *SmPC Sections 4.2, 4.4 and 4.8* • *Package leaflet Sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: • *Recommendation to monitor for liver enzymes (ALT and AST), and bilirubin before and during treatment in SmPC section 4.4.* • *Advice to reduce the dose, interrupt or discontinue tepotinib treatment if patients develop grade 3 events or higher (ALT and/or AST greater than 5 times ULN) in SmPC Section 4.2.* Other routine risk minimization measures beyond the Product Information: *Legal status: subject to medical prescription*

Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. 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 25.03.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. 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.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tepmetko (tepotinib) 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;
- It is approved under a conditional marketing authorisation [REG Art 14-a]

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.>

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication is: Tepmetko as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

3.1.2. Available therapies and unmet medical need

For advanced NSCLC (typically nonresectable stage IIIB and stage IV), cure is not expected due to the extension of disease, and systemic treatments are administered with the aims of mitigating symptoms and extending lifespan.

The advent of immune therapy has reshaped the first-line advanced treatment landscape. Combinations of PD-1/PD-L1/CTLA-4 directed therapies and platinum doublets have achieved ORRs in the 40%-55% range, DoRs of 8-13 months, and notably OS medians of frequently 20+ months (14-30). For patients with ≥ 50% PD-L1 expression, pembrolizumab monotherapy is an option, with similar outcomes.

Second line options include checkpoint inhibitors and docetaxel/ramicirumab-docetaxel with ORRs of 14% -23%, DORs of 16-19 months (longer for pembrolizumab in PD-L1 ≥ 1%; KEYNOTE-010), and OS medians of about 12 months, and platinum doublets for patients who received checkpoint-inhibitor monotherapy first line.

Approximately 3% of NSCLCs harbour MET exon 14 (METex14) skipping alterations, leading to a truncated MET receptor lacking the exon 14 encoded sequences (Network Tcgar, Nature, 2014). Deletion (i.e., skipping of exon 14) results in oncogenic activation of MET by expression of a truncated receptor with increased stability, as well as augmented and prolonged signalling capability, seemingly turning MET into an oncogenic driver (Cortot 2017). Currently, there is no available treatment option that specifically targets advanced NSCLC harboring METex14 skipping alterations. The median OS of METex14 NSCLC patients who never received a MET inhibitor was reported to be in the range of 8 to 11 months (Awad 2019, Wolf 2018). Furthermore, METex14 skipping alterations have been found to be most frequently reported in elderly patients (Schrock 2016, Awad 2019).

3.1.3. Main clinical studies

- The VISION study is the pivotal SAT supporting the MAA for tepotinib for the treatment of patients with advanced (locally advanced or metastatic) NSCLC harboring METex14 skipping alterations. This is an ongoing, global, open-label, single-arm Phase II study of orally dosed tepotinib 500 mg once daily.
- Prospective testing of MET exon 14 skipping mutations was performed centrally on circulating free DNA (cfDNA) obtained from plasma (LBx) with the use of next-generation sequencing (NGS) panel Guardant360® CDx Test Version 2.10 or by evaluating RNA obtained from fresh or archival (formalin-fixed, paraffin-embedded) tumour-biopsy tissue (TBx) with the use of the Oncomine Focus Assay.

- The VISION study comprises three NSCLC cohorts, for the A + C SAF-01 Nov 2020 patient set the numbers of included patients were 152 in cohort A (METex14 skipping alteration positive), 24 in Cohort B (MET amplification and negative for METex14 skipping alterations), 123 in Cohort C (METex14 skipping alteration positive, established to confirm the results of Cohort A).

Cohort A alone was initially considered pivotal in terms of efficacy by the applicant, as Cohort B is outside the proposed indication. Cohort C was considered confirmatory.

Please note that the dose of 500 mg tepotinib in this assessment report (based on tepotinib hydrochloride hydrate, the active ingredient) is the same as the recommended dose of Tepmetko in the SmPC, 450 mg daily (based on the active moiety, the free base of tepotinib).

3.2. Favourable effects

An efficacy update was provided during the procedure with a 01 February 2021 cut off, including patients who received their first tepotinib dose before 01 November 2020. The currently available data for cohort C were included in the initial pivotal data (cohort A):

- In the Cohorts A + C SAF-01 Nov 2020 population of 138 2L+ METex14 NSCLC, the overall response rate (ORR) was 44% (61/138; 95% CI: 36, 53) per RECIST Version 1.1, as determined by an independent review committee (IRC).
- In the same population the median duration of response (mDOR) was 11.1 months (95% CI: 8.4, 18.5).

