Amsterdam, 28 May 2020
EMA/CHMP/279665/2020
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Rayoqta

International non-proprietary name: abicipar pegol

Procedure No. EMEA/H/C/005103/0000

Note

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

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List of abbreviations

%	Percentage
2Q12	2 mg abicipar every 12th week
2Q8	2 mg abicipar every 8th week
ADAs	anti-drug-antibodies
AE	Adverse event
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
anti-PEGs	anti-PEG antibodies
API	Active Pharmaceutical Ingredient
APTC	Antiplatelet Trialist's Collaboration
ATC	Anatomical Therapeutic Chemical
BABs	anti-abicipar binding antibodies
BCVA	best corrected visual acuity
BDP	Bulk Drug Product
BDS	Bulk Drug Substance
BSA	bovine serum albumin
C. Monkey	Cynomolgus Monkey
ChNV	choroidal neovascularization
CI	confidence interval
CME	diabetic macular oedema
CMH	Cochran-Mantel-Haenszel
CNV	choroidal neovascularisation
CRC	central reading centre
CRS	clinical study report
CRT	central retinal thickness
CS	corticosteroids
DA	disc area
DARPin	designed ankyrin repeat protein
DR	deviation report
DS	drug substances
DSMC	data safety monitoring committee
DTT	Dithiothreitol
dVEGF	dog Vascular Endothelial Growth Factor
EC50	half-maximal effective concentration

EEA	European Economic Area
ELISA	enzyme-linked immuno-sorbent assay
EQ-5D	EuroQoL-5 Dimensions Questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
EtOH	Ethanol
FA	fluorescence angiography
Fab	antibody fragment
Fc	fragment crystallisable region of an immunoglobulin
Form	formulations
HCP	host cell protein
HPLC	High Performance liquid Chromatography
HRP	Horseradish Peroxidase
Hrs	hours
HUVEC	Human umbilical vein endothelial cells
hVEGF	human vascular endothelial growth factor
hVEGF165	human vascular endothelial growth factor splicing variant
IC50	Half maximal inhibitory concentration
IFU	Instructions for use
IgG	Immunoglobulin G
INN	International nonproprietary name
IOI	Intraocular inflammation
IOP	intraocular pressure
ISE	integrated summary of effectiveness
ITT	intention to treat
IVT	intravitreal
KD	equilibrium binding constant
kDa	kilo Dalton
KDR	kinase insert domain receptor (VEGFR2)
kon	optimal value of the association rate constant as determined by a non-linear fit of the theoretical curve to the kinetic data
LC	lesion complex
LOCF	last observation carried forward
LOQ	Limit of Quantification
Met	Methionin
MI	multiple imputation
mITT	modified intention to treat

MMRM	mixed-effect model for repeated measures
mPEG-mal	methoxy polyethylene glycol maleimide
MTD	maximum tolerated dose
MW	Molecular Weight
N terminus	Amino terminus of protein
n.a.	not applicable
n.d.	not detected
NABs	neutralising anti-abicipar antibodies
nAMD	neovascular AMD
NEI-VFQ-25¨	National Eye Institute Visual Functioning Questionnaire (25 questions)
OCT	optical coherence tomography
OD	optical density
p.o.	per os
PBS	phosphate buffer saline
PC	positive control
PDGF-AB	isoform AB of plateled-derived growth factor
PDT	photodynamic therapy
PEG	polyethylene glycol
PEG20	20’000 Da polyethylene glycol (of 20 kDa molecular weight)
PEGylated	Modified with polyethylene glycol
pi	Isolelectric point
PL	Patient Leaflet
pm	picomole (picomolar range)
POD	Peroxidase
PP	per protocol
PRN	pro re nata – as needed
ReAD	reoccurrence of active disease
RMP	Risk management plan
RPE	retinal pigment epithelium
Rpm	rounds per minute
rQ4	ranibizumab every 4th week
RT	room temperature
S/N	Signal to Noise
SAE	serious adverse event
SD-OCT	spectral domain optical coherence tomography
SmPC	Summary of Product Characteristics

SOC	standard-of-care
SOP	Standard operation procedure
SPR	Surface Plasmon Resonance
Std	Standard
sVEGFR1-Fc	soluble VEGF receptor1-Fc fusion protein
sVEGFR2-Fc	soluble VEGF receptor2-Fc fusion protein
TEAEs	treatment emergent adverse event
TMB	3,3',5,5' tetramethylbenzidine
VEGF	vascular endothelial growth factor
VEGF-A	vascular endothelial growth factor A (isoforms: 165a, 121a, 165b)
VEGFR1	VEGF receptor1 (Flt1)
VEGFR2	VEGF receptor2 (KDR)
w/o	without
Wet AMD	Neovascular Age-related Macular Degeneration

1. CHMP Recommendation

Based on the review of the data and the applicant's response to the CHMP LoQ on quality, safety, efficacy, the application for Rayoqta in the treatment of neovascular (wet) age-related macular degeneration (AMD),

is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the list of outstanding issues (Section V).

Questions to be posed to additional experts

Not applicable

Inspection issues

GMP inspection(s)

Not applicable

GCP inspection(s)

Not applicable

New active substance status

Based on the review of the data the active substance abicipar pegol contained in the medicinal product Rayoqta is considered to be qualified as a new active substance in itself.

Additional data exclusivity /Marketing protection

Not applicable

Similarity with authorised orphan medicinal products

Not applicable

Derogation(s) from market exclusivity

Not applicable

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Age-related macular degeneration (AMD) is a progressive degenerative macular disease attacking the region of highest visual acuity, the macula. Although the disease rarely results in complete blindness and peripheral vision may remain unaffected, central vision is gradually blurred, severely affecting ordinary daily activities.

AMD is classified as two different types: the non-exudative (or dry) form and the exudative (wet or neovascular) form. The dry form is the most prevalent, but it is not uncommon that the dry form develops into the wet form of AMD in which new choroidal vessels are developed. The latter form causes the worst incapacity and accounts for approximately 90 % of blindness in AMD. Neovascular AMD (nAMD) is characterised by the growth of abnormal blood vessels from the choroid into the sub-retinal pigment epithelium (RPE) space and the subretinal space. The newly formed choroidal vessels have a tendency to leak fluids and this results in the accumulation of sub- or intra-retinal fluids with subsequent separation of Bruch's membrane, RPE and retina. Fluid accumulation leads to retinal oedema and/or the formation of cystic spaces. Further, the choroidal neovascularisation (CNV) may grow through breaks of the membrane behind the retina, towards the macula, often lifting the retina and cause haemorrhage in the sub-retinal space. Eventually, the lesions may turn into scars resulting in a rapid destruction of the macula with severe and irreversible loss of central vision.

Abicipar pegol is indicated in adults for the treatment of neovascular (wet) AMD.

2.1.2. Epidemiology

AMD is the major cause of vision loss in the elderly population in the Western world. It is a disease occurring in elderly to very elderly patients and its prevalence increases steeply with age. Population-based epidemiologic studies have provided estimates of prevalence and incidence of AMD around the world and have shown that AMD is rare before 55 years of age and that it is more common in persons 75 years of age or older.

In the United States, the prevalence of AMD is estimated as 6.5% in adults 40 years and older. In Japan, the prevalence is estimated to approximately 11% from ages 35 to 74 years and in Europe, the prevalence of early AMD is approximately 3.5% at ages 55-59 years and 17.6% at ages $\geq$ 85 years. The dry form accounts for 80-90% of all AMD cases.

2.1.3. Aetiology and pathogenesis

AMD is a disease of the photoreceptors and RPE. In the aging eye, RPE function deteriorates due to genetic predisposition, light induced oxidative stress, and inflammation. In early AMD, lipid deposits (drusen) accumulate on the RPE and photoreceptors.

In early dry AMD, vascularisation is normal and typically, there are no associated symptoms, except blurred vision in some patients. In advanced stages of dry AMD, RPE cells degenerates with the subsequent development of geographic atrophy and a central scotoma.

Dry AMD may develop into wet AMD with CNV. CNV consists of abnormal, leaky blood vessels that grow through Bruch's membrane and leak lipids, fluids, and blood, resulting in oedema and elevation of the retina and consequent blurring and distortion of vision. CNV can be either occult or classic as visualised with fluorescein angiography (FA). Occult CNV is limited to the space beneath the RPE, and vision loss is milder relative to classic CNV, which may penetrate the RPE and grow into the subretinal space.

The process of angiogenesis is multi-factorial, but vascular endothelial growth factor (VEGF) is considered critical both in physiological and in pathological angiogenesis. Most of the severe vision loss due to advanced AMD is attributable to the development of CNV where pro-inflammatory and angiogenic cytokines, including VEGF, are upregulated. Even though overexpression of VEGF likely is not the sole factor behind AMD, elevated levels of VEGF have been found in pathological neovascularisation, both in experimental models and in AMD.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Early symptoms of nAMD tend to be vision changes such as blurred vision, metamorphopsia, and difficulty reading. One or both eyes may be affected. Symptoms gradually progress to loss of vision due to subretinal CNV bleeding. Central vision loss can progress rapidly and is irreversible. Without treatment, nAMD results in severe visual impairment with an average loss of around 4 lines of visual acuity within 2 years of disease onset.

Retinal abnormalities may be detected initially through ophthalmoscopic examination including stereoscopic examination of the retina. Definitive diagnosis requires further examinations such as FA and optical coherence tomography (OCT).

With FA, where sodium fluorescein is injected into the venous circulation, can be used to assess the leakage (fluids), pattern (classic or occult), location (extrafoveal, juxtafoveal, or subfoveal) and extent of CNV lesions.

OCT is a non-invasive method can be used to assess the effect of treatment over time. OCT allows visualization of 2-dimensional, high resolution cross sections of the retina by using differential reflections of light. OCT is used to assess retinal thickness and can be used to assess the presence of intraretinal, subretinal, or sub-RPE fluid.

2.1.5. Management

Currently available treatment options include photodynamic therapy (PDT), laser surgery, and anti-VEGF therapies. In PDT, verteporfin is injected intravenously and activated via laser to close the new blood vessels. Although less common, laser surgery may also be used to destroy abnormal blood vessels in nAMD.

Today, the mainstay of treatment is intravitreal (IVT) injections of the more effective anti-VEGFs that are administered through the IVT route. Macugen (pegaptanib) was the first approved anti-VEGF for the treatment of nAMD in 2006 (EPAR). In 2007, Macugen was followed by the more effective Lucentis (ranibizumab) and in 2012, the similarly effective Eylea (aflibercept) was approved. In addition, Avastin (bevacizumab) is used off-label. The agents differ in structure, molecular weight, and VEGF binding affinity.

Ranibizumab is a recombinant, 48 kDa humanised Fab fragment with a high affinity for VEGF-A through the binding of VEGFR-1 and VEGFR-2 on the surface of endothelial cells. IVT injections (0.5 mg) are administered every 4 week until there are no signs of disease activity. This is followed by an "as needed" (PRN *pro re nata*) or a treat-and-extend regimen (EPAR).

Aflibercept is a 97 kDa recombinant fusion protein that binds VEGF isoforms and placental growth factor. Aflibercept (2.0 mg) is administered every 4 weeks for the first 3 months where after treatment can be given every 8 weeks or with the treat-and-extend regimen (EPAR).

Bevacizumab is a full-length 149 kDa recombinant monoclonal antibody that is used off-label for nAMD in 1.25 mg doses. It is approved for the treatment of metastatic colorectal cancer and other forms of cancer.

Still, there is no curative treatment for nAMD. Even if to a marked extent, the available therapies only slow down the disease progress. The IVT injections are further not free of risks, for example of sight-threatening complications such as infectious endophthalmitis. Finally, since there is an overall need for frequent injections, this results into a significant burden to the patient as well as to the health care system. Thus, there is still an unmet medical need.

2.2. About the product

Abicipar Pegol (elsewhere referred to as "Rayoqta", invented name adopted during the procedure) is a covalent conjugate of a designed ankyrin repeat protein (DARPin) produced in *E. coli* covalently bound to methoxy polyethylene glycol maleimide (mPEG-mal). The molecular weight is approximately 35 kDa of which the protein moiety constitutes approximately 14 kDa. Abicipar Pegol binds to human VEGF-A and inhibits its biological activity.

The targeted indication is: Rayoqta is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD). Abicipar has been developed for ophthalmic use and is administered by IVT injection. Abicipar pegol is formulated as solution for injection in a dosage strength of 2 mg. The proposed posology is two initial monthly injections, one injection 2 months later and there after, one injection every three months. Treatment can also be administered on a bimonthly basis if needed.

2.3. The development programme/compliance with CHMP guidance/scientific advice

A total of 9 studies in patients with nAMD form the basis for the current application. The studies include the evaluation of PK, different doses, efficacy and safety of abicipar. Two of these studies are pivotal phase 3 studies where different dosing intervals are evaluated.

The applicant sought CHMP advice in 2016 (EMEA/H/SA/3303/1/2016/III) with the questions concerning quality, pre-clinical and clinical development.

On the quality side, topics related to starting material, the plan for release and stability testing of drug substance/product, control of impurities, shelf-life, definition of the strength of the product and standards for potency testing were addressed. Non-clinical questions related to the planned PK study in rabbits and the sufficiency of the non-clinical development programme. Clinical topics included acceptance of the PK data package, the extent of data to submit with the initial MAA submission, the extent of the safety database, and the primary and key secondary efficacy endpoints together with the statistical analyses.

Quality and non-clinical

All recommendations given in scientific advice concerning quality have been taken into account. The provided information confirms that stability is not impacted.

In regard of the non-clinical comments, all recommendations have been implemented into the nonclinical sections of the MAA dossier.

Clinical

With regard to the choice of proposed primary endpoint, the proportion of patients with stable vision (defined as patients who lose fewer than 15 letters in BCVA from baseline) at Week 52 using a 10% non-inferiority margin was not agreed. Today, patient and clinician expectation in wet AMD is for improvement in vision making this endpoint far from attractive as a primary endpoint and it was recommended as a secondary endpoint. The proposed 10% NI margin was considered somewhat wide and not sufficiently justified. It was however agreed that a margin in the range of 7% that is met through evidence from the pooled studies would be considered acceptable for the assessment of non-inferiority.

The key secondary endpoint, the mean change from baseline in best corrected visual acuity (BCVA) was recommended as the primary endpoint. The proposed NI margin of 5 letters for each individual study was considered wide and a margin in the range of 3-4 letters was considered reasonable. The 4

letter proposed by the applicant in the pooled studies was tentatively agreed as acceptable for the assessment of non-inferiority.

The applicant has not followed the recommendations regarding the choice of primary and key secondary endpoints.

The recommendations concerning the clinical PK given in this advice have been incorporated and respective topics have been addressed in the dossier.

There are no specific CHMP guidelines.

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMA/13255/2016 on the granting of a class waiver.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Drug Substance

The name, address, and responsibility of each site involved in manufacture and/or testing of drug substance is given. A QP declaration is provided, confirming that the manufacture of abicipar pegol drug substance is performed under GMP conditions. A GMP certificate is additionally provided for the DS manufacturing site. Furthermore, GMP certificates and Manufacturing authorizations for the two quality control testing sites are provided. The information provided on GMP for manufacturing of the drug substance is considered sufficient. As outlined by the applicant, for drug substance, the potency testing outside the EU is acceptable. The concern that release testing has to take place at a test site located within the EU only applies to drug product

Critical intermediate mPEG-Mal

A QP declaration from the manufacturer of Abicipar pegol is provided, stating that an on-site audit has been performed in April 2019 by Allergan. GMP compliance has been confirmed for the mPEG-Mal process. The information provided on GMP for the manufacture of mPEG-Mal is considered sufficient.

Drug Product

Name, address and responsibilities of the manufacturing, testing and release sites for drug product are listed. DP manufacture, IPC-, release- and stability testing as well as packaging and kit assembly areperformed by a named site. An alternative testing site for CBPA (cell based potency assay) is proposed. Valid GMP certificates as well as manufacturing authorisations for both sites are provided. The information provided on GMP for the manufacture of the drug product is considered sufficient.

GLP

All the pivotal safety pharmacology and toxicology studies were conducted in compliance with GLP regulations, and the designs of the individual studies conformed to the requirements outlined in the respective ICH guidelines. Although ocular toxicity was investigated as part of the GLP-conform intravitreal single- and repeat-dose toxicity studies, additional stand-alone intravitreal ocular tolerance studies in female rabbits were conducted during process development to compare local tolerance between drug lots manufactured by different processes. Although generally an absolute requirement, non-GLP compliance of these additional studies appears acceptable in this particular situation.

GCP

According to the applicant, all clinical trials were performed in accordance with GCP.

In February and May 2018, a GCP-inspection of Study 150998-006 was made by the MHRA. The inspection (resulted in 6 major findings, in the areas of Computer Systems Validation, Data Integrity, Data Integrity Control Processes, Monitoring, Pharmacovigilance and Record keeping/Essential Documents (TMF). There were no critical findings however and the Data Integrity findings did not relate to the trial in question. At the investigator sites there were no Critical or Major findings.

Nine additional inspections have been made and the applicant has provided an updated list of GCP and non-GCP inspections. One of the GCP-inspection reports (Contract Research Organisation, INC Research/ inVentiv Health. Surrey GU17 9AB, UNITED KINGDOM, Investigator, Barnet Hospital, UNITED KINGDOM) is missing and should be provided. The applicant is also asked to comment on critical and major findings. Further, the close-out report for one of the 3 post-submission GCP inspection is not yet available but will be provided with the Day 180 response.

No further inspection is deemed necessary.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

PRIME

Not applicable

Accelerated assessment

Not applicable

Conditional marketing authorisation

Not applicable

Marketing authorisation under exceptional circumstances

Not applicable

Biosimilarity

Not applicable

Additional data exclusivity/ marketing protection

Not applicable

New active substance status

The applicant requested the active substance abicipar pegol 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.

Orphan designation

Not applicable

Similarity with orphan medicinal products

Not applicable

Derogation(s) from orphan market exclusivity

Not applicable

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMA/498952/2015 on the granting of a class waiver.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

Abicipar pegol (recommended INN and USAN) is a PEGylated composite protein. IUPAC name as well as company code and CAS registry number are supplied. The protein component consists of an alternative scaffold domain based on ankyrin repeats containing binding domains targeted against human Vascular Endothelial Growth Factor A (VEGF-A). This type of protein is also known as a designed ankyrin repeat protein (DARPin®). The protein contains a polypeptide linker with a carboxy-terminal cysteine.

The finished product is presented as a liquid sterile single-use 2 ml glass vial containing 16 mg/ml solution abicipar pegol for intravitreal injection.

The product is available as a vial-only pack or as an ancillary kit (vial+injection kit).

3.1.2. Active Substance

General Information

Abicipar pegol is a PEGylated composite protein.

The protein component in abicipar pegol is referred to as unPEGylated abicipar, and consists of 135 amino acids [(-)met], which has a calculated average mass of approximately 14 kDa and a calculated pI of. It contains a two domain (N2C) ankyrin repeat specific to human VEGF-A, with a polypeptide linker terminating with a single cysteine residue at its C-terminus (to allow conjugation to mPEG-Mal). The protein is expressed in *E. coli*.

Methoxy polyethyleneglycol is covalently linked to the terminal carbon atom of propylamine and maleimidopropionate is also linked to the propylamine by amide bond. The molecular weight of a methoxy-polyethylene glycol (mPEG)-chain without linker and activating group is about 20 kDa.

Abicipar pegol binds to and inhibits the biological activity of human VEGF-A. VEGF has been shown to cause neovascularisation, the growth of new blood vessels from pre-existing vasculature. The binding of abicipar pegol to VEGF-A prevents the interaction of VEGF-A with its receptor on the surface of endothelial cells, thus reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

Manufacture, process controls and characterisation

Description of the manufacturing process and process controls – abicipar pegol drug substance

The abicipar pegol drug substance is manufactured and released at a named sitemPEG-Mal is manufactured at a different named site. A QP declaration is provided, confirming that the manufacture of drug substance as well as the manufacture of the critical intermediate is performed under GMP conditions. A GMP certificate is additionally provided for the DS manufacturing site. Furthermore, GMP certificates and Manufacturing authorizations for the two quality control testing sites are provided. For drug substance, the potency testing outside the EU is acceptable. The concern only applies to drug product.