3.3. Uncertainties and limitations about favourable effects

In view of the uncontrolled pivotal evidence supporting this application, the impact on PFS and OS is uncertain. The MAH is therefore recommended to conduct and submit the results of two non-interventional studies based on prospectively collected registry data. The planned prospective registry will be able to collect OS data from patients harbouring METex14 NSCLC mutations treated with standard of care or tepotinib. Registry data will be analysed in a non-interventional external control study to VISION, and a comparative effectiveness and safety study on tepotinib versus best available care.

3.4. Unfavourable effects

Tepotinib is a selective MET inhibitor and shares some safety issues with previously EU approved products that inhibit MET as part of their mechanism of action, Xalkori (crizotinib), Cometriq and Cabometyx (both cabozantinib). Such common adverse reactions may represent class effects and include oedema and liver enzyme elevations (observed for both approved substances), and hypoalbuminaemia (observed for cabozantinib). Non-clinical studies have identified the liver/hepatobiliary system as target organ of tepotinib toxicity. Furthermore, interstitial lung disease (ILD) is a labelled reaction for crizotinib.

The pivotal safety population consists of 291 patients in VISION cohorts A and C with NSCLC patients with tumours harbouring MET exon 14 skipping alterations, representative of the sought target population (01 February 2021 DCO).

In VISION cohorts A and C, 60% of patients had a severity grade ≥ 3. SAEs were reported in 47% of patients, with SAEs considered related to study drug in 14%. TEAEs leading to death were observed in 12% of patients, while study drug-related TEAEs leading to death were observed in < 1% (0.7 %).

The most commonly reported TEAEs in VISION cohorts A +C were oedema (77%), mainly peripheral oedema (66%), nausea (30%), and diarrhoea (28%).

Oedema TEAEs were severe (grade ≥3) in 13% of patients, nausea and diarrhoea in 1% or less.

ILD or ILD-like reactions were reported in 6 patients (2.7%), 1 case was fatal.

One case fulfilling Hy's law for drug- induced liver injury was observed, leading to death.

SAEs most commonly reported as treatment-related by investigators concerned pleural effusion (3.4%), peripheral oedema (2.7%) and generalised oedema (1.7%).

Both severe and serious events of oedema are common. The exact mechanism is not clear and there seem to be no possibility for preventive measures. The time to onset for oedema is short, the resolution rate low and the time to resolution is long (median 344-485 days), in need of further characterisation.

Based on an exposure-QTc analysis for the VISION study, a relationship between exposure and QTc-prolongation was observed at exposures that can be achieved in patients receiving the tepotinib dose 500 mg proposed for approval.

Reduced albumin laboratory values were recorded in 87% of patients, with grade ≥ 3 low albumin values in 8%. Any grade hypoalbuminaemia was reported as TEAE in 28%.

Liver enzymes ALT and AST as well as other liver function tests were elevated in a high proportion of tepotinib-treated patients. For both tests, grade ≥3 elevations occurred in less than 5% of patients. Alkaline phosphatase (ALP) was increased in 65% of patients (grade ≥3, 2.1%). Severe hepatotoxicity has been included in the RMP as an Important potential risk.

High creatinine laboratory values were recorded in 63% of patients and were reported as TEAE in 27%.

TEAEs lead to dose interruption (temporary discontinuation) in 49% of patients, dose reduction in 31%, and to permanent treatment discontinuation in 24%, while 14% of patients had a TEAE considered to be study drug-related that lead to permanent treatment discontinuation. Permanent discontinuations were due to oedema and pulmonary events.

Interstitial lung disease (ILD), QT interval prolongation and Severe oedema are included as Important identified risks, and Pleural effusion and Severe hepatotoxicity as Important potential risks in the RMP of tepotinib.

3.5. Uncertainties and limitations about unfavourable effects

The safety population in the target population of NSCLC with METex14 skipping alterations is relatively small, n = 291, and the single-arm study design hampers causality assessment.

The median duration of exposure to tepotinib in the pivotal safety population of VISION cohorts A + C was 6.4 months. This is considered short from a safety assessment perspective, in light of the reported median duration of response of 11-14 months. Further analyses to better delineate the safety profile in responding patients showed that the frequencies of many AEs clearly increased with exposure time, as may generally be expected. For some, such as oedema, a pattern of cumulative toxicity was observed.