Overall the manufacturing process is sufficiently described in tables and a detailed narrative description of the upstream and downstream process was submitted.

Control of Materials

Cell banks

The starting materials i.e. the host cell line and the plasmids are described in detail. An overview as well as a detailed narrative of the construction of the expression vector, transformation and cloning leading to the Master Cell Bank Derived from a characterized Reference Cell Bank (RCB) a two-tiered cell banking system with Master Cell Bank (MCB) and Working Cell Bank (WCB) was established. The MCB and WCB was characterized for sequence, viability, strain identity, genetic stability and purity (contamination control) and the results are presented. An acceptable comparability study to show the phenotypical and genetical equivalence of the cells was presented.

Overall, the cell banks have been tested according to ICH Q5B and ICH Q5D and the results obtained are considered acceptable and in support of using the cell banks for commercial manufacture of abicipar pegol.

Raw materials

Raw materials used are listed and none are of animal origin. Materials are released based on the supplier´s Certificate of Analysis (CoA). Most raw materials and all excipients comply with compendial standards. For non-compendial raw materials, detailed specifications are presented. Chromatographic resins (critical material) are released based on the supplier´s CoA Critical raw materials were identified based on risk assessment. The information presented on raw materials is considered sufficient.

Control of Critical steps and intermediates

Critical process parameters (CPPs) together with their operating range and proven acceptable range as well as in-process controls (IPCs) with their acceptance criteria (action limits) are provided in a tabulated overview. The applicant defined appropriate actions in case of exceeding ranges/limits established for in-process controls.

Minor issues concerning the western blot method and the RP-HPLC method remains unresolved **(OCs).**

Process validation and/or evaluation

Process performance qualification (PPQ) was performed. CPP and IPC limits were met for all PPQ batches. Also the intermediate as well as the drug substance met the predefined specification limits. Thus, the conducted process validation confirmed that the drug substance manufacturing process can perform effectively and reproducibly to produce an active substance meeting its predetermined specifications. This conclusion is further supported by batch data which met all release criteria. Some deviations that occurred during validation activities were sufficiently addressed. The applicant sufficiently addressed additional points concerning the process validation.

In addition to the process validation, further supportive evaluation studies on impurity and residuals clearance validation, media-, buffer- and process-hold validation, extractable and leachables, resin lifetime/cleaning/storage validation, mixing homogeneity, microbial control and transport validation were performed. The set points and operating ranges are considered appropriately defined as based on the Quality-relevant range determined in combination with the degree of control possible for the individual parameters during manufacture. Chromatography resin lifetime studies have been completed and established a maximum amount of cycles. no data concerning lifetime studies needs to be updated. Overall, the approach taken to design and characterize the abicipar pegol drug substance process is considered acceptable and in accordance with current guidelines.

Product quality attributes (QAs) were identified in a quality target product profile. The quality attributes were assessed based on analytical and non-clinical data and product knowledge. Besides mandatory critical quality attributes (CQAs) based on guidelines or compendial requirements, impact and uncertainty scores were assigned to the other quality attribute and the overall criticality score was the basis for considering the QA as critical or non-critical. Non-critical QAs were regarded important for demonstrating process consistency and are designated as pharmaceutical quality attributes (PQAs). Overall, the strategy for assessment of QAs is reasonable and acceptable.

Process development and comparability

In general, the process development has been appropriately addressed. A summary and justification of changes is presented in tabulated form. The main goal of process changes was to enhance the impurity profile. Overall the comparability exercise is acceptable. Concerning impurities, the applicant showed a consistent improvement of the manufacturing process.

Overall conclusion, abicipar drug substance manufacturing process

Overall, the abicipar pegol drug substance manufacturing process is considered appropriately designed, characterized, verified and controlled. The applicant has demonstrated that when the process is operated within established parameters it can perform effectively and reproducibly to produce drug substance meeting its quality target product profile and predetermined specifications. All issues from the list of questions have been appropriately addressed.

Characterisation

Concerning the elucidation of physicochemical properties and biological activity, a panel of standard and state-of-the art methods was used. Minor issues concerning characterisation results were appropriately addressed.

Impurities

Concerning impurities, a comprehensive discussion on potential process and product-specific impurities has been provided.

In addition, the HCP has been validated with regard to accuracy, precision, specificity, linearity, quantitation limit, range and robustness by spike/recovery analysis (data presented in S.4.3 Validation

of analytical procedures). Overall, the HCP assay has been developed, qualified and validated according to the recommendations in Ph. Eur. 2.6.34.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The release specification includes tests for general quality attributes, identity, protein concentration, purity and impurities, residual host cell protein, potency, bacterial endotoxins and bioburden:

Overall the presented drug substance specification is acceptable. Most but not all of the applied tests for release testing are also used for stability testing. Omission of testing for host cell protein is acceptable, since a change of this quality attribute during storage seems unlikely.

Compendial methods are listed and are mostly according to Ph.Eur. Equivalence to Ph.Eur. was shown for the USP based pH method.

Compendial endotoxin and bioburden test methods were verified. For non-compendial methods a detailed description of the method is provided. In general, the analytical procedures are described in sufficient details. Information on the reference standards and controls are included. System suitability criteria and sample acceptance criteria are specified and are in general found suitable.

The submitted method validation summaries indicate that all pre-defined acceptance criteria of the analytical method validation were met and thus the analytical methods for commercial release and stability testing seem generally suitable for their intended use.

Overall, all results passed the acceptance criteria of the current commercial specification or the specification at the time of testing.

Acceptance limits justifications for each specification are provided. In most cases the setting of the acceptance criteria is performed statistically using tolerance intervals.

No national or international reference standard is available for abicipar pegol. However, the potency unit is defined relative to the WHO certified $VEGF_{165}$ reference standard that has an assigned value for potency in a human umbilical vein endothelial cell assay.. A two tiered references standard system with primary- (PRS) and working reference standard (WRS) was established for abicipar pegol. Production, qualification and re-qualification of the references standards was described.Questions regarding the reference standard system were appropriately addressed by the applicant. Details on the assignment of potency were appropriately addressed.

Batch analysis

Batch analyses data for several batches has been provided. all comply with the specification at the proposed specification and support manufacturing process consistency.

The majority comply with the specification at the time of testing, **the applicant has been requested to comment on three apparent out of specification results and further clarifications are required.**

Container closure

General information on type and nature as well as specifications and technical drawing of the primary packaging material was included into the dossier. A short overview of safety testing comprising compliance with standards for quality of the plastic, reactivity testing, food contact requirements and TSE as well as an overview of performed tests for protection from mechanical impacts is shown. Studies on extractables were conducted by the supplier. For toxicity evaluation the calculated amount of extractables per maximum daily dose was compared to the threshold of toxicological concern. The

extractables were also subjected to an in-vivo nonclinical single dose acute systemic toxicity study. In both cases the toxicity of extractables per maximum daily dose were considered to be lower than the toxic amount. The primary packaging material is deemed suitable for the drug product, and additional appropriate information was integrated into the dossier concerning "unidentified extractables".

Stability

A shelf-life of 36 months for drug substance when stored in at the recommended long-term storage conditions of -65°C to -90°C is proposed. This shelf-life claim is primarily based on 36 months stability data available from one primary stability batch stored in and from three supporting stability batches stored in. These stability batches were manufactured using the same process and scale as intended for commercial manufacturing. An acceptable comparison of stability trends of drug substance stored in the and proposed commercial showed that the supporting stability batches can be regarded representative of the proposed commercial batches.

As expected for recombinant proteins certain degradation trends were observed for various quality attributes when stored at higher temperature conditions. This also confirmed the suitability of the stability indicating methods.

In general, the shelf-life claim as proposed above is acceptableAvailable additional stability data was provided that confirm the stability of the drug substance for the proposed shelf life.

3.1.3. Critical intermediate mPEG-Mal

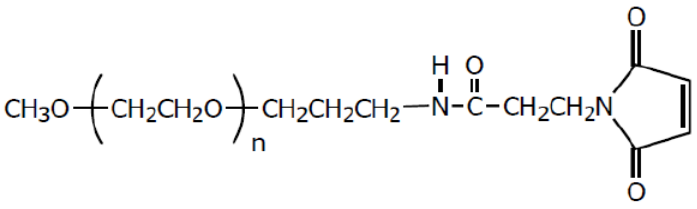
General Information

Methoxypolyethylenglycol (mPEG-Mal) is a 20kDa molecule consisting of methoxy polyethyleneglycol (mPEG) covalently linked to maleimidopropionate (Mal) and is defined as critical intermediate in the manufacture of Abicipar pegol to prolong the half-life of Abicipar.

Figure 1

Figure 1 Structure of mPEG-Mal

General Structure



Chemical Text Formula

$CH_3O\text{-}(C_2H_4O)_n\text{-}(CH_2)_3\text{ -NHCO- }CH_2CH_2\text{-}C_4H_2NO_2$

n = about 450, the average number of oxyethylene groups

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

mPEG-Mal is manufactured by a named manufacturer. GMP compliance has been confirmed for the mPEG-Mal process by a respective QP declaration by the manufacturer of abicipar pegol.
IPCs are established for each manufacturing step, respective acceptance criteria are set.

A risk assessment on all impurities of mPEG-Mal has been performed including elemental impurities, residual solvents and reagents, as well as impurities originating fromsynthesis. The control tests applied fulfil compendial requirements. Omission of routine testing of certain parameters is sufficiently explained and deemed justified.

All materials which are used in the manufacture of mPEG-Mal are listed and are adequately controlled. Storage conditions of mPEG-Mal are defined

Characterisation

The mPEG-Mal molecule is sufficiently characterized by appropriate state of the art techniques.

Reducing substances (organic impurities) are controlled according to Ph. Eur. requirements.

Elemental impurities were investigated according to a risk assessment. No genotoxic impurities are identified.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The control strategy established for mPEG-Mal is based on current guidance, compendial requirements (Ph. Eur., USP, JP) and prior knowledge of the manufacturer.
The specification criteria for each parameter included in the mPEG-Mal are discussed, explained and sufficiently justified.
Specification limits/ranges are adapted in line with development of the manufacturing process.

Analytical procedures and reference standards

Analytical procedures

Method validations have been performed for all non-compendial methods including water content according to Karl Fischer titration following USP requirements. No method validations were performed for bacterial endotoxins and bioburden as these are compendial methods for which method validation is not required. All test methods applied are considered suitable for their intended use.

Reference standards

For the determination of average molecular weight commercially available reference standards are used.
An in-house standard, is established for the determination of terminal activityThe procedure and qualification testing when a new in-house reference standard is established is described. The procedure for the establishment of a new in-house standard is presented.

Batch analysis

Batch analyses data for several mPEG-Mal batches (i.e. all batches which were used in the manufacture of abicipar pegol) are provided. The acceptance criteria for all parameters of all batches are fulfilled.

Container closure

The primary packaging system. composition are provided. Compliance with compendial requirements is confirmed.

Stability

Long term as well as accelerated stability studies are conducted on four and two mPEG-Mal batches respectively (i.e. Stability Testing 1 and 2).
Stability Testing 1 is completed, and Stability Testing 2 is ongoing with four batches. For three of these batches 36 months data are available, and for one batch 18 months data, and 12 months data are at hand.
Long term data indicate appropriate stability of mPEG-Mal as all test parameters are within their acceptance criteria. A slight downward trend is observed for BHT content over time, which is not considered critical.

Forced degradation has not been conducted as accelerated conditions over a longer period are considered to be more representative to show a degradation profile.

The proposed re-test period for mPEG Mal when stored at the intended storage conditions can be accepted..

3.1.4. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the product

Abicipar pegol (16 mg/mL) drug product is a colourless to slightly yellowish solution in a sterile single-use 2 mL Type 1 glass vial. An adequate volume is added to the vial to ensure that the required injection volume can be delivered.
Abicipar pegol is presented in two configurations, i.e. a sterile 2 ml single-use vial only and as an ancillary kit which contains the single use vial and a CE marked medical device.

The strength of Abicipar pegol is defined as protein content of the protein moiety only as required according to current guidance. This is also reflected in the product information.

No overages are present in the product.

Pharmaceutical development

Components of the drug product
Abicipar pegol drug substance is a PEGylated composite protein.
The protein component consists of an alternative scaffold domain based on ankyrin repeats containing binding domains targeted against human Vascular Endothelial Growth Factor A (VEGF-A). The excipients used in abicipar pegol drug product are compendial ingredients The drug product formulation comprises of the same drug substance
Formulation development

The formulation used in clinical phase III is identical to the commercial formulation.

Comparability between the different formulations used during development
has been demonstrated on stability.
Manufacturing process development

The abicipar pegol drug product manufacturing process consists of formulation of the drug substance, sterile filtration and aseptic filling steps.

The DP manufacturing process did not undergo many changes during developmentBased on the data provided the processes applied throughout development are comparable in the sense of delivering a product of the desired quality meeting its quality attributes.

A drug product process characterization study at the intended commercial scale was performed to demonstrate abicipar pegol drug product manufacturing process robustness and consistencyThe characterization studies examined the effects of various set-points on product quality attributes. The characterization runs met all pre-defined acceptance criteria.

In addition, consecutive full-scale drug product lots have been manufactured using the current set-points or ranges established by process characterization studies, and prior knowledge.

Drug product manufacturing process control strategy

CQAs are defined for the abicipar pegol DP, product control is based on IPC and CIPC testing, while each operation unit of the manufacturing process is defined as CPP or KPP. Each process step is evaluated for its criticality to affect product quality attributes.

A summarizing table is provided listing all unit operations, process equipment, process parameters, set-points, operating ranges, KPP/CPPs, controls, as well as the potential effects on product quality attributes.

The manufacturing process control strategy is based on sound knowledge of product and process and seems appropriate.

Container closure system

Abicipar pegol, solution for injection is provided in a single-use 2 mL volume, Type I glass vials The primary container closure system complies with compendial requirements.

Leachable studies have been performed.

Medical device:
The syringe and needles are provided separate from the medicinal product and thus are regarded non-integral. All ancillary kit components are CE marked.

Manufacture of the product and process controls

Manufacture

The abicipar DP manufacturing process is a standard process and respective descriptions are given in sufficient detail.

Hold times are applied based on respective evaluation studies and are deemed appropriate based on study data.

No reprocessing or rework of the drug product is applied.

A risk assessment on leachables/extracatbles has been performed by the applicant for the container closure system as well as for single use components. Extractables have been investigated on the container closure system. Leachables investigation has been performed with drug product samples.

Leachables in aged drug product are below the Threshold of Toxicological (TTC) concern. Based on the toxicity data provided it is considered that there is no toxicological risk from single use materials or container closure system.

Process controls
IPCs (in-process controls) and CIPCs (critical in-process controls) are presented in tabular form with their acceptance criteria and reference is made to compendial methods, if applicable.

The acceptance limits/ranges applied are deemed adequate as demonstrated in various process characterization and validation studies.

Process validation / verification

Process validation
Process validation was appropriately performed and it could be demonstrated that the manufacturing process is capable to deliver a product of the desired quality.

Shipping validation
The transport of the bulk and the final DP is validated ,
All vials were within their acceptance criteria.

Equipment sterilization
Sterilization of manufacturing process equipment/container closure system coming into contact with DP are validated. The sterilization/irradiation validations are shortly described and all processes are re-validated at regular intervals. For vial sterilization, equipment and components sterilization cycle requalification results are provided. The data show that all acceptance criteria are met and that the sterilization program is suitable to ensure appropriate safety for the DP with regard to equipment-derived contamination.

Product specification, analytical procedures, batch analysis

Specifications

The justification of specifications is based on the identified CQAs, batch data derived from non-clinical, clinical and commercial manufacture, the corresponding commercial DS specification and compendial requirements. Specification limits were tightened for some parameters according to batch release and stability data.

The statistical approach using a tolerance interval for specification setting was comprehensively explained and can be accepted.

ICH Q6B was taken into consideration.

Characterization of impurities
Other product-related variants are assessed in 3.2.S. Drug Substance in the respective chapters.

Elemental impurities deriving from the drug substance and excipients, product contacting manufacturing process equipment and container closure system were evaluated by a risk assessmentin line with the requirements of guideline ICH Q3D. Based on the results no specific risk is expected for abicipar pegol DP.

Analytical procedures and reference standards

Analytical procedures
Compendial and non-compendial test methods are used for the control of the DP. For the non-compendial methods method descriptions are provided.

Transfer validations were conducted for some test methods as appropriateand the transfer validation criteria were defined individually for each test method and respective studies performed. The results are presented in summarizing tables for each method. All acceptance criteria were met for each parameter and test method.

In summary, all test methods were appropriately validated and shown to be suitable for their intended use.

Reference standards
The same reference standards are used for drug substance as well as for drug product. Reference standards are discussed in the drug substance section.

Batch analysis

Batch analyses data are provided

Container closure

Abicipar pegol DP is filled in Type 1 glass vials and closed with a rubber stopper and seal with a flip-off disk. The primary packaging materials are commonly used for parenteral solutions and comply with Ph. Eur. requirements. Certificates of conformity are provided.

Sterilization conditions for vials, stoppers and seal caps are provided.

Stability of the product

In accordance with ICH guideline Q1A(R2) and Q5C, data is provided for primary stability lots and PPQ batches

The following storage conditions are applied on the primary stability batches: long term stability for up to 36 months and accelerated for up to 12 months.

The following storage conditions are applied on the PPQ batches: long term stability for up to 36 months and accelerated conditions for up to 6 months

Accelerated studies are completed, long term investigations are ongoing.

Results
Currently the following stability data are available: For the primary stability batches 36 months data are available for few batches and 24 months data for more batches stored at long term conditions (°C). 9 months stability data are available for the PPQ batches
Primary stability batches:

- 12 months data for two batches and 6 months data for 4 batches at accelerated conditions
- 6 months data for five batches and 3 months data for one batch at accelerated conditions

PPQ batches:

6 months data for all PPQ batches are provided.
Accelerated stability investigations are completed for all batches (Primary and PPQ batches).

Long term storage: All batches met their acceptance criteria at all time points when stored at. Slight degradation was observed over time. As a consequence monomer content and decreased slightly, while no trend was seen for CBPA potency.
The data at hand demonstrate that storage of abicipar pegol DP at long term conditons is appropriate.

Accelerated conditions: The stability data obtained from the accelerated conditions reveal an expectable decrease of purity due to the formation of HMW (mainly dimers) and LMW (mainly unpegylated abicipar protein and C-terminal truncations of unpegylated protein) as well as deamidation of the abicipar protein when stored at higher temperatures. A decrease of pH is attributable to the temperature- and time-dependent conversion. Increases in total free PEG are observed due to the dePEGgylation of abicipar.
No trends are observed for appearance, osmolality protein concentration, endotoxin or bioburden.
A slight darkening trend is noted for the visual appearance of the solution after 6 months at accelerated conditions.
Potency is not affected at accelerated conditions over 12 months, however, a slight downward trend is seen at accelerated conditions which corresponds to the decrease in purity at elevated temperatures.
The data demonstrate that the DP is not stable at higher temperatures and support storage at a maximum temperature.

Losses of PS20 are based on hydrolysis of the ester bond over time and possibly due to enzymatic activity of residual host cell proteins. Degradation of PS20 with respect to particle formation has been shown to be of no concern and was justified by data from development studies.

The stability data obtained from PPQ batches (long term and accelerated condition) so far support the findings from the primary stability batches.

Proposed shelf life:
Based on the stability data at hand the following shelf life for the DP is proposed: **24 months when stored inthe commercial packaging configuration.**

The following issues are addressed: **Provision of updated stability data for all ongoing stability studies to support a shelf life of 36 months, clarification of pending potency results for certain batches after 18 months and 6 months respectively at long term storage, explanation for significant decreases in potency near to specification limits after 24 and 6 months respectively at long term storage**

Photostability
Sensitivity to light exposure (cool white light at 1.2 million lux hours, UV light at 200 Watt hours/m²) of abicipar pegol DP was investigated; either in the primary packing system (glass vials) only or the filled vial in the outer carton. Significant oxidation of methionine and tryptophan was seen in samples stored only in the primary packaging system. Apart from oxidation an increase in subvisible particles as well as accumulation of degradation products (HMW, LMW) was observed. CBPA potency, total PEG, and monomer content decreased severely.
Uncertainties on the fate of PEG at elevated temperatures are clarified: Decreases of PEG- are mainly attributable to the formation of forms. Unpegylated forms are observed at an amount of about. Additional species are of misincorporations at and variants. These are all product-related species

generated during protein translation only and do not increase upon storage. No PEG fragments are observed by using EAX-HPLC with UV detection.
Samples stored in the outer carton (marketing pack) were not affected at all.
Based on the data provided it is obvious that abicipar pegol DP is sensitive to light exposure.
Secondary carton packaging as light protection during shelf life is highly appreciated.

The post-approval stability protocol has been updated in this respect that three batches (post-PPQ batches) will be included in the long term stability program.

Post approval change management protocol(s)

A post approval change management protocol has been included

Overall, the control strategy for the DP is considered appropriate.

Low endotoxin recovery risk assessment
Overall, the LER risk assessment including the factors accounted for, the studies performed, the results obtained, and the justifications provided, is considered comprehensive, scientifically sound and in support of using the proposed risk based approach for release of abicipar pegol DS and DP.
Uncertainties in endotoxin test method selection for LER testing are clarified.

Adventitious agents

Abicipar pegol is expressed in *E.coli*. Defined medium components were used. No animal-derived materials were used. Based on this, the applicant concludes that the risk of transmitting virus or TSE from abicipar pegol is negligible. This conclusion is considered acceptable. The cell banks have been tested for absence of atypical colonies, spore formers, atypical cells, and bacteriophages. The product is tested for bioburden, endotoxin, and sterility at relevant stages of the drug substance and drug product manufacturing process, respectively Thus, the risk of presence of contaminating bacteria or fungi is considered negligible. Based on this, the abicipar pegol product is considered safe in terms of absence of adventitious agents.

GMO

Not applicable

3.1.5. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The quality dossier was provided in a well-structured and organized manner, supported by explanative tables and flowcharts. Equivalence to Ph.Eur. monographs were appropriately confirmed based on the applicant's answers to the LoQ.

The manufacturing processes for abicipar pegol drug substance and drug product as well as for the critical intermediate mPEG-Mal have been described in sufficient detail; all raw and starting materials used in the manufacture are listed identifying where each material is used in the process.

mPEG-Mal is defined as critical intermediate in the manufacturing process of abicipar pegol . Its manufacture is performed under GMP conditions. Information on the quality and control of mPEG-Mal as well as of its starting materials, has been provided.

All excipients used for drug product formulation comply with compendial requirements. An appropriate control strategy ensures that material of sufficiently high quality will enter the market.

Relevant process controls and in-process controls ensure a consistent routine manufacture. Process validation supports the conclusion that the manufacturing process for drug substance as well as for drug product generates drug substance respective drug product meeting its predetermined specifications and quality attributes. The provided drug substance and drug product batch analyses data support this conclusion. Comparability throughout the development has been demonstrated. Container/closure systems comply with compendial requirements.

Abicipar pegol is expressed in *E.coli*. Defined medium components were used. No animal-derived materials were used. Thus the viral risk and TSE risk are negligible.

Hence, no major objections are raised, other concerns are identified. Prior to granting the marketing authorization, the list of questions as outlined below should be addressed by the applicant.

3.2. Non clinical aspects

3.2.1. Pharmacology

The main objective of the nonclinical pharmacodynamic program was to confirm the *in vitro* binding affinity and potency, as well as to evaluate efficacy in relevant *in vivo* models of retinal vascular leakage. Furthermore, the applicant provided a safety pharmacology study, evaluating ocular and systemic safety of abicipar in the cynomolgus monkey.

Abicipar was assessed alone or in comparison with ranibizumab (Lucentis®), bevacizumab (Avastin®), and aflibercept (Eylea®). The binding of abicipar to VEGF-A and the subsequent inhibition of VEGF-A/VEGFR-mediated activity *in vitro* has been evaluated in a receptor competition assay and in 4 cell-based VEGF-A dependent assays. Binding affinity to VEGF in solution was determined using a kinetic exclusion assay. The calcium mobilization in human umbilical vein endothelial cells was measured using calcium-sensitive Fluo-4 AM and FLIPR. Finally, the inhibition of angiogenesis *in vitro* was evaluated using a three-dimensional model of vessel sprouting.

The inhibitor potency measurements from all the *in vitro* systems presented by the applicant are dependent to a large extent on the sensitivity of the assay. Endpoints in these assays range from a simple receptor phosphorylation to calcium release and to cell proliferation. The sensitivity of each assay is a function of the concentration of VEGF-A necessary to generate a replicable signal. Due to the stoichiometric relationship between VEGF-A and the cytokine binding agents, where one molecule of the binding agents with a single antigen binding site maximally binds one molecule of VEGF-A, potency measurements for a given compound vary with the concentration of VEGF-A employed in the assay. As such, a comparison of different inhibitors seems only useful, when all the comparator compounds of interest are tested in the same assay.

Abicipar was tested against ranibizumab, bevacizumab and aflibercept in the study BIO-13-1048 (VEGF Neutralization Potency of AGN-150998, Ranibizumab, Bevacizumab, and Aflibercept Assessed with a Cellular Calcium Mobilization FLIPR Assay). Abicipar dose-dependently inhibited VEGF-induced calcium mobilization in human umbilical vein endothelial cells (HUVEC) in the provided study setup.

Polyethylene glycol (PEG) is a water soluble polymer often used to modify the pharmodynamic properties (e.g. half-life) of recombinant therapeutic proteins. is commonly employed due its specificity and stability,

The study "VEGF-A Neutralization Potency in a Cell-based Calcium Mobilization Assay of Abicipar-3 Variants that Differ" (BIO-14-1077) was initiated to determine whether this transformation resulted in

any change in abicipar's VEGF-A neutralization potency of the drug *in vitro*. No significant differences were found under the provided *in vitro* study conditions between mean potencies (IC50) of abicipar and abicipar.

The efficacy of abicipar *in vivo* has been studied in both, rodents and rabbits. Anti-VEGF activity *in vivo* was evaluated in a rat Argon Laser-induced choroidal neovascularization model, and a rabbit model of chronic retinal neovascularization. Furthermore, the *in vivo* activity was assessed in a rabbit model of retinal vasculopathy induced by intravitreal VEGF-A165 injection.

In the study "Pilot evaluation of the efficacy of intravitreal and administration of DARPins in a rat Argon Laser-induced choroidal neovascularization model" (study number M25C0608), at 50 mg/ml and DARPin 30H3PEG20 (15 µg) was intravitreally injected. Both applied substances did not significantly reduce fluorescein leakage, but were shown to produce a significant reduction of the anatomic volume of choroidal neovascularization in the rat study. Finally, intravitreally administered DARPin TF30H3PEG20 (15 µg) showed inhibition of fluorescein leakage and reduction of ChNV volume but without reaching statistical significance.

Two different DARPin solutions were administered intravitreally to rats in this study (M25C0608) performed by IRIS. TF30H3PEG20 and 30H3PEG20 (5 mg/ml = 15 µg) were listed in the section "denomination, test items for i.v.t. administration". Both solutions showed different results during the study, reflecting differences in vitreal clearance between the compounds in the rat.

Abicipar (120 µg) completely suppressed VEGF-A-induced vascular leak 2 weeks following a single intravitreal injection in the rabbit study "Pharmacodynamic Comparison of AGN-150998 with Ranibizumab in a Rabbit Model of VEGF-induced Retinal Vasculopathy" (study number BIO-12-960). Vascular leak was significantly inhibited ($p<0.05$) in this study, when eyes were re-challenged with VEGF at week 4. Retinal vessel tortuosity and vasodilation in response to VEGF challenge were also significantly inhibited ($p<0.05$) at week 4. In contrast, while an equimolar dose of ranibizumab (170 µg) completely suppressed retinal leakage, vascular tortuosity, and vasodilation at week 2, these effects were no longer statistically significant 4 weeks after the ranibizumab treatment. At the 6-week time point, the effects of abicipar (120µg) were not significantly different from those of the vehicle control.

To address the impact of drug product *in vivo*, the study "Pharmacodynamic Comparison of Abicipar-3 Variants that Differ in their Ratios in a Rabbit Model of VEGF-induced Retinal Vasculopathy" (BIO-14-1056) was performed. The objective of this study was to assess whether these differences may affect abicipar's *in vivo* antivascular endothelial growth factor-A (VEGF-A) activity. Animals received a single intravitreal injection of abicipar consisting of either the predominantly (abicipar) or an equal ratio of (abicipar). Recombinant human VEGF-A was administered at selected times after the intravitreal injection of the test articles, and retinal vasculopathy was quantified from measurements of increased vascular permeability (vascular leak), vessel tortuosity and vasodilation. Compared with vehicle-treatment, a single intravitreal injection of 120 µg abicipar-3 =79%:12% significantly suppressed retinal vascular fluorescein leakage through 4 weeks, and suppressed tortuosity/vasodilation at 2 weeks. A single intravitreal injection of 120 µg abicipar-3 =46%:46% significantly suppressed retinal vascular fluorescein leakage through 6 weeks, and suppressed tortuosity/vasodilation through 4 weeks. A single intravitreal injection of 170 µg ranibizumab completely suppressed retinal vascular fluorescein leakage and tortuosity/vasodilation at 2 weeks, but the effect was lost at 4 weeks.

The human dose of abicipar pegol and aflibercept is 2 mg, however the molecular weight of aflibercept is approximate 100 kDa, hence abicipar pegol will be dosed at a higher molar dose compared to aflibercept in humans, but was approximately equimolar in the rabbit model. All in all, in vivo proof of concept is considered established for abicipar pegol in terms of prevention. The effects shown in the

rat model are not expected to be the maximal effect due to rapid vitreal clearance of biologics in rodents.

Further observations from stability studies have documented that the is temperature dependent and when stored at 40 °C, the conversion is complete within 1 to 2 weeks. Consequently, regardless of of the starting material, within 1 to 2 weeks of its intravitreal injection abicipar remaining in ocular tissue should consist entirely. However, it would have been of interest to see a steady state ratio dosing group included into this study.

A GLP compliant i.v. safety pharmacology study was performed in conscious cynomolgus monkeys (692987 A Comprehensive Safety Pharmacology Study of MP0112 Given by Intravenous Injection to Cynomolgus Monkeys). The animals were given abicipar in 2 phases. Single IV doses of 15 and 45 mg/kg abicipar were administered in a dose escalation phase to the animals with subsequent evaluation of cardiovascular, respiratory, and central nervous system safety parameters. In a second phase, a new group of monkeys was given a single IV dose of 45 mg/kg abicipar with evaluations of cardiovascular parameters and body temperature. There were no deaths in this study. Slight tremors of short duration were recorded for one animal following the high-dose administration, which was considered not to be a test article-related effect, as it was an isolated finding of slight severity.

Furthermore, there was a sustained reduction in heart rate during the 2 to 20 hours post-dosing period in animals treated with 15 mg/kg in this safety pharmacology study. This finding exceeded the natural decline observed during the control dosing session. In addition, relative to predose measurements, the 45 mg/kg dose of abicipar (in Phase 2) was associated with a minor increase in blood pressure. In addition, there was a reduction in heart rate following the 45 mg/kg dose, during the 2 to 20 hours post-dosing period, which was consistent with changes noted following the 15 mg/kg dosing session. As these decrease in heart rate followed the same time course as increases in systemic blood pressure it was considered that these decreases may have been a compensatory response to the higher blood pressure. Although there was a slight, transient increase in the QTc interval duration noted (in the 45mg/kg group and during the control article dosing session), there were no clearly treatment-related changes seen in any of the measured ECG intervals (QRS, PR, QT and QTc).

The lack of pharmacodynamic interaction studies is considered acceptable. SmPC section 4.4 Special warnings and precautions for use, states that concomitant use of abicipar pegol with other VEGF inhibitors whether ocular or systemic is not recommended. Section 4.5. includes a reference to section 4.4.

In summary, abicipar exhibited concentration-dependent inhibition of VEGF-induced angiogenesis *in vitro.* Abicipar binds all soluble VEGF-A isoforms with high affinity, potently neutralizes VEGF-A165 effects *in vitro*, and effectively blocks neovascularization and vascular leakage in animal models.

In vivo abicipar administration reduced the area of neovascularization in the rat model of corneal neovascularization and blocked vascular leakage in the rabbit model of chronic neovascularization. The duration of inhibition of vascular leakage by abicipar was longer than that of an equimolar dose of ranibizumab in a rabbit model of VEGF-A–induced retinal vasculopathy.

Nonclinical PD studies demonstrated no difference in potency, or duration of action between a predominatelyversus a predominately of abicipar.

The pharmacology of abicipar pegol was adequately characterized to support the registration of Abicipar Pegol Allergan at a dose of 2 mg/eye for the treatment of nAMD.

3.2.2. Pharmacokinetics

Pharmacokinetic and toxicokinetic studies with abicipar were conducted in rats, rabbits, dogs, and monkeys. PK/TK data was used to support dosing rationale and to construct an in silico mechanistic, multi-compartment PK model to predict exposure in humans. Toxicokinetic studies on abicipar were conducted in compliance with GLP.

Validated ELISAs were used to measure abicipar concentrations in rat, rabbit, dog, and monkey serum. Qualified ELISAs were used to measure abicipar concentrations in amniotic fluid and ocular tissue samples. The immunogenicity of abicipar in rat, rabbit, dog, and monkey was evaluated in serum samples using qualitative ELISAs. Assays were validated for precision, sensitivity, specificity, selectivity, and reproducibility. Sera were screened for binding anti-drug antibodies, but not for neutralizing potential of ADAs.

Ocular absorption of abicipar after **intravitreal** injection was studied in rabbits. Batches from different process development steps at doses from 1 – 4 mg/eye were tested and ocular and systemic exposure was assessed. An increase of $T_{1/2}$ from ~3.5 to >6 days was observed when comparing and in an invitreal injection pilot study, respectively. $T_{1/2}$ of abicipar pegol in vitreous of rabbits was confirmed between 3.9 – 7.5 days in other PK studies. Abicipar was rapidly absorbed with highest concentrations found in vitreous humor, retina and choroid. After adminsitration of 1 mg/eye Cmax were found to be between 20000-40000 nM in vitreous humor, depending on the DP Formulation and DS Process batch with the final drug formulation showing the highest concentrations. Abicipar distributed into the retina and choroid at concentrations at least 65000 to 100000 times greater than the IC50 (25 pM) value for VEGF inhibition in a VEGF-A-dependent calcium mobilization assay in HUVEC.

When abicpiar in the predominantly was compared to abicipar in the predominantly , only slight differences in PK paramters (Cmax, $AUC_{0\text{-tlast}}$, and $T_{1/2}$) were observed in vitreous humor, choroid and serum (<1.2-fold differences). Differences appeared to be slightly higher in retina and aqueous humor (<1.7-fold), with high interspecies variability observed in this study. Although the retina represents the target tissue, these slight deviations may be explained by known inherent variability in ocular tissue sampling resulting in very high SD (C_{max} 42100 ± 6100 nM vs 31600 ± 7300 nM). Most importantly, no significant differences in efficacy were observed between the predominantly and the predominantly in nonclinical PD studies. Thus, PK of abicipar in its predominantly can be considered comparable. Observed differences are regarded of minor concern, especially when bringing to mind data which shows that more than 90% of abicpiar is converted to the within ~10 days after administration, independent of the predominantly present in the DP before administration.

Whereas no differences in distribution were observed between drug products manufactured by varying processes when measuring serum levels, abicipar distribution into the retina and the choroid was much higher after administration of DP Formulation 2 (planned commercial formulation) than with DP Formulation 1 material (5 to 30-fold higher C_{max} observed in choroid and retina, respectively). The applicant justifies these deviations by the use of two different tissue collection techniques (frozen vs fresh tissue). According to submitted data DP Formulation did not affect serum concentrations in this study and the applicant concluded that the similarity in the serum data suggests similarity in the ocular PK as well because abicipar was shown to clear from the eye to the systemic circulation and thus the PK in this two compartments should be related. Although it is not agreed that only 'small ocular PK differences' were observed, no safety concerns were raised with regard to TK of different process materials according to toxicological data submitted. Overall, the observed differences in ocular TK are therefore regarded to be of minor concern.

Intravitreal injection of abicipar DP Formulation 1 at doses ranging from 0.07 to 4.55 mg/eye resulted in a dose-related increase in **serum** levels of abicipar in male and female rabbits. Notably,

administration at the highest dose resulted in 2.5 to 3-times higher serum concentrations in males than in females (C_{max} 135 vs 50 nM, $AUC_{0\text{-}last}$ 9734 vs 3394 nM*h).

An IVT bridging TK study in rabbits comparing 1 and 2 mg/eye abicipar DP Formulation 1 to DP Formulation 1 revealed no significant differences in any of the measured serum PK parameters. $AUC_{(0\text{-}t)}$ ratios between the two processes were calculated as 0.98 and 1.03 for 1 mg and 2 mg per eye dose, respectively. Similar bridging studies in rabbits were also conducted between abicipar DP Formulation 1 (DP, and DP at 2 mg/eye. While C_{max} between the three tested lots were comparable, slight differences in $AUC_{(0\text{-}t)}$ resulted in ratios around 0.77 for the two lots normalized to independent of the formulation used. However, high variability was observed within this study. Overall, TK between the tested lots appeared comparable. Overall, systemic exposure appeared to be comparable across successive development changes in these studies.

Repeated intravitreal dosing of abicipar DP Formulation at doses of 0.07, 0.28 and 1.3 mg/eye resulted in a dose-related increase of serum levels but decreased with number of administrations over 56 days in rabbits (3 doses). Dose-related increase was also observed with manufacturing material when administered to rabbits. However, material showed higher systemic exposure at all time points observed (D1, D60, D120) when compared to material. Again, the serum levels decreased with the number of individual administrations, with larger decreases observed at higher dosage (3 mg/eye). These findings may be associated with ADA formation.

Dose-relationship but no decline in serum levels (no impact of ADAs) of abicipar was observed in beagle dogs after repeated intravitreal dosing.

Repeated **intravenous** dosing of rats at doses up to 50 mg/kg/day () over 4-weeks resulted in dose-dependent increase of **serum** abicipar but neither accumulation nor decrease in serum levels was observed over time. Similar data was observed with lots tested in rats in the DART studies at doses up to 15 mg/kg/day. On gestation day 20, dam sera were compared to fetal sera concentrations to investigate potential placental transfer of abicipar. Only minimal levels of drug were detected in fetal sera (~5 nM at the highest dose tested), resulting in fetal-to-maternal serum ratios of not more than 0.06% at any of the tested doses, indicating almost no placental transfer of abicipar in rats.

With abicipar , slight accumulation with the number of administrations was observed in male and female rats (accumulation ratios of up to 1.8 and 1.5 in males and females, respectively). Similar accumulation ratios were detected in female rabbits using DS at the same dose levels over 20 days. Again, fetal-to-maternal serum ratios were appeared (maximally 0.12%). Repeated intravenous administration of abicipar over two weeks showed similar results in rabbits as observed in rats, i.e. dose-dependent increase in serum levels, but no accumulation and no declines in serum concentration with repeated dosing.

In a 4-week intravenous injection toxicity study in the cynomolgus monkey followed by a 4-week recovery period administering 0.015, 0.15, 1.5 and 15 mg/kg/day of abicipar) slight accumulation of serum abicipar was observed at high doses in male animals only. However, no significant systemic gender-related effects were observed for abicipar.

Ocular distribution studies were conducted with interim material. Ocular PK parameters of material was shown to be comparable to, thus obtained distribution data is regarded representative for commercial process drug product.

After intravitreal injection of 1.17 mg/eye in rabbits, highest concentrations of labeled abicipar were detected in vitreous humor, retina and choroid (retinal pigmented epithelium – RPE). Maximal mean radioactivity concentrations (C_{max}) in serum were 290-fold lower than those observed in the vitreous and concentrations of radioactivity in the brain were 64-fold lower than those observed in serum, indicating limited penetration of drug-related material through the blood-brain barrier.