3.6. Effects Table

Table 58: Effects Table for Tepmetko (tepotinib) in advanced NSCLC with METex14 skipping alterations (data cut-off: 01 February 2021)

Effect	Short Description	Unit	Treatment (tepotinib)	Uncertainties/ Strength of evidence /Comment
Favourable Effects **2L+ VISION population:** **Vision Cohorts A +C SAF-01 Feb 2021, n = 138 patients**				
ORR	Rate of RECIST 1.1. responses by independent review	%	44 (36, 53)	With certainty a drug effect. Of less clear clinical benefit than outcome measures possible to use in controlled trials.
DoR	Duration of response	Months	11.1 (8.4, 18.5)	Addresses clinical relevance of responses but is limited by relevance only for responders.
Unfavourable Effects (DCO 01 February 2021)				
TEAE Grade ≥ 3 Serious TEAE (SAE) TEAE leading to dose interruption TEAE leading to dose reduction TEAE leading to permanent discontinuation TEAE treatment-related leading to permanent discontinuation TEAEs leading to death TEAE treatment-related leading to death		%	60 47 49 31 24 14 12 <1	Percentage of patients with adverse event
Oedema Generalised oedema Hepatobiliary toxicity SMQ Nausea Diarrhoea Vomiting		%	77 5.8 41 30 28 14	
Laboratory abnormalities Albumin low Creatinine high ALP high ALT high AST high		%	 87 63 65 44 (grade ≥3: <5) 37 (grade ≥3: <5)	

Abbreviations: TEAE: treatment-emergent adverse event, SAE: treatment-emergent serious adverse event, SMQ: Standardised MedDRA query

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable effects

Efficacy as demonstrated by ORR and DoR is considered relevant and is expected to provide clinical benefit in adult patients with previously treated advanced non-small cell lung cancer (NSCLC)

harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping.

The CHMP considered that, in the absence of studies capable of isolating drug effects on PFS and OS, the activity of the drug in terms of ORR/DoR was not sufficiently high to establish the utility of tepotinib for first line use.

Unfavourable effects

The tepotinib safety profile is characterised by early and very frequent reactions of oedema (77%) and gastrointestinal reactions, mostly mild to moderate in severity. Severe reactions (≥ Grade 3) of oedema (13%) were common, impacting on the tolerability of the treatment and causing discontinuations. Hepatotoxicity is very frequently observed, with laboratory abnormalities for some liver enzymes at 35-60%, mostly mild-moderate, but require monitoring and resulted in dose reductions and delays. In addition, severe and fatal reactions involving ILD/ILD-like reactions and hepatotoxicity impact on the B/R balance.

Despite tolerability issues, tepotinib toxicity could overall be considered clinically manageable and acceptable in the proposed indication.

3.7.2. Balance of benefits and risks

The overall B/R of Tepmetko in the claimed indication for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping alterations is positive in 2L.

Further to the SAG responses, the CHMP acknowledged that according to the SAG-O majority the magnitude of ORR and DOR is such that a clinical benefit is considered likely and that tepotinib was associated with an acceptable safety profile that is consistent with the safety profile of some targeted therapies in this setting. However, for the first-line use, CHMP has also considered the limitations of the provided data from a single-arm trial, that selection bias cannot be ruled out, as well as uncertainties regarding long term efficacy outcomes.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

A conditional marketing authorisation was initially requested by the applicant. However, after the submission of confirmatory data from cohort C, the CHMP considered the dataset to be comprehensive in the sense of the CMA legislation. Therefore, a full marketing authorisation has been considered acceptable.

3.8. Conclusions

The overall benefit/risk balance of Tepmetko is positive, subject to the conditions stated in section 'Recommendations'.

Divergent position is appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Tepmetko is favourable in the following indication:

Tepmetko as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

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.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that tepotinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Appendix

1. Divergent position to the majority recommendation

APPENDIX

DIVERGENT POSITION DATED 16 December 2021

DIVERGENT POSITION DATED 16 December 2021

TEPMETKO EMEA/H/C/005524/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of TEPMETKO indicated for the following indication:

TEPMETKO as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

The reason for divergent opinion was the following:

Tepmetko has shown activity across different lines in a single-arm trial (SAT – VISION study). However, the dossier is not considered suitable for full approval. Since, the application is based on a SAT, evidence is less robust than in a randomised controlled trial (RCT) and selection bias cannot be ruled out. Even though the ORR and DOR results from Cohort A of the VISION study were replicated in Cohort C, these endpoints are not surrogate endpoints for OS and PFS in NSCLC. Available treatment options have established efficacy and safety in RCTs and shown OS and PFS benefits. Thus, a conditional marketing approval (CMA) would have been a more appropriate regulatory pathway for Tepmetko. Confirmatory data from a randomized clinical trial are considered necessary to address the above uncertainties.

CHMP Members expressing a divergent opinion:

Silvijus Abramavicius

Christophe Focke

Christian Gartner

Armando Genazzani

Ilko Getov

Agnes Gyurasics

Andrea Laslop

Outi Mäki-Ikola

Jan Müller-Berghaus

Sinan Bardakci Sarac

Ingrid Wang

Martina Weise