Metabolism studies have not been conducted. According to ICH S6, the expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids. Therefore, the metabolic pathways are generally understood. Classical biotransformation studies as performed for pharmaceuticals are not needed. A discussion on how the methoxy polyethylene glycol maleimide (mPEG-Mal)-moiety of abicipar pegol is expected to be metabolised and/or eliminated was provided.

The applicant argues that no specific characterization for abicipar pegol is necessary as protein therapeutics are typically catabolised. Vacuolation, which is a typical known adverse effect associated with PEG accumulation in various tissues, was not observed in the eye in repeat dose ocular toxicity studies following either 3 bi-monthly intravitreal doses of up to 3 mg/eye in rabbit or 7 monthly intravitreal doses of up to 3.6 mg/eye in dog. In addition, data with a structurally similar pegylated molecule from the DARPin platform suggest that pegylated DARPins are eliminated from the eye intact.

No dedicated studies on excretion of abicipar were conducted. Studies of excretion into milk were also not conducted. This is accordingly depicted in the SmPC under 4.6 Fertility, pregnancy and lactation.

It is acknowledged that systemic $T_{1/2}$ of abicipar in serum ranged from 4.97 to 9.48 hours in rats, 21 hours in rabbits and 11 to 16 hours in monkeys following IV dosing. Monkeys were the only animal species in which increased and repeated dosing resulted in increased $T_{1/2}$ due to reduction in clearance rate of abicipar from serum.

Studies on pharmacokinetic drug interactions were not conducted.

An in silico mechanistic, multi-compartment PK model was constructed using ocular tissue data obtained from intravitreal pharmacokinetic studies conducted in rabbits. This data was used to construct a model for estimation of human PK after abicipar dosing. The animal model fitted well against the measured abicipar concentrations in vitreous and aqueous humor, retina, choroid and serum. After scaling this data to the human model using aqueous und serum data, the human model again fitted well against the measured abicipar concentrations in serum and aqueous humor from patients with nAMD and diabetic macular edema, respectively.

Human abicipar and VEGF vitreal concentrations were simulated over a 52-week period using the proposed phase 3 dosing regimens with an abicipar dose of 2 mg. Simulation for the suggested 2Q8 and 2Q12 regimens in patients resulted in permanent vitreal abicipar concentrations above the calculated IC50 value for VEGF inhibition. Additionally, complete suppression of VEGF concentrations were predicted over the same time period. Thus, predictions for human PK by multi-compartment PK model support dose selection and treatment regimen of 2 mg/eye 2Q8/2Q12.

3.2.3. Toxicology

The toxicology profile of abicipar has been established through ocular and systemic toxicology, reproductive and developmental toxicology, and safety pharmacology studies.

All single-dose and all pivotal repeat-dose and developmental and reproductive toxicity studies have been conducted in compliance with GLP. Intravitreal local tolerance studies were not conducted in accordance with GLP, which is generally a requirement for such studies. However, ocular toxicity after intravitreal administration of abicipar was also investigated during GLP-compliant single- and repeat dose toxicity studies and separate local tolerance studies. Thus, lack of GLP compliance for these studies is deemed reasonable.

Abicipar binds to VEGF-A from various pharmacologically relevant species, including rats, rabbits, dogs, and primates. For systemic toxicology studies, rats were chosen as the rodent species and monkeys were chosen as the non-rodent species. The choice of monkeys for investigations on systemic

toxicology and safety pharmacology is justified by the strong binding of abicipar to homologous monkey and human VEGF-A. Rabbits and dogs were selected for toxicity evaluation of intravitreally administered abicipar. Rabbits and dogs are commonly used in toxicological studies where the eye is the target. This selection is justified by the large vitreous volume of these animal models which allows intravitreal injection without injury to the lens and retina and permits wide field ophthalmic examination to rapidly and sensitively detect signs of inflammation or other adverse effects in the eye.

Dose selection and dosing regimen was supported by PK/TK data. After intravitreal injection, abicipar distributed into the retina and choroid at concentrations at least 65 000 to 100 000 times greater than the IC_{50} (25 pM) value for VEGF inhibition in a VEGF-A-dependent calcium mobilization assay in HUVEC. Predictions for human PK by multi-compartment PK model supported dose selection and treatment regimen of 2 mg/eye 2Q8/2Q12.

No abicipar-related effects on viability, clinical signs, absolute and relative food consumption, absolute body weights and body weight gain, hematology, serum chemistry, or organ weights were observed after intravitreal injection.

A single dose IVT study in rabbits given abicipar at the final DP Formulation yielded an ocular NOAEL of 2 mg/eye. This dose is approximately equivalent to 5 mg/eye in humans (assuming experimentally derived vitreous volumes of 1.5 ml for rabbits and 4 ml for humans, respectively). Dose-related, low levels of abicipar were present in serum of all abicipar-treated rabbits. There were no systemic findings up to the highest doses tested (4.55 mg/eye for DP Formulation, 2mg/eye for DP Formulation, DP Formulation, and DP Formulation).

In study TX12065-TX in rabbits was used, which is a drug product formulation 1 lot made from interim batch. This lot was shown to have a and These impurity levels exceed those levels seen for the drug substance batches made from final material. A NOAEL of 2 mg/eye was determined for this batch, with moderate levels of cell infiltration and ocular inflammation observed at this dosage.

Abicipar was repeatedly administered via the intravitreal route to rabbits and dogs. In rabbits abicipar administered as 3 injections at 2-month interval resulted in an ocular NOAEL of 1 mg/eye which corresponds to approximately 3 mg/eye in humans. Repeated injection of the highest dose of 3 mg/eye resulted in severe intraocular inflammation in rabbits. No systemic adverse effects were observed at this dose which led to 32-fold higher systemic exposure than humans are exposed to after intravitreal injection of 2 mg/eye.

Dogs were injected with DP formulation material. Following 7 injections at monthly intervals, the ocular and systemic NOAEL was observed to be the highest dose tested, which was 3.6 mg/eye (equivalent to 7 mg/eye in humans; 60-fold of the human systemic exposure).

After a second injection of abicipar in the same eye, the inflammatory response was often more severe than after the first injection, but the severity tended to plateau after the third and subsequent administration. Apart from intraocular inflammation and its consecutive symptoms, no other ocular or systemic adverse effects were observed in rabbits or dogs after repeated intravitreal administration of abicipar.

Repeat-dose intravenous toxicity studies were conducted in rat, rabbit and monkey.

Rats were administered doses of 0.15, 1.5, 5, 15 or 50 mg/kg abicipar, 3 times per week for a period of 1 month followed by a 1 month recovery period. High dose of 50 mg/kg was not well tolerated and resulted in mortality and various signs of clinical toxicity (kidney tubular degeneration, proteinuria, hepatotoxicity). These adverse findings could be associated with known anti-VEGF effects on these VEGF-dependent tissues. Lower doses of 15 and 5 mg/kg led to decreases in body weight and food consumption, increases in kidney, spleen and liver weights, and edema of various organs, respectively.

Vascular and perivascular inflammation and increases in white blood cell counts were observed in various organs at ≥15 mg/kg. The study NOAEL was thus determined to be 1.5 mg/kg abicipar. At this dose only minor changes in some clinical parameters and kidney were observed. Systemic exposures at the NOAEL were ~615 and 41 times higher, respectively, than the corresponding C_0 and $AUC_{0\text{-tlast}}$ in humans after IVT dose of 2 mg/eye.In a tolerability study, non-pregnant NZW rabbits (3 females/group) were IV dosed with of 1, 3, or 10 mg/kg abicipar, daily for a period of 2 weeks. No adverse effects were observed in this study. On day 13, ADAs were present in all animals tested. Effect of ADAs on serum concentration have not been evaluated in this study.

In a 1-month monkey study with 1-month recovery period no mortalities or abicipar-related clinical changes were observed. ADAs were present in all 4 monkeys at the end of the recovery period after administration of the highest tested dose of 15mg/kg. However, no effect on serum concentration was observed even after repeated dosing, indicating that lack of toxicity was not due to lack of exposure. Due to the lack of adverse effects the highest tested dose (15 mg/kg) was defined as the NOAEL in monkeys. Systemic exposure at the NOAEL was approximately 8750 times (C_{max}) and 795 times ($AUC_{0\text{-tlast}}$) higher than after intravitreal injection of 2 mg/eye in humans.

Summarized, ocular NOAELs in intravitreal animal studies were comparable to proposed clinical dosage (2 mg/eye), thus resulting in quite low ocular safety margins. However, systemic exposure after IVT injection was shown to be very low and systemic NOAELs after intravenous administration of abicipar (1-15 mg/kg/day) revealed much higher safety margins.

Toxicokinetic studies were integrated into single and repeat-dose toxicity and reproductive and developmental toxicity studies. TK data is discussed in detail as part of the pharmacokinetics section above.

Studies on genotoxicity and mutagenicity have not been performed for abicipar. Neither the protein nor the PEG moiety of the drug product are expected to interact with DNA or to have genotoxic potential. The succinimide linker was shown to be non-reactive with DNA and non-genotoxic as well. Process- and product related impurities are not expected to be genotoxic.

Carcinogenicity studies with abicipar were not performed. The applicant justified absence of carcinogenicity studies accordingly: the DARPin scaffold and the PEG moiety are not expected to interact with DNA nor to induce cell proliferation. Abicipar is regarded a growth-inhibitor by binding to VEGF. No tumorigenic potential is known for other already approved anti-VEGF agents. Available nonclinical data of toxicity studies conducted with abicipar did not indicate any adverse findings that would raise concern for potential carcinogenicity of abicipar. Thus, based on the weight of evidence and consistent with ICH S6(R1), carcinogenicity studies for abicipar are not warranted.

The interim lot was used for conduction of the pivotal developmental and reproductive toxicity (DART) studies via intravenous route of administration. Dedicated comparability studies did not include this drug substance. Improved ocular tolerability in nonclinical testing was shown for final material compared to (study TX13130-TX), but not separately tested for. Thus, single dose toxicity study TX12065-TX represents the only 'comparability' study justifying the use interim material for pivotal DART studies. Justification for the use of non-commercial abicipar DS lot for evaluation of reproductive and developmental toxicity is discussed in section 3.2.5. Discussion on non-clinical aspects.

Abicipar, was administered at IV daily doses of 1, 3, and 10 mg/kg to male rats (25/group) from 28 days prior to mating, throughout mating for up to 15 days, and to female rats (25/group) from 14 days prior to mating, throughout mating to gestation day 7. Ten and 12 of 25 males were found dead or euthanized in extremis in the 3 and 10 mg/kg dosage group, respectively. One female animal was euthanized in extremis in the highest treatment group. Adverse findings in these animals included clonic convulsions, breathing difficulties, hypoactivity, and hypothermia.

Most of the surviving males showed broken or missing incisors starting from the 3 mg/kg dose. At even higher doses, males were reported with decreased body weight and food consumption, whereas reduction in body weight was already observed at 1 mg/kg dose in females.

Lower male and female fertility and copulation/conception indices were noted at ≥3 mg/kg. No drug-related effects were noted on reproductive performance for males and females or on spermatogenesis endpoints in males at 1 mg/kg, whereas cauda epididymal sperm concentrations were lower in males dosed at ≥3 mg/kg.

Intravenous administration of abicipar at 1 mg/kg (lowest dose tested) in the conducted rat fertility study resulted in increased implantation loss and reduction of intrauterine survival of embryos. These adverse effects are in line with known pharmacological effects of anti-VEGF agents, particularly the requirement of VEGF-A for endometrial function.

Internal adverse findings in males at all dosage levels included kidneys (pale, enlarged, with dark red discoloration), thymus (size reduction), prostate, seminal vesicles, coagulating glands, left and right epididymis, testis and/or bile ducts (distended and/or thickened). Pale kidneys were also observed in female animals at 10 mg/kg.

Based on the adverse findings observed in both genders at all dose levels, NOAELs for male and female systemic toxicity, male reproductive toxicity and early embryonic toxicity could not be determined in the frame of this EFD study (<1mg/kg). The NOAEL for female reproductive toxicity was considered to be 1 mg/kg. No effects on male spermatogenesis or female reproductive performance were observed at 1 mg/kg.

Systemic exposures at the NOAEL in the FED study were measured to be >20 times higher than serum levels in humans after intravitreal dosing of 2 mg/eye.

The NOAEL of the embryo-fetal development study in rats resulted in even higher systemic exposure (> 215-fold compared to humans). No adverse effects on dams or on intrauterine growth and survival and fetal morphology were observed in this study up to the highest tested dose level of 10 mg/kg. Thus, 10 mg/ml was defined to be the NOAEL for both maternal and embryo/fetal developmental toxicity within this study.

Within embryo-fetal development studies in rabbits, decreased fetal body weight was noted in all treatment groups starting at 1 mg/kg, which gave a systemic exposure at least 41 times higher than that observed in humans. NOAEL in litter was thus <1mg/kg/day in this study. Significantly lower food consumption of dams was observed at 10 mg/kg only. Contrary to rat studies, no adverse effect on intrauterine survival was detected in rabbits up to 10 mg/kg. Low placental transfer of abicipar to the amniotic fluid (0.15% of the mean maternal serum concentration) at 10 mg/kg and to fetal blood (fetal-to-maternal concentration ratios in serum: zero at 1 mg/kg, 0.06% at 3 mg/kg, 0.12% at 10 mg/kg) was observed in rabbits, but not in rats.

Fetal malformations were not observed in any of the conducted DART studies.

Studies on pre- and postnatal development have not been conducted. Absence of pre- and postnatal development studies is justified according to ICH S6(R1): extensive public information is available regarding the potential reproductive and/or developmental effects of anti-VEGF compounds. Mechanistic studies indicated that similar effects are likely to be caused by abicipar, which obviates the need for formal reproductive/developmental toxicity studies. Conduction of pre- and postnatal development studies is not expected to add new information on this drug product.

Although ocular toxicity was investigated as part of the GLP-conform intravitreal single- and repeat-dose toxicity studies discussed above, additional stand-alone intravitreal ocular tolerance studies in female rabbits were conducted during process development to compare local tolerance (frankly

intraocular inflammation) between drug lots manufactured by different processes. Although generally an absolute requirement, non-GLP compliance of these additional studies appears acceptable in this particular situation.

These studies were supported to evaluate the innate immune response to impurities from the different manufacturing processes.

Antigenicity of abicipar was evaluated in the frame of single- and repeat-dose toxicity studies. No separate immunogenicity studies were performed.

Repeated IVT doses of abicipar led to a higher incidence and titer of anti-drug antibodies (ADA) in rabbit serum compared to dog serum. The rabbit is recognized as a species with high immunologic reactivity. The ADA response was variable for individual rabbits and even following repeated high doses, some animals had low ADA serum titers.

Many animals, including monkeys, were found ADA-positive without ADAs affecting abicipar levels and/or without intraocular inflammation. Especially the situation in monkeys thus shows that decreased toxicity was not directly associated with decreased systemic drug exposure. Systemic abicipar exposure was hardly affected by ADAs in dogs and monkeys. Overall, the level of systemic exposure achieved in toxicological studies can thus be considered adequate for safety evaluation.

However, in some rats toxicokinetic values were highly correlated with presence of ADA, with decreased serum AUC after repeat dose in individual animals expressing high titer ($\geq$ 1:160) ADA. One animal had a marked decrease in its serum AUC value on Day 120, which correlated with a high antibody titer that ranged from 1/640 to 1/10240. In the medium dose group, none of the animals that had low antibody titers showed notable decreases in AUC values, in the high dose group, three animals showed marked decreases in AUC values between Day 1 and Day 120, which correlated with the high antibody titers that ranged from 1/640 to 1/81920. Individual animals having large decreases in systemic exposure and high ADA titers also exhibited pronounced ocular inflammation by ophthalmology and histopathology examination.

3.2.4. Ecotoxicity/environmental risk assessment

Abicipar pegol PEC surfacewater value is below the action limit of 0.01 µg/L. In accordance with the legally effective guideline 'Guideline on the environmental risk assessment of medicinal products for human use - First version' [EMEA/CHMP/SWP/4447/00 corr 2], PBT assessment is thus not required for abicipar pegol.

3.2.5. Discussion on non-clinical aspects

The provided in vitro data from Abicipar Pegol Allergan demonstrated a high binding affinity to its target (VEGF-A). In cell-based models this binding translates into the inhibition of VEGF-A receptor activation. Similarly, this binding translates into the inhibition of retinal vasculopathy and neovascularization in animal models.

Submitted results from in vitro and in vivo studies showed abicipar to be equipotent to aflibercept, and more potent than ranibizumab and bevacizumab.

Although changes made to the manufacturing and storage processes resulted in different ratios, they had no impact on the potency of abicipar. In vitro stability data using an artificial vitreous model demonstrated (~90% conversion within 13 days at a temperature of 37 °C) under physiological conditions. This insight leads to the conclusion, that the is predominant in vivo, regardless of during administration.

The safety pharmacology study in conscious cynomolgus monkeys showed no effects of abicipar on the respiratory and central nervous systems. The lower dose of 15 mg/kg had no effects on systemic blood pressure, pulse pressure, or electrocardiographic parameters and was assigned to be the NOAEL. The 45 mg/kg high dose produced a slight increase in systolic, diastolic, and mean arterial pressure, between approximately 2 to 7 hours after dosing. However, decreases in heart rate observed between approximately 2 and 20 hours after dosing with vehicle, 15, and 45 mg/kg doses were 15, 27, and 36% respectively, suggesting a dose-related abicipar effect on heart rate (probably compensatory for increased blood pressure) on top of a natural decrease. At the NOAEL in the IV cardiovascular, respiratory and CNS safety pharmacology study in monkeys, systemic exposure was over 10,000 times higher than the systemic exposure observed in humans.

Intravitreal injection of different DS and DP formulations of abicipar at the proposed ocular NOAELs (1-3.6 mg/eye) to rabbits and dogs resulted in intraocular inflammation. Findings included cell infiltration into the vitreous and aqueous humor, multifocal opacities, increased hyalocytes, and increased mononuclear cells in the anterior uvea, choroid and retina. These findings appeared to be dose-dependent, and were mild to moderate in severity. Adverse effects were reported to decrease with time and were often reversible during recovery period. Nevertheless, all doses tested resulted in a more or less pronounced ocular inflammation and not all animals showed complete recovery after treatment was stopped. Accordingly, individual NOAELs were determined for the respective studies.

Anti-VEGF potency was shown to be comparable between abicipar from the different processes during manufacturing development. Drug substance from successive manufacturing processes was comparable in all attributes tested, and HCP impurity content (reference is made to the quality AR). Differences in ocular toxicity between predominantly were not observed during toxicity testing.

In the last process change, changes were introduced that further reduce impurities in the . As lot was tested at very high systemic exposure levels (resulting also in very high systemic NOAELs), the applicant argues that the process changes introduced in the last development step would not be expected to significantly impact on systemic toxicity, which was attributed to (unchanged) anti-VEGF pharmacology. According to comprehensive quality assessment this argumentation is regarded acceptable. It is possible that changes in impurity levels (e.g. the intended decrease in HCP) may be an important driver of intraocular inflammation after IVT injection but are not expected to significantly impact on systemic or developmental and reproductive toxicity. Thus, interim lot could be regarded as a worst-case impurity scenario compared to commercial drug product and therefore appears qualified and representative for conduction of DART studies.

Systemic findings following IV administration of abicipar in rats occurred only at exposure levels correlating with high safety margins compared to clinical intravitreal human dose and were predominantly due to known systemic pharmacologic effects of anti-VEGF agents (e.g. slight increase in blood pressure in safety pharmacology). The absence of adverse findings in monkeys may have been due to the susceptibility of more rapidly growing rats to inhibition of VEGF-inhibition, according to the applicant's discussion. Furthermore, the applicant argues that inflammation in various organs after repeated IV administration in rats may have been a result of process-derived impurities present only in early development stage material () causing multisystem sepsis in small animals. This appears reasonable as no such multi-organ inflammation could be observed in DART studies using material showing reduced impurity levels (especially HCP as discussed later). Although intravenous clinical use of another anti-VEGF therapeutic, bevacizumab, was associated with mucocutaneous haemorrhage, arterial and venous thromboembolic events, congestive heart failure/cardiomyopathy, and gastrointestinal perforations, none of these findings were reported in nonclinical studies with abicipar. This suggests that much higher systemic exposures would be required for these adverse effects to occur which are by far not achieved after intravitreal injection of abicipar.

Adverse effects observed in the DART studies were to be expected for an anti-VEGF compound as abicipar and can be generally explained by the known systemic mechanism of such compounds acting on reproduction and development. Animal studies indicate that abicipar can impair male and female fertility. However, DART studies were conducted using intravenous administration leading to relatively high systemic exposures of abicipar when compared to intravitreal administration of 2 mg/eye proposed for human treatment (systemic exposure in animals was at least 20-fold higher than in humans in the DART studies). Therefore, observed adverse effects in the conducted DART studies are not expected to occur in humans at low systemic exposure. Adverse findings are **accordingly depicted in the SmPC** under '4.6 Fertility, pregnancy and lactation' and '5.3. Preclinical safety data'.

According to data submitted by the applicant, drug substance produced by manufacturing resulted in lower incidences and/or less pronounced manifestations of intraocular inflammation in rabbits after intravitreal injection of 3 mg/eye when compared to material. As also mentioned by the applicant, other impurities are already known inducers of ocular inflammation/uveitis. It is acknowledged that data showed only minimal

Despite the conflicting data on correlation of ADAs and intraocular inflammation in nonclinical studies, animal data might nevertheless help understanding ADA impact on intraocular inflammation in the clinical situation. In clinical studies it apparently seems as development of ADAs does correlate with development of intraocular inflammation. It is acknowledged that animal models generally do not represent the immunogenic situation in humans, however ADAs and ocular inflammation coincidently appear in both, animals and humans. The applicant discussed this ambiguous issue and presented an overall conclusion on immunogenicity and its possible correlation with onset and development of intraocular inflammation in animals and humans.

3.2.6. Conclusion on non-clinical aspects

In conclusion, abicipar has high binding affinity to VEGF-A and effectively inhibits VEGF-A- mediated in vitro and in vivo activities. Submitted results from in vitro and in vivo studies showed abicipar to be equipotent to aflibercept, and more potent than ranibizumab and bevacizumab.

From the pharmacokinetic point of view, it was shown that only minor systemic exposure occurred after intravitreal injection of abicipar. Highest exposure was found in vitreous humor, retina and choroid. Overall, the various process and formulation changes appeared comparable on the pharmacokinetic level.

Overall, the toxicology programme revealed adverse findings in single and repeat dose as well as developmental and reproductive toxicity (DART) studies after intravenous injection. However, these findings are attributable to known pharmacological anti-VEGF effects and especially findings in DART studies were not unexpected considering high systemic exposures of VEGF-inhibitor abicipar in these studies. However, according to PK/TK data such high systemic exposure will not be reached after intravitreal administration of abicipar at proposed clinical doses providing acceptable safety margins. Moreover, this information has been accordingly included in the SPC.

Intravitreal injection of abicipar resulted in intraocular inflammation in most of the animals tested. Rationale behind onset and development of intraocular inflammation is not yet completely elucidated but may be associated with ADAs, process related impurities, e.g. host cell proteins and endotoxins. Intraocular inflammation also occurs in human. Correlation with development of anti-drug antibodies could not be unambiguously clarified by nonclinical data.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

The PK, efficacy and safety of abicipar has been evaluated in a total of 9 studies. There are 6 studies for the purpose of evaluating PK, preliminary safety and efficacy including 3 studies exploring different doses of abicipar. There are two pivotal phase 3 studies where different dosing intervals are evaluated. There is one clinically complete safety and efficacy study to evaluate a modified production process of abicipar.

In addition, a clinical development programme in subjects with diabetic macular oedema is ongoing. This is not further addressed.

Table 1: Listing of conducted clinical studies in subjects with nAMD.

Study Number	Description	Number of Patients and Dose Levels[a]	Number of Treatments and Duration of Follow-up
MP0112-CP01 (terminated early)	Phase 1, multicenter, open-label, non-controlled, single ascending-dose clinical study	32 total; Abicipar: 0.04 mg: 9 0.15 mg: 7 0.4 mg: 6 1 mg: 6 2 mg: 4	Single-dose with 16-week follow-up
150998-012 (complete)	Phase 1, multicenter, randomized, open-label, parallel-group clinical study	30 total; Abicipar: 2 mg single dose: 15 2 mg 3 doses: 15	Single dose with 12-week follow-up Multi-dose: 3 doses over 8 weeks with 20-week follow-up post 1st injection
1771-101-008 (complete)	Phase 1, multicenter, open-label, single-arm clinical study	11; Abicipar 2 mg, 3 doses	3 doses over 8 weeks with 20-week follow-up post 1st injection
150998-001 (complete)	Phase 2 study with 3 stages		
Stage 1	Multicenter, open-label, non-controlled, single ascending-dose clinical study	24 total; Abicipar: 1 mg: 3 2 mg: 6 3 mg: 6 4.2 mg: 9	Single-dose with 24-week follow-up
Stage 2	Multicenter, double-masked, parallel-group, active-controlled clinical study	183 total; Abicipar: 3 mg: 58 4.2 mg: 67 Ranibizumab: 0.5 mg: 58	Up to 2 doses with 32-week follow-up post 1st injection
Stage 3	Multicenter, double-masked, parallel-group, active-controlled clinical study	64 total; Abicipar: 1 mg: 25 2 mg: 23 Ranibizumab: 0.5 mg: 16	3 doses of abicipar or 5 doses of ranibizumab with 20-week follow-up post 1st injection
150998-002 (complete)	Phase 2, multicenter, randomized, double masked, parallel group, active controlled clinical study	25 total; Abicipar: 1 mg: 10 2 mg: 10 Ranibizumab: 0.5 mg: 5	3 doses of abicipar or 5 doses of ranibizumab with 20-week follow-up post 1st injection
150998-003 (complete)	Phase 2, multicenter, randomized, double masked, parallel group, active controlled clinical study	25 total; Abicipar: 1 mg: 10 2 mg: 10 Ranibizumab: 0.5 mg: 5	3 doses of abicipar or 5 doses of ranibizumab with 20-week follow-up post 1st injection

Study Number	Description	Number of Patients and Dose Levels[a]	Number of Treatments and Duration of Follow-up
1771-201-008 (complete)	Phase 2, multicenter, single-arm, open-label clinical study	123; Abicipar 2 mg	5 doses of abicipar with 28-week follow-up post 1st injection
150998-005 (complete)	Phase 3, multicenter, randomized, double masked, parallel group, active controlled clinical study	934 total; Abicipar 2 mg: 2Q8: 312 2Q12: 312 Ranibizumab 0.5 mg: rQ4: 310	For the Week 52 analysis: Abicipar 2 mg: 2Q8: 6 active/8 sham 2Q12: 8 active/6 sham Ranibizumab 0.5 mg: rQ4: 14 active/0 sham For the entire study with follow-up to Week 104): Abicipar 2 mg: 2Q8: 14 active/11 sham 2Q12: 10 active/15 sham Ranibizumab 0.5 mg: rQ4: 25 active/0 sham
150998-006 (complete)	Phase 3, multicenter, randomized, double masked, parallel group, active controlled clinical study	942 total; Abicipar 2 mg: 2Q8: 313 2Q12: 314 Ranibizumab 0.5 mg: rQ4: 315	For the Week 52 analysis: Abicipar 2 mg: 2Q8: 6 active/8 sham 2Q12: 8 active/6 sham Ranibizumab 0.5 mg: rQ4: 14 active/0 sham For entire study with follow-up to Week 104): Abicipar 2 mg: 2Q8: 14 active/11 sham 2Q12: 10 active/15 sham Ranibizumab 0.5 mg: rQ4: 25 active/0 sham

2Q8 = 2 mg abicipar every 8th week, 2Q12 = 2 mg abicipar every 12th week, rQ4 = 0.5 mg ranibizumab every 4th week

a. Number of treated patients

3.3.1. Pharmacokinetics

Clinical pharmacokinetic (PK) data was presented from seven clinical studies in patients with nAMD:

- one Phase 1 single ascending-dose study (MP0112-CP01) in 32 patients with doses of 0.04, 0.15, 0.4, 1 and 2mg
- one Phase 1 single and repeat dose pharmacokinetic study (150998-012) in 30 patients with the 2mg dose intended for marketing
- three Phase 2 safety, tolerability, and efficacy studies (150998-001, 150998-002 and 150998-003) providing PK data for a total of 182 patients with mainly 1 and 2mg doses (stage 1 in study 150998-001 included also 3 and 4.2 mg). Studies 150998-002 and 150998-003 were performed in Japanese patients.
- and two pivotal Phase 3 registration studies (150998-005 and 150998-006) applying the intended 2mg dose in a total of 357 (193 + 164) patients.

Table 1 provides a listing and brief description of the clinical program for nAMD. More details about the design and PK sampling time points for each study are provided in **Table 2**.

Additional PK data from studies 1771-101-008 and 1771-201-008 has been presented after the clock-stop. Since the data is only considered supportive due to the limited number of samples and patients,

the presented dta is not included in this document. For further information please refer to the clinical assessment report of the D120 LoQ.

In each study the PK parameters were derived using individual serum concentration-time profiles by non-compartmental analysis and presented using descriptive statistics. In addition, a population PK analysis was performed applying a non-linear mixed effects modelling approach including additional data from two studies in patients with diabetic macular edema (DME):

- a Phase 1 single ascending dose study (MP0112-CP02) in 18 patients
- a Phase 2 safety, tolerability, and efficacy study (150998-004) in 119 patients.

Special populations were only analysed in the context of the Population PK modelling approach.

Serum concentrations of free abicipar pegol were measured in all studies. Only in one study additional concentrations of total abicipar pegol (free + VEGF-bound) was measured and the concentrations for VEGF-bound abicipar pegol calculated (total - free).

Table 2: Summary of clinical studies included in the PK analysis including nAMD and DME patients

Study #	Phase	Disease Type, Total Patients	Patients with Abicipar PK Sampled	Intravitreal Abicipar Dose (mg)	Duration (weeks)	PK Timepoints
MP0112-CP01^	1/2	AMD, 32	32	0.04, 0.15, 0.4, 1, 2 mg single dose	16	Baseline, Day 3, Weeks 1, 2, 4, 8, 12
MP0112-CP02^	1/2	DME, 18	18	0.04, 0.15, 0.4 mg single dose	16	Baseline, Day 3, Weeks 1, 4, 12, 16
150998-001*^	2	AMD, 24 (Stage 1) 183 (Stage 2) 54 (Stage 3)	24 (Stage 1) 70 (Stage 2) 48 (Stage 3)	1, 2, 3, 4.2 mg single dose (Stage 1); 3, 4.2 mg PRN after Week 4 (Stage 2) 1, 2 mg at Weeks 0, 4, and 8 (Stage 3)	24 (Stage 1) 32 (Stage 2) 20 (Stage 3)	Baseline, 1 h, Day 3, Weeks 1, 2, and 4 (Stages 1 and 2) and Weeks 6 and 8 (Stage 2) Baseline, 1 h, Day 3, Weeks 1, 4, 8, and 12 (Stage 3)
150998-002*^	2	AMD, 25	20	1, 2 mg at Weeks 0, 4, and 8	20	Baseline, 1 h, Day 3, Weeks 1, 8, and 8 + 2 days
150998-003*^	2	AMD, 25	20	1, 2 mg at Weeks 0, 4, and 8	20	Baseline, 1 h, Day 3, Weeks 1, 8, and 8 + 2 days
150998-004*^	2	DME, 151	119	1, 2 mg at Weeks 0, 4, 8, 16, 24; 2 mg at Weeks 0, 4, 8, 20	28	Baseline, 1 h, Day 3, Weeks 1, 8, and 8 + 2 days
150998-005#	3	AMD, 939	193	2 mg at Weeks 0, 4, and 8 then Q8W through Week 96; 2 mg at Weeks 0, 4, and 12 then Q12W through Week 96	104	Baseline, Day 3, Weeks 24, 24 + 2 days, 48 + 2 days, 96 + 2 days
150998-006#	3	AMD, 949	164	2 mg at Weeks 0, 4, and 8 then Q8W through Week 96; 2 mg at Weeks 0, 4, and 12 then Q12W through Week 96	104	Baseline, Day 3, Weeks 24, 24 + 2 days, 48 + 2 days, 96 + 2 days
150998-012#	1	AMD, 30	30	2 mg at Week 0, 4, and 8 (Group 1); 2 mg single dose (Group 2)	20 (Group 1) 12 (Group 2)	Baseline, 3 h, Days 2, 3, Weeks 1, 2, 4 (groups 1 and 2) and Weeks 8, 8 + 1 day, 8 + 2 days, 9, 10, 12, 14, 16, 20 (group 1) and Weeks 6, 8, and 12 (group 2)

AMD – age-related macular degeneration, DME – Diabetic macular edema, PK – Pharmacokinetic(s), PRN – as required, Q8W – every 8 weeks, Q12W – every 12 weeks.

The studies have been performed with different versions of the drug product, the formulation and the drug substance manufacturing process were revised during the development resulting in formulation 1 and 2 manufactured by. No formal bioequivalence study has been performed to compare the different versions. Instead, analytical and nonclinical studies have been performed for the comparability assessment showing an acceptable correlation between formulations and processes (please refer to the respective sections in the Quality and Non-clinical parts for more details). Most patients were included in trials evaluating the final formulation intended for marketing (Formulation 2(). In these trials, PK data for abicipar pegol were collected for 329 patients (45% of all patients with sampled PK data).

Analytical methods:

Two separate ELISA methods were established and validated for the measurement of free and total abicipar pegol in human serum including selectivity, dilution linearity, working calibration range, intra- and inter assay precision and accuracy and stability. Some documentation could not be located in the dossier.

The assay for determination of free abicipar pegol was fully validated in study report 341435, where the coating antibody was (critical reagent). The report 341975 (also named AN12004-BM with addendum AN12004-BM-A1) documents the change to a coating antibody and the partial validation of the assay after this change. The coating antibody was used for the assay since then. The reports AN13038-BM, AN14040-BM(-A1) and AN15018-BM document the qualification of the introduction of new lots of reference standard and critical reagents.

The assay for determination of total abicipar pegol was fully validated in study report AN14067-BM.

For free abicipar pegol, the lower limit of quantification was and upper limit of quantification was. For total abicipar pegol, the lower limit of quantification was and the upper limit of quantification was.

Detection of antibodies included a screening procedure and subsequently a determination of neutralizing antibodies or PEG antibodies. The applicant validated the different methods including screening cut-point, correction factor determination, drug competition test and drug competition test cut-point determination assay specificity and drug interference. The method related parameters such as intra- and inter-assay precision, assay sensitivity, selectivity, titration and prozone effect. Prozone effect was detected at high ADA concentration (between to dilutions) of the positive control.

The applicant found that analysis of study samples with MP0112 concentrations greater than or equal to may yield false negative antidrug antibody results.

The applicant validated the neutralizing antibody method including parameters as cut point determination, sensitivity, specificity, selectivity, drug tolerance, intra- and inter-assay precision, assay ruggedness, robustness, short-term, and freeze/thaw stability. The applicant found that drug concentrations above may negatively impact the ability of the assay to detect neutralizing antibodies.

The applicant validated the PEG antibody method and found that the assay for PEG antibodies tolerates <= of AGN-150998 at the LLPC level.

Population PK model:

A population PK model has been developed based on concentration data of free abicipar pegol from 733 subjects (4166 serum free abicipar pegol measurements). Data was included for doses between 0.04 mg up to 4.2 mg with the majority of samples for the intended dose of 2 mg. All values for doses below 1mg were BLQ and therefore not included for the model building. For the final model building process 1443 observations (35%) from 621 patients were used as only these were above the lower limit of quantification (0.3nM).

A one-compartment model, parameterized in terms of CL, Vc, and absorption half-life (from vitreous compartment into the systemic circulation), was chosen by the applicant.

The inter-individual variability (IIV) and the inter occasion variability (IOV) estimates on the absorption half-life ka in the final PK model were large with coefficients of variation of 70% and 92%, respectively. The IIV on CL was moderate with 37%.

In the Goodness of Fit plots for the final model deviations between the model and the observed data can be seen, especially around and before day 180. Therefore and together with the other identified shortcomings, the final model cannot be considered adequate to describe the observed data in total. It does, however, capture the general trend of the data and might subsequently be suitable for a general

descriptive purpose. Since interference of ADAs in the applied assays is likely, the results for ADA positive patients are most likely underestimated.

A variety of covariates have been evaluated: disease (DME vs AMD), sex/gender, race (Japanese vs. non-Japanese), creatinine clearance (CLCR), body weight, age, iris color, best-corrected visual acuity (BCVA), retinal thickness (CRT), concomitant ocular and systemic medications, and presence of antidrug antibodies (ADAs).

Only body weight and the presence of antidrug antibodies were identified as significant covariates on CL/F. No significant covariate was identified for the other parameters, Vc and ka.

CLCR has previously been found to significantly influence the PK (CL) of other anti-VEGF-A drugs. Therefore, its potential influence especially on CL was also analysed separately. Although including CLCR in the model reduced the OFV compared to the base model, CLCR was not included in the final model. CLCR was correlated with body weight (R=0.61), whose inclusion resulted in a greater reduction of the OFV and additionally explained the variability associated with CLCR. Therefore, only body weight and not CLCR was included as significant covariate in the final model.

The effect of the significant covariates body weight and the presence of antidrug antibodies were further analysed graphically using forest plots. The presence of antidrug antibodies increased CL by 1.65-fold resulting in a 39.7% decrease of serum AUCss. The estimated effect of body weight was compared to a typical subject of 78kg (based on the included patients). AUCss was increased by a median of 29.8% in a subject with low body weight (60 kg), while median exposure would be decreased by a median of 22.9% in a 100-kg subject.

Exploration of the effect of the different formulations of abicipar pegol used during the development did not show any effect on either CL or ka based on the final PK model, which is consistent with the non-compartmental data from the individual studies and the analytical and non-clinical comparability analyses.

Absorption:

Abicipar pegol is administered to the target organ via an intravitreal injection where abicipar pegol binds with high affinity to its target VEGF-A forming an inactive and very stable complex.

The subsequent absorption into the systemic circulation is low and reveals variable serum concentrations for both free and VEGF-bound abicipar pegol. A single 2 mg dose of the to-be-marketed formulation was evaluated in several studies. In these studies mean Cmax values for free abicipar pegol have been found ranging from 0.998 ± 0.744 nM to 1.55 ± 1.66 nM (see **Table 3**). VEGF-bound abicipar pegol has only been measured in one study resulting in a mean Cmax of 1.04 ± 0.76 nM. The ratio between free and VEGF-bound abicipar pegol in the systemic circulation is approximately between 1.5 and 1.8.

$AUC_{0\text{-}tlast}$ [nM•day] varied for a single injection between 4.88 ± 3.95 and 6.50 ± 5.50 for free abicipar pegol and between 8.75 ± 6.33 and 13.1 ± 9.6 for VEGF-bound abicipar pegol. The higher AUC for VEGF-bound abicipar pegol can be explained by the longer serum $T_{1/2}$ and is considered less relevant due to the inactivity of the VEGF-bound form.

Further, the absorption into the systemic circulation of abicipar pegol is slow: T_{max} ranging from 1-3 days for free abicipar pegol, and T_{max} ranging from 7-8 days for VEGF-bound abicipar pegol.

Comparably low systemic exposures of active substance have been observed between formulations and different manufacturing processes (see **Table 3**). This is in line with the results of analytical and nonclinical studies concerning the comparability of formulations/products.

No food interaction studies have been performed, which is acceptable. No food effect is expected, as abicipar, Allergan is given intravitreal.

Table 3: Comparison of Serum Pharmacokinetic Parameters of Free Abicipar Across Drug Substance Processes and Formulations Following a Single Intravitreal Injection of 2 mg Abicipar in Patients with Neovascular Age-Related Macular Degeneration

Abicipar Process	Cmax (nM)	AUC0-tlast (nM●Day)	Tmax (Days)	N	Study Number
Formulation 1	2.66 ± 1.61	9.11 ± 7.60	1	6	150998-001 (Stage 1)
	1.05 ± 0.60	NC	3	22	150998-001 (Stage 3)
Formulation 1	2.03 ± 2.18	NC	3	10	150998-002
	1.98 ± 2.13	NC	3	10	150998-003
Formulation 2	1.52 ± 1.05	6.50 ± 5.50	1	14	150998-012
	1.04 ± 0.76	NC	3	78	150998-005
	1.38 ± 1.26	NC	3	84	
	1.55 ± 1.66	NC	3	70	150998-006
	0.998 ± 0.744	NC	3	83	

NC = not calculable; Data presented as mean ± standard deviation; T_{max} presented as median

Distribution

The distribution of free abicipar pegol is similar to endogenous human antibodies within the vascular and extracellular spaces.

No information is given for VEGF-bound abicipar pegol, but it is not expected to distribute outside the vasculature due to its larger molecular weight.

Elimination

Abicipar pegol is slowly cleared from the target organ, the eye, in both forms – free and VEGF-bound into the systemic circulation. Free abicipar pegol reached systemic T_{max} after 1-3 days with a $T_{1/2}$ from the eye to the systemic circulation of up to 9.6 days (mean 4.5 days) while VEGF-bound abicipar pegol reached serum T_{max} after 7-8 days with an eye-to-serum $T_{1/2}$ of up to 11 days.

Free abicipar pegol in serum showed an estimated typical $T_{1/2}$ of 9.5 hours leading to concentrations BLQ within 1-4 weeks depending on the administered dose (2mg: 2-4 weeks) while VEGF-bound abicipar pegol exhibited a serum half-life of approximately 6.4 to 11.0 days with no detectable serum concentrations after 2-8 weeks.

In the PopPK analysis significant covariate for systemic clearance were identified: The presence of ADAs increased systemic clearance by 1.65 fold, while systemic clearance was increased or decreased

by body weight. The effect of body weight was however considered to be not clinically relevant due to the higher IIV on CL of 37%.

The excretion of abicipar pegol was not investigated. Since abicipar pegol is a therapeutic protein and therefore assumed to be degraded to amino acids and protein fragments.

No active metabolites of abicipar are known.

Dose proportionality and Time dependency

All serum concentrations for doses below 1 mg were BLQ. Serum concentrations could be measured for administered doses of 1, 2, 3 and 4.2 mg. For all investigated doses serum concentrations were below the limit of quantification after 1- 4 weeks. A slightly less than dose proportional increase in exposure ($AUC_{0\text{-}last}$) was observed for doses of 2mg and above.

Repeated abicipar pegol administration was only performed for the 2 mg dose. The exposure after three monthly injections was similar to the observed exposure after the first injection (see also next section).

It is noted that dose proportionally was assessed in this study with an earlier version of the product and not with the final to be marketed abicipar pegol product. However, conclusions are still considered informative to characterise abicipar pegol PK. Abicipar pegol is administered as a fixed dose (2mg) only and does not accumulate with the proposed dosing regimen, therefore dose proportionality is less relevant in clinical practice.

Abicipar pegol was administered in different dosing regimen in single and multiple doses in the included studies. In addition both phase III studies (-005 and -006) investigated different dosing intervals for a long term treatment - 2Q8 and 2Q12. PK data was collected for 307 patients (2Q8: 146; 2Q12: 161) two days after the first injection and after the injections at week 24 and 48. Another sampling is planned after week 96.

Free and VEGF-bound abicipar pegol C_{max} were in general similar between single and multiple dosing regimen. Only data for free abicipar pegol is available for the different dosing intervals 2Q8 and 2Q12, but results can be extrapolated to VEGF-bound abicipar pegol as the ratio seems rather stable. The presented systemic concentrations of free abicipar pegol are in general similar between both intervals with high variability, which has also been observed with a single dose.

No accumulation was observed for free and VEGF-bound abicipar pegol after three monthly IVT injections (study 150998-012) which represents the most frequent dosing regimen tested. PK data for free abicipar pegol for the 2Q8 and 2Q12 dosing regimen in studies 150998-005 and 150998-006 do also not indicate accumulation over 48 weeks. The latter being the intended dosing regimen for this MAA. Given the low systemic exposure and the fast clearance of free abicipar pegol, accumulation is considered unlikely also during long term treatment with the intended regimen.

The presence of anti drug antibodies (ADAs) decreased the systemic exposure considerably after repeat dosing. Auc0-tlast dropped from 6.15 to 1.92 nM*day.

Special populations

The applicant did not perform dedicated studies with renal or hepatic impaired patient.

Patients with different stages of renal impairment were however included in the clinical trials based on the co-morbidities of the target elderly population. A potential impact of renal impairment and creatinine clearance were analysed in the popPk analysis and found to be non-significant. Nevertheless, creatinine clearance was correlated with body weight - a significant covariate and the data showed in general high variability.

No influence of hepatic impairment on the PK of abicipar pegol is expected due to its elimination via degradation and its low concentration compared to daily protein intake.

The elderly population is the main target population for abicipar pegol and the majority of data was generated in this population.

No difference in the PK have been identified between male and female patients as well as between Japanese and non-Japanese patients.

No data is available for children which is acceptable since the European Medicines Agency issued a class waiver for all classes of medicinal products for treatment of age-related macular degeneration and diabetic macular oedema (CW/0001/2015).

The proposed wording on special populations in section 4.2 of the SmPC is:

Special populations

Elderly

No dose adjustment is required in the elderly (see section 5.1).

Hepatic impairment

Abicipar Pegol Allergan has not been studied in patients with hepatic impairment.

Renal impairment

Dose adjustment is not needed in patients with renal impairment (see section 5.2).

Paediatric population

There is no relevant use of abicipar pegol in the paediatric population for the indication of wet AMD. See section 5.1.

Interactions

No dedicated interaction studies have been performed for abicipar pegol. The applicant discussed potential direct and indirect interactions based on literature and previously authorized other drugs approved for the treatment of nAMD including the same method of action (VEGF-binding).

The assumed elimination of abicipar pegol through degradation does not involve CYP proteins excluding interactions with drugs via this pathway. Further, a potential interaction via altered pro-inflammatory cytokine levels is not expected for abicipar pegol. As well as, interactions through unspecific binding are unlikely due to abicipar pegol's high affinity and specificity to VEGF-A.

A potential interaction with other anti-VEGF-medicinal products has not been studied but seems very likely. Respective concomitant medication should therefore not be administered neither ocular nor systemic (see attached documents SmPC &PIL).

Besides other anti-VEGF-medicinal products, the interaction potential of abicipar pegol is overall considered low, both for systemic exposure and in the target organ.

3.3.2. Pharmacodynamics

The mechanism of action of abicipar is through the binding of soluble isoforms of VEGF-A. By binding to VEGF-A, abicipar prevents these isoforms from binding to their receptors and activating VEGF signalling pathways.

No specific PD studies have been conducted since it is not ethically justified to administer a drug through IVT injection to healthy volunteers or to do intraocular sampling in. Reference is given to the Non-clinical section. Pharmacodynamic aspects have been addressed in the Phase III clinical studies that are supported by earlier Phase I and II studies (See Clinical Efficacy). No specific studies on secondary pharmacology or PD interaction studies have been conducted.

Immunogenicity

Immunogenicity was assessed in the 7 studies that included PK analyses (MP0112-CP01, 150998-001, 150998-002, 150998-003, 150998-005, 150998-006, and 150998-012) as summarised in the below table. The studies evaluated different drug substances (DS) and formulations (Form) of abicipar. In all studies but Study MP0112-CP01 where only anti-abicipar binding antibodies (BABs) were evaluated, the development of BABs, neutralising anti-abicipar antibodies (NABs) and anti-PEG antibodies were evaluated. All studies but Study 150998-001 included treatment-naïve subjects with nAMD. In Stage 1 of Study 150998-001, subjects with advanced nAMD were enrolled; however, their previous treatment status is not clear.

Table 4: Immunogenicity assessment in clinical studies with abicipar

Study	Formulation/ Treatment	Abicipar dose (mg)	Sampling schedule
MP0112-CP01 EU	Form 1 (), single	0.04, 0.15, 0.4, 1, 2	Pre-dose, w. 4, 8, 12
150998-001 Global	Form 1 (), Stage 1: single Stage 2: 2 injections Stage 3: 3 injections	Stage 1: 1, 2, 3, 4.2 Stage 2: 3, 4.2 Stage 3: 1, 2	Stage 1: Pre-dose, w. 4, 8, 16, 24 Stage 2: Pre-dose, w. 2, 4, 8, 20 Stage 3: Pre-dose, w. 4, 12, 20
150998-002 Japan	Form 1 (), repeat	1, 2 vs. ranibizumab o.5 mg	Pre-dose, w. 4, 8, 12, 16, 20
150998-003 US	Form 1 (), repeat	1, 2 vs. ranibizumab o.5 mg	Pre-dose, w. 4, 8, 12, 16, 20
150998-005 Global	Form 2 (), repeat	2	Pre-dose, w. 4, 12, 28, 52 and in case of significant AE
150998-006 Global	Form 2 (), repeat	2	Pre-dose, w. 4, 12, 28, 52 and in case of significant AE
150998-012 US	Form 2 () Group 1: 3 injections Group 2: single	2	Group 1: Pre-dose, w. 4, 8, 12, 14, 16, 20 Group 2: Pre-dose, 4, 6, 8, 12

Pre-existing immunogenicity

Pre-existing immunogenicity was low. In the earlier studies (MP0112-CP01, 150998-001, 150998-002 and 150998-003), one subject out of 268 subjects enrolled to any of the abicipar-treatment groups had pre-existing BABs and NABs. In the confirmatory studies and in Study 150998-12, less than 1% of subjects were positive for pre-existing BABs, NABs or anti-PEGs.

Immunogenicity following drug exposure

In the Phase I and II studies following a single, or the first IVT injection, BABs developed in 0% to 40% of subjects. Also NABs developed after the first injection, but to a lower extent (0% to 13% of subjects). Serum titers were overall low and generally observed from weeks 6 to 8. The incidence of BABs and NABs increased following repeated injections with up to 60% and 33% being BAB- and NAB-positive, respectively. Titers were highly variable, remained stable or decreased by the last visit. Anti-PEGs were detected in 2 patients in Study 150998-001 only.

In the pivotal Phase III Studies 150998-005 and 150998-006, the incidence of BABs peaked within the first 12 weeks in both abicipar 2 mg abicipar every 8th week (2Q8) and 2 mg abicipar every 12th week

(2Q12) dose groups, plateaued at Week 28, and declined by Week 52. In the pooled studies, the maximum number of patients developing BABs at any visit was 32.0% and 36.3% in the abicipar 2Q8 and 2Q12 dose groups, respectively, see below table. After repeat injections, the incidence of NABs reached a maximum of 24.4% and 29.9% for abicipar 2Q8 and 2Q12, respectively. Among subjects developing BABs and NABs, for both regimens, these were persistent in approximately 85%. The incidence of Anti-PEGs was detected in approximately 6% of subjects.

The incidence of BABs was slightly higher in Study 150998-005 with 35% and 38% of subjects in the 2Q8 and 2Q12 dose groups, respectively, developing BABs at any time. In Study 150998-006, the corresponding figures were 29% and 35%. A slightly higher proportion of subjects developed NABs in the 2Q8 treatment arm in Study 150998-005 (26.4% vs. 22.4%) while in the 2Q12 treatment arms, the incidence between studies was similar (30.5% vs. 29.3%).

Table 5: Pooled Summary of the Antibody Responses in Studies 150998-005 and 150998-006 (Safety Population)

Abicipar 2Q8						
Injection	**0**	**1**	**3**	**5**	**8**	
Visit	**Baseline**	**4**	**12**	**28**	**52**	**Any visit[a]**
N	611	609	573	524	487	625
BAB Incidence (%)	4 (0.7)	36 (5.9)	149 (26.0)	128 (24.4)	92 (18.9)	200 (32.0)
BAB Titers	15	40	320	320	320	640
(median [range])	(10 – 40)	(10 - 2560)	(10 – 10240)	(10 – 163840)	(10 – 81920)	(10 – 163840)
NAB Incidence (%)	0 (0.0)	8 (1.3)	95 (16.6)	90 (17.2)	73 (15.0)	152 (24.3)
Anti-PEG Incidence (%)	4 (0.7)	7 (1.2)	14 (2.4)	4 (0.8)	3 (0.6)	23 (3.7)
Anti-PEG Titers (median [range])	80 (40 – 640)	40 (20 – 80)	30 (20 – 160)	100 (20 – 320)	20 (20 – 640)	40 (20 – 640)
Abicipar 2Q12						
Injection	**0**	**1**	**2**	**4**	**6**	
Week	**Baseline**	**4**	**12**	**28**	**52**	**Any visit[a]**
N	608	599	581	528	486	625
BAB Incidence (%)	1 (0.2)	40 (6.7)	187 (32.2)	157 (29.7)	118 (24.3)	227 (36.3)
BAB Titers	10	40	320	640	640	640
(median [range])	(10 – 10)	(10 – 640)	(10 – 81920)	(10 – 40960)	(10 – 20480)	(10 – 81920)
NAB Incidence (%)	0	9 (1.5)	118 (20.3)	128 (24.3)	93 (19.1)	187 (29.9)
Anti-PEG Incidence (%)	4 (0.7)	16 (2.7)	17 (2.9)	8 (1.5)	5 (1.0)	35 (5.6)
Anti-PEG Titers (median [range])	30 (20 – 80)	60 (20 – 640)	40 (20 – 160)	40 (20 – 80)	40 (20 – 80)	40 (20 – 640)

Anti-PEG = anti-polyethylene glycol against the PEG moiety of abicipar; BAB = binding antibodies against abicipar; NAB = neutralizing antibodies

[a] The overall result for a subject is considered to be positive if the patient has at least one positive result in any visit.

Antibody responses at week 52 and 104 is summarised in the below table.

Table 6: Summary of Antibody Response, Week 52 and Week 104, Safety Population, Studies 150998-005 and 150998-006 Pooled

	Abicipar 2Q8 Any Visit by Week 52a	Any Visit by Week 104[a]	Abicipar 2Q12 Any Visit by Week 52a	Any Visit by Week 104[a]
N	625	625	625	625
BAB Incidence (%)	200 (32.0)	212 (33.9)	227 (36.3)	243 (38.9)
BAB Titers (median [range])	640 (10 – 163840)	320 (10 – 1310720)	640 (10 – 81920)	640 (10 – 655360)
NAB Incidence (%)	152 (24.3)	159 (25.5)	187 (29.9)	196 (31.4)
Anti-PEG Incidence (%)	23 (3.7)	25 (4.0)	35 (5.6)	37 (5.9)
Anti-PEG Titers (median [range])	40 (20 – 640)	40 (20 – 640)	40 (20-640)	40 (20 – 640)

Anti-PEG = anti-polyethylene glycol against the PEG moiety of abicipar; BAB = binding antibodies against abicipar;
NAB = neutralizing antibodies
[a] The overall result for a patient is considered to be positive if the patient has at least one positive result in any visit.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics

Abicipar pegol is administered to the target organ via an intravitreal injection where abicipar pegol binds with high affinity to its target VEGF-A forming an inactive and very stable complex. Both – free and VEGF-bound abicipar pegol are subsequently absorbed into the systemic circulation. The systemic ratio between free and VEGF-bound abicipar pegol is approximately between 1.5 and 1.85.

Clinical PK data for systemic abicipar pegol have been collected in seven studies in nAMD patients and two studies in patients with diabetic macular edema (DME). Additional PK data from two currently ongoing studies are expected to be submitted during the procedure. Free serum abicipar pegol has been measured in all studies (738 patients), while VEGF-bound abicipar pegol was only measured in one study in a very limited number of patients (N=24). Additional PK data from studies 1771-101-008 and 1771-201-008 has been presented after the clock-stop. This additional data is only considered supportive due to the limited number of patients compared to the overall dataset. Nevertheless, the results of both studies are consistent with the PK results presented previously.

The limited number of data for VEGF-bound abicipar pegol is also due to ADA interference with the assay. Potential interference of ADAs for the measurement of free abicipar have not been studied but are considered probable, which was also acknowledged by the applicant. Therefore serum level of free abicipar pegol in ADA positive patients are likely to be underestimated. However, the number of ADA positive patients is limited. Therefore the overall analysis of pharmacokinetics is still considered valid.

The presented studies have been performed with different versions of the drug product as the formulation and the drug substance manufacturing process were revised during the development. No formal bioequivalence study has been performed but analytical and nonclinical studies showed an acceptable correlation between formulations and processes. Beyond that, the clinical PK data package generated with the abicipar pegol product version intended for marketing is large and adequate for the assessment of systemic PK properties (329 patients).

Both – free and VEGF-bound abicipar pegol - are slowly absorbed into the systemic circulation from the vitreous with a T_{max} of 1-3 days for free and 7-8 days for VEGF-bound abicipar pegol. The estimation of

T_{max} needs however further justification (LoQ), $T_{1/2}$ from the eye was up to 9.6 days for free and up to 11.0 days for VEGF- bound abicipar pegol. Low systemic concentrations were found after intravitreal application; for a 2 mg dose with the abicipar pegol version intended for marketing the mean Cmax of free abicipar pegol was ≤ 1.55 ± 1.66 nM, the mean Cmax of VEGF-bound abicipar pegol was ≤ 1.04 ± 0.76 nM. $AUC_{0\text{-tlast}}$ varied for a single injection between 4.88 ± 3.95 and 6.50 ± 5.50 nM*day for free and between 8.75 ± 6.33 and 13.1 ± 9.6 nM*day for VEGF-bound abicipar pegol. The higher AUC for VEGF-bound abicipar pegol might be due to the longer serum $T_{1/2}$, but is considered less relevant due to the inactivity of the VEGF-bound form of abicipar pegol. The distribution of free abicipar pegol is similar to endogenous human antibodies within the vascular and extracellular spaces. The pharmacokinetic profile of VEGF-bound abicipar pegol was not studied in more detail since the complex is assumed to be inert due to its high specific and stable binding. No data is availbale on the distribution of the complex, however it is agreed that due to its high molecular weight a distribution outside the vasculature is unlikely.

Systemic exposure increased with increasing dose and appeared to be slightly less than dose proportional at doses above 2 mg (the dose planned for registration). No systemic accumulation was observed for free or VEGF-bound abicipar pegol regardless of the applied administration schedule (2Q8, 2Q12) over a 48 week observational period. Overall, the clearance is rather rapid: Free abicipar pegol in serum showed a $T_{1/2}$ of 9.5 hours leading to concentrations BLQ within 1-4 weeks depending on the administered dose (2mg: 2-4 weeks) while VEGF-bound abicipar pegol exhibited a serum half-life of approximately 6.4 to 11.0 days with no detectable serum concentrations after 2-8 weeks.

While the mean systemic concentration was low, a relatively high variability was observed throughout the clinical PK studies, which could also not be explained by a variety of covariates tested in the population PK analysis. Only body weight and the presence of antidrug antibodies were identified but a high variability remains (absorption half-life: IIV: 70% and IOV: 92%; clearance: IIV: 37%.). A highly variable background for the analysis of systemic PK parameters is likely already introduced by the variable leakage from the vitreous into the systemic circulation and other factors might contribute subsequently, like body weight, renal clearance and ADA status. The clinical relevance of this high variability had to be clarified. Therefore, the maximum possible systemic exposure to be achieved with the intended dose of abicipar was estimated by sketching a 'worst-case' scenario in terms of identified factors of variability including body weight, renal clearance and ADA status. The simulated maximum values (17.9nM for Cmax and 113nM*Day for AUC) are lower than the systemic NOAEL in rats receiving apicipar pegol via IV infusion. Further, the highest observed serum concentration in the clinical studies was 10.6nM and no adverse events were observed that would be expected as result of systemic VEGF-inhibition. Consequently, the potential risk for clinically relevant systemic effects of free-VEGF is considered minimal.

The provided population PK model cannot be considered adequate to describe the observed data in total but the model captures the overall trend and is only of supportive character. However, the underestimated values of ADA positive patients resulting from the assay need to be kept in mind.

Special population:

No difference in PK have been identified between male and female patients as well as between Japanese and non-Japanese patients. The elderly population represents the target population for abicipar pegol and is therefore represented adequately. No data is available for children but this is acceptable since the European Medicines Agency issued a class waiver for all classes of medicinal products for treatment of age-related macular degeneration and diabetic macular oedema (CW/0001/2015).

The applicant did not perform dedicated studies in renal or hepatic impaired patient. While no influence of hepatic impairment on the PK of abicipar pegol is expected due to its elimination via degradation

and its low concentration compared to daily protein intake, creatinine clearance has been identified to influence the PK of other anti-VEGF-drugs. Due to co-morbidities of the target elderly population, PK data from patients with different stages of renal impairment were available and analysed separately in the population PK analysis. No significant influence on the PK of different stages of renal impairment or creatinine clearance was identified.

Interactions:

No dedicated interaction studies have been performed for abicipar pegol. The applicant discussed potential direct and indirect interactions based on literature and previously authorized other drugs approved for the treatment of nAMD including the same method of action (VEGF-binding). While no interactions are expected involving CYP proteins, altered pro-inflammatory cytokine level or interactions through unspecific binding, potential interaction with other anti-VEGF-medicinal products seem however likely and require respective amendments to the SmPC. Besides other anti-VEGF-medicinal products, the interaction potential of abicipar pegol is overall considered low, both for systemic exposure and in the target organ.

Exposure relevant for safety evaluation:

The relatively low systemic exposure of free abicipar pegol and its rapid clearance from the system result in a low potential for systemic VEGF inhibition. No dedicated analysis has been performed but adverse events associated with systemic VEGF inhibition have been defined as adverse events of special interest including arterial thromboembolic events (ATEs). ATEs have been observed in both phase III studies at similar rates for both dosing regimen and the comparator ranibizumab – also a VEGF-A inhibitor (see safety assessment). Although, this is reassuring, the sensitivity to detect such events or a respective exposure-adverse event relationship in the performed trials is considered low. Although high variability of the data was observed, a potential risk for clinical implications of higher systemic levels of abicipar pegol is considered minimal (see above).

No clinical PK data are available for the target organ –the eye- itself as it is not ethically justified to do intraocular sampling in patients. The ocular PK of abicipar pegol has been studied in rabbits. The applicant provided a comprehensive discussion of recent literature focussing on the comparability of ocular pharmacokinetics in rabbits and humans. Although physiological differences between human and rabbit eye exist, the properties of the rabbit eye seem sufficiently comparable to the human eye to allow extrapolation of data for abicipar pegol. Further, given the observed vitreal half-life and the intended dosing regimen, a potential accumulation of abicipar pegol in the eye is considered minimal.

Also, potential effects of ADAs on intraocular abicipar pegol were not investigated in humans, at the same time an impact of ADA status on the efficacy and safety has been observed during clinical assessment and led to major concerns (see following clinical sections). ADAs reduce the systemic exposure of free abicipar pegol by an increased systemic clearance (1.65-fold) according to popPK analysis, indicating relevant interaction potential. The potential local interaction of abicipar pegol and ADAs in the human eye is unclear especially in patients with nAMD when the blood-retinal barrier becomes "leaky". No clinical data can be obtained due to ethical considerations. Further, no literature is available about potential correlations of systemic ADAs to local ocular effects. The developed PopPK modelling suggests that vitreal clearance was not impacted by the presence of ADAs. It is however unclear, whether the model and the obtained systemic PK data are suitable to inform such conclusions.

Abicipar pegol is a protein conjugate consisting of the designed ankyrin repeat protein (DARPin®) covalently bound to a 20 kDa methoxy polyethylene glycol maleimide (mPEG-Mal). The applicant provided a discussion based on a few publications but could not provide further information concerning the elimination of the PEG part of the composite molecule in both the eye and the circulation system, but no non-clinical findings indicate an accumulation of the PEG moiety in the eye or other tissues.

Accumulation of the PEG moiety in the eye is considered unlikely. Consequently, a potential connection with the observed intraocular inflamations is also considered minimal. Although, based on the provided information a risk for accumulation of PEG in other tissues cannot be ruled out, it is considered minimal and likely not clinically relevant: PEG accumulation in different tissues after administration of other drugs has so far been observed after long term treatment with much higher doses of the respective drugs. The applied IVT dose and the observed systemic abicipar pegol concentrations are much lower than for those products. Additionally, the expected treatment duration in the patient population, although potentially life long is currently unlikely to be long enough to lead to PEG accumulation in tissue with the observed much lower concentrations.

Pharmacodynamics

Abicipar, as a pegylated composite protein, has a mechanism of action similar to ranibizumab and aflibercept. Thus, its key action is through the binding to and neutralising the effect of VEGF-A with a subsequent reduction of neovascularisation and oedema in subjects with nAMD. No specific clinical pharmacodynamic studies have been conducted, but PD parameters (e.g. central retinal thickness, CRT) have been evaluated in the efficacy and safety studies with abicipar as well as in a retinal vasculopathy model in the non-clinical setting.

The applicant has explained that DARPin moiety of abicipar aims to overcome some limitations of monoclonal antibodies by facilitating manufacturing (expressed in bacteria), avoiding bivalent target binding, reducing systemic exposure and creating a very high-affinity molecule. However, there is a high incidence of antibodies against abicipar. Abicipar (34 kDa) has a lower molecular weight than ranibizumab (48 kDa) and an ~6-fold higher molar dose. Abicipar also has a higher binding affinity for VEGF and a longer vitreal half-life (See Non-clinical), compared with ranibizumab. Together, the administration of an increased molar dose, a higher binding affinity and longer vitreal half-life, according to the applicant, abicipar aims at reducing the treatment burden by lowering the number of IVT injections required compared with other anti-VEGF therapeutics. This is further addressed in the clinical efficacy and safety studies.

Immunogenicity is one of the concerns related to the administration of therapeutic proteins, which can result in loss of response or adverse effects. Only occasional subjects (≤1%) had BABs at baseline. In patients treated with abicipar 2 mg, a large proportion of patients developed anti-drug antibodies (ADAs) after treatment, a proportion already after the first injection. The prevalence of BABs ranged from 0% to 75% after a single dose, and from 13% to 46% after repeated doses. For NABs, the prevalence was up to 13% after single dose and was generally increased after repeated doses (range 9% to 33 %). The appearance of PEG antibodies was lower with a prevalence of 0% to 5.7% after repeated doses. Titers generally increased after repeated administration of abicipar. With the exception of no or a low incidence of BABs at the lowest doses in the earlier studies, across studies, there was no clear correlation with dose and the incidence of BABs. A large proportion of the BABs were neutralising.

In the pivotal studies (Studies 150998-005 and 150998-006), the incidence of BABs peaked within the first 12 weeks in both abicipar 2Q8 and 2Q12 dose groups, plateaued at Week 28, and declined by Week 52. Up to week 52, the maximum number of patients developing BABs at any visit was 32% and 36% in the abicipar 2Q8 and 2Q12 dose groups, respectively. After repeat injections, the incidence of NABs reached a maximum of 24% and 30% for abicipar 2Q8 and 2Q12, respectively. Thus, the majority of BABs were neutralising. Anti-PEGs were detected in approximately 5% of subjects.

During the 2nd treatment year, an additional 27 and 31 subjects in the 2Q8 and 2Q12 treatment arms developed BABs, i.e. an additional 4% and 5% of patients developed BABs. The corresponding numbers for NABs were 35 and 37 (corresponds to approximately 6%) and 12 and 12 (i.e. approximately 2%) for Anti-PEGs.

Since very few subjects were BAB positive at baseline, it is not possible to conclude whether a positive pre-existing BAB status might increase the probability of developing BABs or NABs upon treatment with abicipar. Further, all or essentially all subjects (not clear for the limited number of subjects enrolled in Stage 1 of Study 150998-001) were treatment-naïve and this should be addressed in the SmPC **(SmPC)**.

A main concern related to abicipar is that a large proportion of patients develop intraocular inflammation (IOI) and the risk of experiencing an IOI is 10-fold increased in subjects with ADAs. The clinical relevance on efficacy and safety for the pivotal efficacy and safety studies is discussed in the below parts of the report.

3.3.4. Conclusions on clinical pharmacology

Overall, the pharmacology programme is considered acceptable. A large proportion of patients develop BABs and NABs. This increases the risk of developing IOIs that also have an impact on efficacy and safety and of major concern, see below parts of the report.

3.3.5. Clinical efficacy

See **Table 1**.

The clinical development programme for abicipar included Study MP0112 CP01 (Phase I), Studies 150998 001, 150998 002 and 150998 003 (Phase II) that evaluated different single and repeat doses of abicipar while the two pivotal Studies 150998 005 and 150998 006 (Phase III) evaluated different dosing intervals of 2 mg abicipar pegol. In addition, one safety and efficacy study, Study 1771-201-008 evaluates a modified drug substance production process of abicipar.

Dose-response studies and main clinical studies

Dose response studies

The selection of the 2.0 mg dose of abicipar pegol for Phase III studies were based on non-clinical PD data that focused on the durability of efficacy and Phase I/II clinical studies conducted in nAMD patients (Studies MP0112 CP01, 150998 001, 150998 002 and 150998 003).

All studies included subjects with evidence of active primary progressive subfoveal CNV, increased CRT and an impaired BCVA. Evaluations of efficacy differed somewhat between studies but included visual acuity, CRT, changes in FA, proportion of subjects receiving rescue therapy, and time to rescue therapy. All, or essentially all, subjects (not clear for the limited number of subjects enrolled in Stage 1 of Study 150998-001) were treatment-naïve.

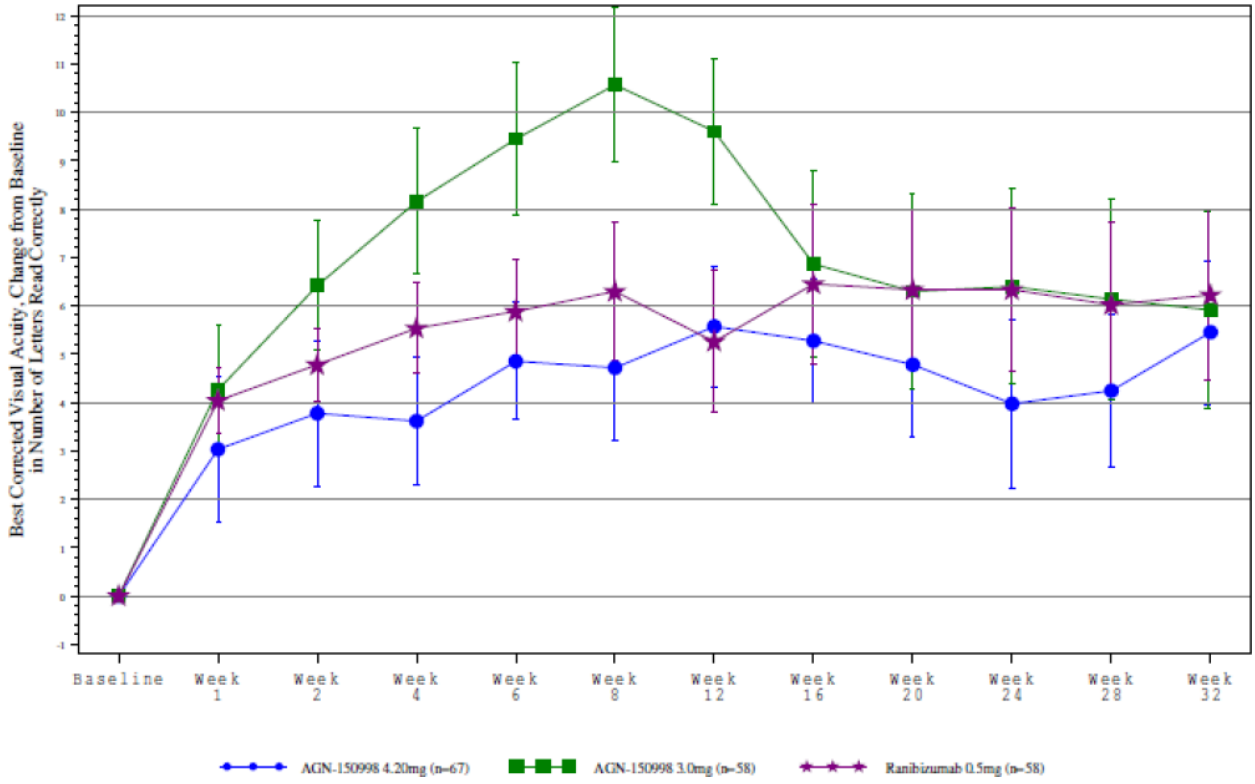
Study 150998-001 was a single and repeat dose study in three stages:

- Stage 1: open-label, single dose, non-controlled, dose escalation evaluating up to 4.2 mg abicipar in 24 subjects randomised 1:1:1:1.
- Stage 2: randomised double-masked comparison of 3.0 and 4.2 mg abicipar vs. ranibizumab in 183 subjects randomised 1:1:1. Patients received treatment at baseline and at week 16 or between week 4 and week 16 in case of active disease. Patients were followed up to week 32.
- Stage 3: randomised double-masked comparison of 1.0 and 2.0 mg abicipar vs. ranibizumab in 64 subjects randomised 2:2:1. Abicipar was administered at baseline, week 4 and week 8 (and sham weeks 12 and 16) vs. 0.5 mg ranibizumab administered every 4 weeks up to week 16. Patients were followed up to week 20.

In Stage 1, abicipar 1.0 mg was selected as the starting dose since this was the maximally tolerated dose in previous phase 1 studies conducted by Molecular Partners using the original manufacturing process (abicipar-1). Selection of the 2.0 mg, 3.0 mg and 4.2 mg doses was based on a rabbit GLP bridging toxicology study that compared the drug product (abicipar-2) used in this study with drug product (abicipar-1) tested in the previous phase 1 studies conducted by Molecular Partners.

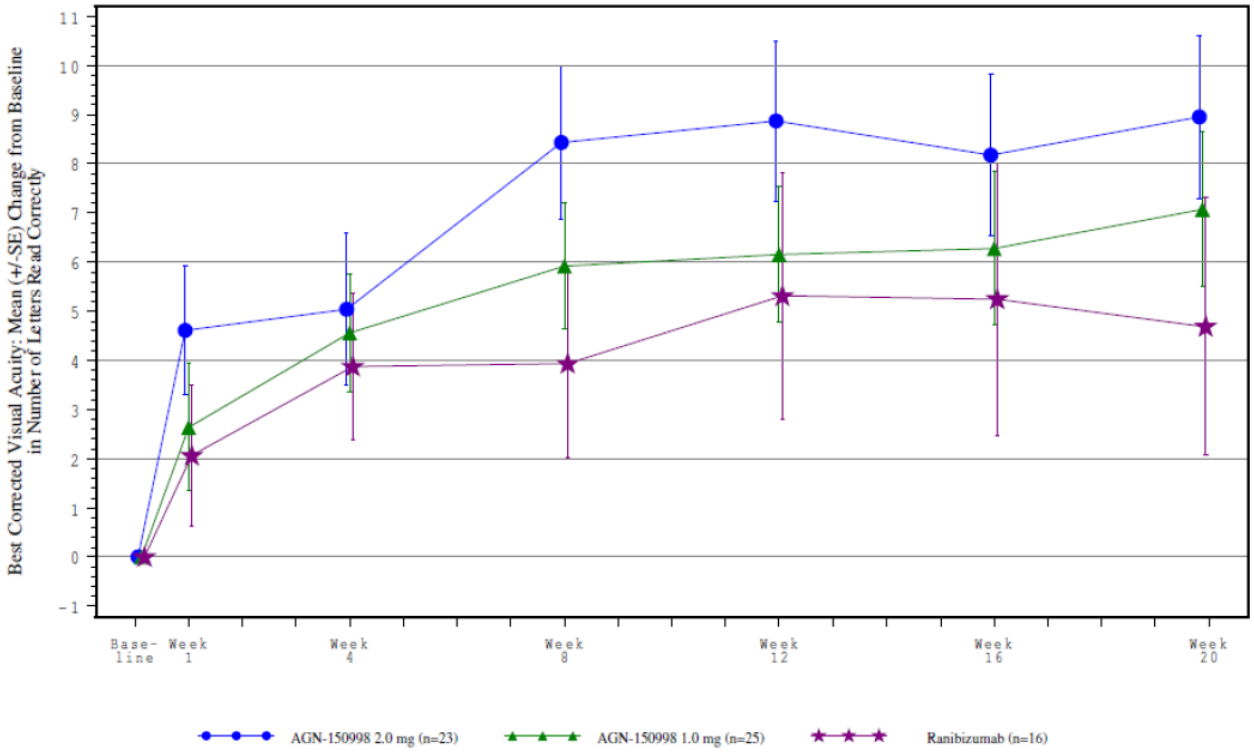
In Stage 1, there was a dose-dependent reduction of CRT that appeared to reach a plateau at the 3 mg dose, the median time to escape to standard of care (SOC) was around week 8 to 12 and the mean BCVA improved by 3 - 13 letters without any clear dose response. In Stage 2, the median time to recurrence of active disease was 57 – 59 days without any significance difference between treatment arms. The 3.0 mg abicipar group was numerically favoured with regard to an initial improvement in BCVA, see below figure, while the 4.2 mg dose gave a somewhat larger reduction in CRT. There were no statistically significant differences between any of the groups.

Figure 2: Mean Change in BCVA From Baseline by Visit for the Entire Study Period (mITT Population)



In Stage 3, for gains in BCVA, the 2.0 mg abicipar dose was favoured over the 1.0 mg dose group and ranibizumab, see below figure. However, the 1.0 mg dose group was most effective in reducing the CRT. There were no statistically significant differences between treatment arms at any time point.

Figure 3: Mean Change from Baseline in BCVA over time



Studies 150998-002 and 150998-003 were identically designed, but conducted in different geographical regions (Japan and US, respectively). Each study was 20 weeks, multicentre, randomised, double-masked, parallel-group, and active-controlled evaluating 1.0 or 2.0 mg abicipar vs. ranibizumab in 25 patients randomised 2:2:1. Abicipar was administered every 4 weeks for a total of 3 injections through Week 8 and ranibizumab 0.5 mg administered every 4 weeks through Week 16 for a total of 5 injections.

The main efficacy outcomes that demonstrate a favour for ranibizumab are summarised in the below table.

Table 7: Key efficacy outcomes Studies 150998-002 and 150998-003 (mITT Population)

	Study 150998-002			**Study 150998-003**		
	Abicipar 2 mg (N=10)	Abicipar 1 mg (N=10)	Rzb (N=5)	Abicipar 2 mg (N=10)	Abicipar 1 mg (N=10)	Rzb (N=5)
	Primary efficacy: Mean change in BCVA from baseline to Week 16					
BCVA (Letters) (SD)- change from baseline	8.9 (9.16)	7.8 (8.51)	17.4 (8.08)	10.1 (10.5)	4.4 (8.96)	15.2 (6.72)
Difference Abicipar vs. Ranibizumab	-7.9	-9.9		-4.6	-11.6	
90% CI	-15.7, -0.1	-17.7, -2.1		-12.6, 3.4	-19.6, -3.6	
BCVA Subjects (%) that gain BCVA	**Subjects that gain ≥10 or ≥15 letters in BCVA from baseline to Week 16**					
Gain of ≥10 letters, n (%)	6 (60)	4 (40)	4 (80)	5 (50)	5 (50)	4 (80)
Gain of ≥15 letters, n (%)	3 (30)	3 (30)	4 (80)	4 (40)	0	2 (40)
BCVA Subjects that gain BCVA	**Subjects that gain ≥10 or ≥15 letters in BCVA from baseline to Week 20**					
Gain of ≥10 letters, n (%)	5 (50)	5 (50)	4 (80)	4 (40)	4 (40)	3 (60)
Gain of ≥15 letters, n (%)	2 (20)	3 (30)	3 (60)	3 (30)	3 (30)	3 (60)

Main studies

Title of Study

Study 150998-005 *Safety and Efficacy of Abicipar Pegol (AGN-150998) in Patients With Neovascular Age-related Macular Degeneration (CEDAR Study)*

Study 150998-006 *Safety and Efficacy of Abicipar Pegol (AGN-150998) in Patients With Neovascular Age-related Macular Degeneration (SEQUOIA Study)*

The studies are identical in design and evaluated *abicipar Formulation 2.*

Methods

The studies are global, multicentre, double-masked, randomized, 104-week, parallel-group, active controlled, non-inferiority studies to evaluate the safety and efficacy of abicipar compared with monthly ranibizumab in treatment-naive patients with nAMD. Patients were to be randomized by region to 2 mg abicipar every 8th week (2Q8), 2 mg abicipar every 12th week (2Q12) or to monthly ranibizumab with a 1:1:1 allocation ratio as illustrated in **Figure 4** further below.

Study 150998-005 recruited patients from the US, the EU, Switzerland, Israel, New Zealand, Asia and South America. Study 150998-006 recruited patients from the US, the EU, Australia, Canada, Asia, South America, Russia, South Africa and Turkey (2 sites).

Study Participants

Main inclusion criteria:

- Male and female subjects, 50 years or older.
- Active sub- and/or juxtafoveal CNV lesions (1 to 200 µm from the centre) and presence of retinal fluid on OCT and/or fluorescein leakage under the fovea.
- Area of the CNV lesion (including both classic and occult components), must have been > 50% of the total lesion area
- BCVA between 73 and 24 letters (Snellen equivalent 20/40 to 20/320) for the study eye.
- BCVA of ≥34 letters (20/200) for non-study eye.

Main exclusion criteria:

- History of recurrent or currently active ocular or intraocular inflammation at baseline.
- History or clinical evidence of diabetic retinopathy, diabetic macular oedema, or any retinal vascular disease (including CNV) other than AMD.
- Previous use of verteporfin photodynamic therapy (PDT) or any ocular antiangiogenic therapy (e.g. aflibercept, bevacizumab, ranibizumab, pegaptanib) for any ocular disease or any other treatment for AMD.
- Treatment with ocular corticosteroid injections or implants within 6 months prior to baseline or with fluocinolone acetonide implant (Iluvien®) within 36 months prior to baseline.
- Total lesion size > 12 disc area (DA) (30.5 mm^2 including blood, neovascularization, and fibrosis)
- Structural damage to the centre of the macula that is likely to preclude improvement in BCVA.

Inclusion and exclusion criteria related to anatomical ocular characteristics were to be confirmed by the central reading centre (CRC).

Treatments

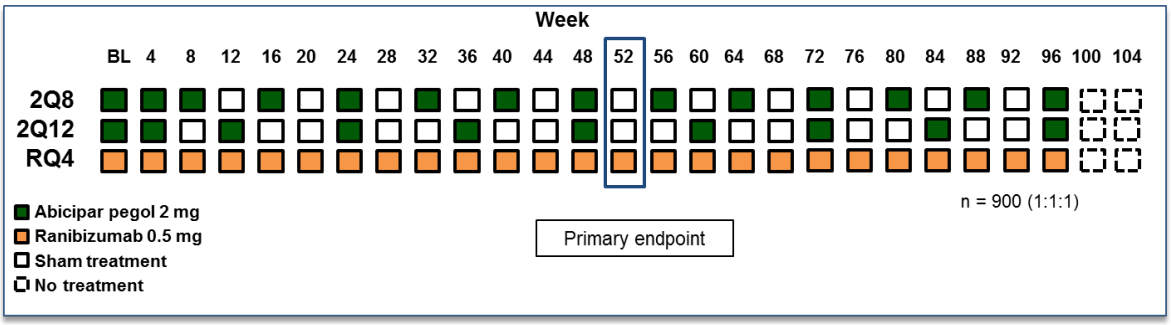
In both pivotal studies, subjects were randomised to IVT treatment (50 µl) with either:

- 2 mg abicipar administered at 8-week intervals (2Q8) following 3 initial IVT injections (baseline [Day 1] and Weeks 4 and 8)
- 2 mg abicipar administered at 12-week intervals (2Q12) following 3 initial IVT injections (baseline [Day 1] and Weeks 4 and 12)
- 0.5 mg ranibizumab every 4 weeks (rQ4)

Due to the differences in regimens between treatment arms, subjects not scheduled for an active treatment at the monthly visit received a sham injection to maintain masking.

The treatment schedule is summarised below.

Figure 4: Design of and treatment schedule in Phase III Studies 150998-005 and 150998-006



2Q8 = 2 mg abicipar administered at baseline (Day 1) and Weeks 4 and 8, followed by dosing at 8-week intervals though Week 96; 2Q12 = 2 mg abicipar administered at baseline (Day 1) and Weeks 4 and 12, followed by dosing at 12-week intervals through Week 96; rQ4 = 0.5 mg ranibizumab administered every 4 weeks from baseline (Day 1) through Week 96

Objectives

The primary objective of both studies was to assess the safety and efficacy of abicipar compared with ranibizumab in treatment-naïve patients with neovascular AMD. The primary efficacy comparison is to be made in a non-inferiority setting evaluating the proportion who lose fewer than 15 letters in BCVA from baseline at Week 52 applying a non-inferiority margin of 10% at an alpha level of 0.049.

Secondary objectives included an evaluation of the mean change from baseline in BCVA at Week 52 applying a non-inferiority margin of 5.0 letters.

Outcomes/endpoints

Efficacy and safety endpoints were identical in the two pivotal studies.

Primary efficacy endpoint

- The proportion of patients with stable vision (i.e. patients who lost fewer than 15 letters in BCVA) from baseline to Week 52.

Key secondary endpoint

- The mean change in BCVA from baseline to Week 52.

Secondary and other endpoints

The most important secondary and other efficacy endpoints included

- The proportions of patients with BCVA improvement of ≥ 15 and ≥10 letters from baseline at Week 52.
- The mean change in CRT from baseline to Week 52 as recorded with SD-OCT.
- National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25) Change in Composite Score from Baseline to week 52

Additional secondary and other efficacy endpoints included change in BCVA and CRT over time, additional responder analyses and anatomical evaluations (subretinal fluid, intraretinal fluid, cystoid spaces, neovascular lesion complex, evaluated by a CRC).

Randomisation and masking

The randomisation procedure was clearly described with regard to the assignment of patients to the three treatment groups 2Q8, 2Q12, and rQ4. Within each region, allocation to treatment groups was stratified by the following 3 factors using a ratio of 1:1:1:

- Disease characteristics of the study eye assessed by the investigator at screening and subsequently confirmed by the CRC prior to baseline (Day 1):
    - Lesion type of choroidal neovascularization (predominantly classic vs minimally classic or occult)
      and
    - CRT defined as the central 1000 µm from centre of fovea (values ≤ 400 vs > 400 µm) as measured from the internal limiting membrane to the top of the RPE
- Visual function at baseline (Day 1):
    - BCVA (≤ 55 vs > 55 letters)

An automated interactive voice response system/interactive web response system (IVRS/IWRS) was planned to be used to manage the randomization and treatment assignment based on a central randomization scheme.

As regards masking, the following persons were kept masked to study drug identification: patients, all site personnel responsible for performing BCVA and CRT assessments, assessing investigator responsible for all assessments except the post injection assessment and central reading centre personnel involved in the assessment of images. The injecting ophthalmologist and any assistants who prepared the material for injection (or sham treatment) were planned to be unmasked to treatment. To maintain masking, patients randomized to abicipar were to receive a sham injection during the study visits when they were not scheduled to receive their assigned study medication. Ranibizumab (Lucentis) was planned to be provided and masked by packaging the commercial supplies inside of an outer carton that looked identical to the packaging of abicipar.

Masked study treatment (or sham treatment) was to be administered into the study eye by IVT injection. One eye was assigned as the study eye for the duration of the study. To maintain masking, patients randomized to abicipar received a sham injection during the study visits when they were not scheduled to receive their assigned study medication. For the sham injections, the study eye of each patient was prepared using a standard protocol as if they were to receive an intravitreal injection as

defined in the procedure manual. For the sham injection, the treating investigator pressed the blunt end of the needleless syringe against the eye, mimicking an intravitreal injection.

Statistical methods

The primary efficacy endpoint was the proportion of patients with stable vision at Week 52, defined as vision loss of fewer than 15 letters in BCVA from baseline. Patients who escaped to standard of care by meeting the protocol criteria were considered failures for the primary endpoint of stable vision at Week 52.

The following pair of statistical hypotheses for testing non-inferiority of abicipar to ranibizumab was planned to be tested:

Null hypothesis:

Abicipar (2Q12 or 2Q8) is inferior to ranibizumab by the specified non-inferiority margin of 10% or more in the proportion of patients with stable vision at Week 52.

Alternative hypothesis:

Abicipar (2Q12 or 2Q8) is inferior to ranibizumab by less than the specified non-inferiority margin of 10% or is superior to ranibizumab in the proportion of patients with stable vision at Week 52.

The primary analysis of the primary efficacy variable was planned to be performed using the PP population based on a stratified method with Cochran-Mantel-Haenszel (CMH) weights.

Within the framework of this method, the difference in the proportions between each abicipar arm and ranibizumab (abicipar group minus ranibizumab group) and the corresponding 2-sided 95.1% confidence interval (CI) for non-inferiority testing was planned to be calculated. Specifically, the CIs for treatment group differences were to be calculated using the CMH weighted method with the baseline BCVA (≤ 55 versus > 55 ETDRS letters) as a stratification factor. Missing data for BCVA was to be imputed using the last observation carried forward method (LOCF). The non-inferiority test was planned to be performed at Week 52 with a non-inferiority margin of 10% at an alpha level of 0.049. This alpha reflected an adjustment of 0.001 for the unmasked data review by the data safety monitoring committee (DSMC) for safety assessments. The total alpha spent of 0.001 for the DSMC was based on the assumption of no more than 10 unmasked reviews during the study, with 0.0001 allocated to each review. Thus, the overall alpha for the study was considered to be preserved at the 0.05 level.

For hypothesis testing, if the lower limit of the 95.1% CI for the difference between an abicipar group and ranibizumab was greater than or equal to -10%, non-inferiority of the abicipar group was supposed to be established.

Multiplicity for the primary efficacy analysis over the treatment regimens investigated was planned to be controlled using a gatekeeping procedure defined by the following sequence to control the overall type I error rate at the 0.05 level:

Step 1: Testing for non-inferiority of abicipar 2Q8 against ranibizumab (rQ4)
Step 2: Testing for non-inferiority of abicipar 2Q12 against ranibizumab (rQ4)

Hence, hypothesis testing for abicipar 2Q12 against ranibizumab was valid only if non-inferiority for abicipar 2Q8 against ranibizumab was established beforehand.

If both abicipar groups had demonstrated non-inferiority to ranibizumab using the PP population, hypothesis testing for superiority was performed using the ITT population for each abicipar group following the same order as defined above for non-inferiority testing. Superiority of abicipar over

ranibizumab was supposed to be demonstrated if the lower confidence limit for the treatment difference was greater than zero.

For the key secondary efficacy endpoint mean change from baseline in BCVA at Week 52, statistical analysis for non-inferiority was planned to be based on the PP population using a MMRM, which was to include BCVA data from baseline (Day 1) to Week 52. The model was planned to include treatment group, region, baseline BCVA in the study eye, baseline CRT (≤ 400 μm or > 400 μm) in the study eye, lesion type of choroidal neovascularization (predominantly classic versus minimally classic or occult) from the confirmation at screening, visit, visit-by-baseline BCVA interaction, and treatment-by-visit interaction as fixed covariates using an unstructured covariance matrix. The difference in BCVA mean change from baseline between each abicipar arm and ranibizumab (abicipar group minus ranibizumab group) and the corresponding 2-sided 95.1% CI was to be calculated based on the MMRM model. The non-inferiority test was planned to be performed at Week 52 using a margin of 5 letters. Non-inferiority of abicipar was considered to be established if the lower limit of the CI was > - 5.0 letters.

Results

Participant flow

Subject retention and pattern of discontinuations were similar between studies.

Across the studies, 80 to 84 % of patients in the abicipar treatment arms completed Week 52, while 91.3 to 93.7% of subjects completed the first treatment year in the ranibizumab treatment arms. At Approximately 70% of patients in the abicipar and 83% in the ranibizumab treatment arms, respectively completed the 104-week studies. The higher dropout rate in the abicipar treatment arms, were mainly due to a higher proportion of subjects discontinuing treatment due to ocular AEs in the abicipar treatment arms (8-11% during the 1st year and 11-14% during the 2nd year) compared to ranibizumab (1-2%).

Figure 5: Study 150998-005, Patient disposition up to week 104 (ITT)

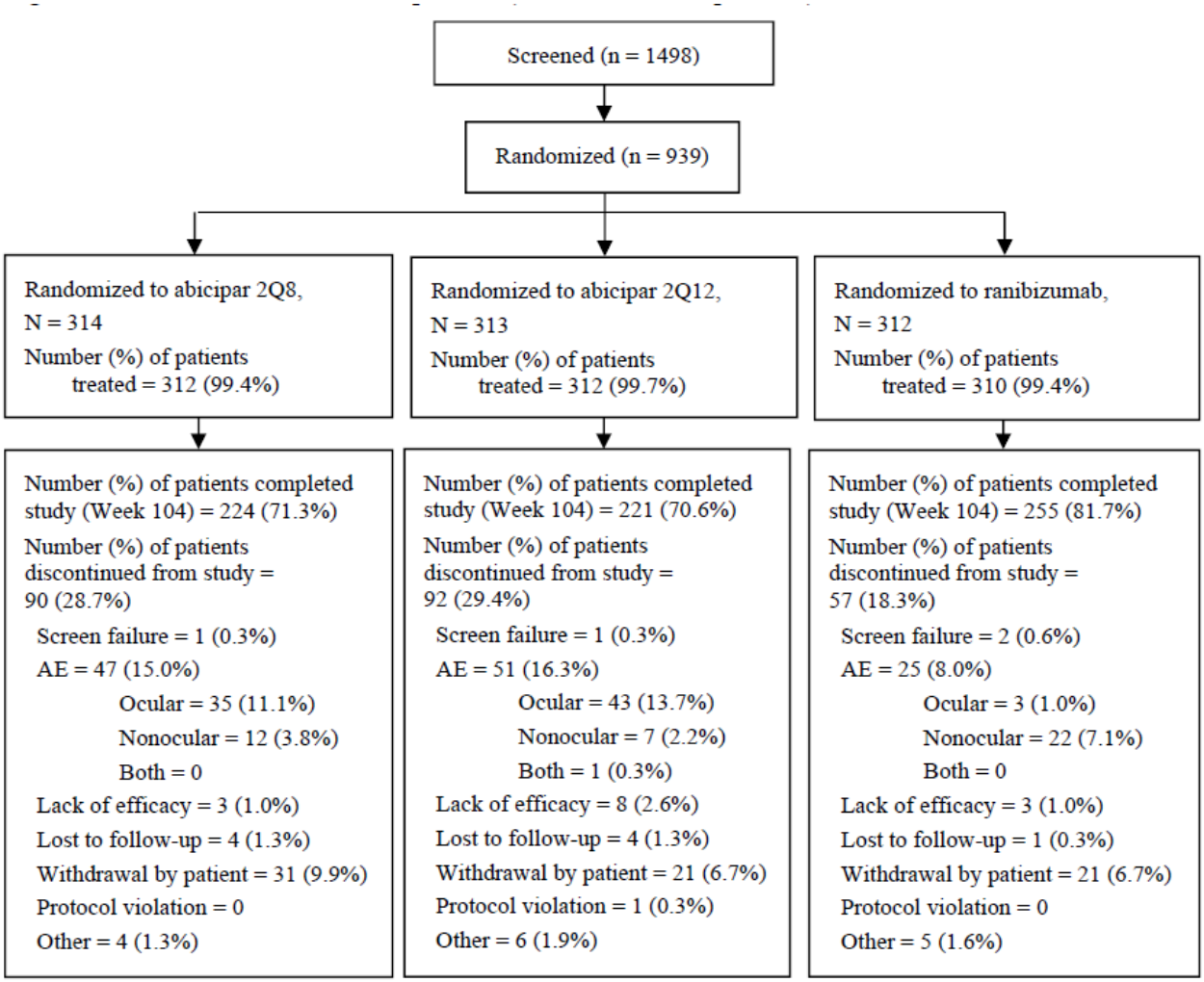
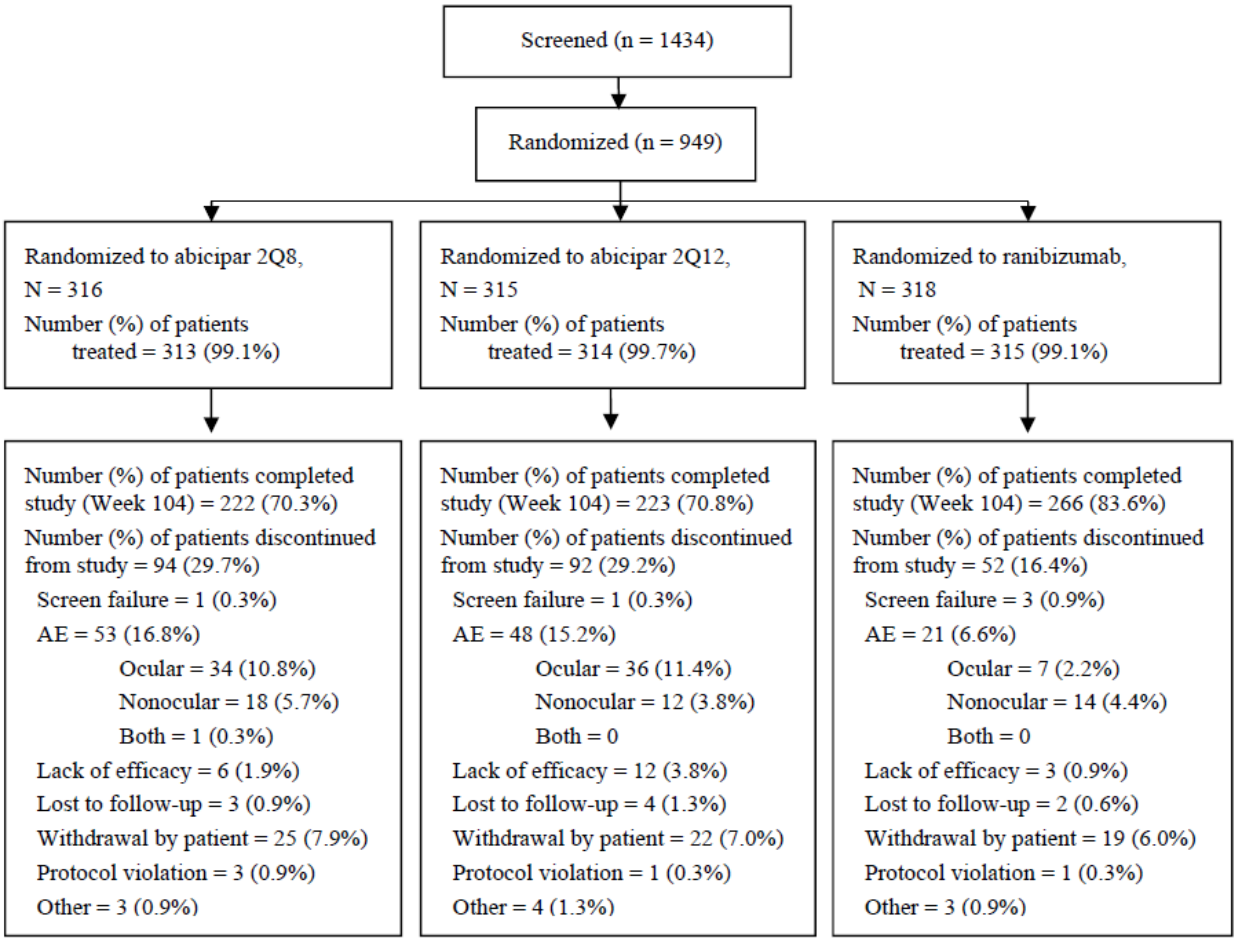


Figure 6: Study 150998-006, Patient disposition up to week 104 (ITT)



Baseline data

Overall, in Studies 150998-005 and 150998-006 combined, the ITT population included 44% males and 55% females, and the mean age was 76 years, ranging from 50 to 99 years. Most patients were white (81%) or Asian (13%). Baseline demographics were well balanced within studies. Except for slightly higher proportions of Whites in Study -005 and Asians in Study -006, demographics were also similar between studies.

The key demographics for the individual studies are summarised in the below table.

Table 8: Demographic Characteristics, Studies 150998-005, 150998-006 (ITT)

	Study 150998-005				Study 150998-006			
Parameter	**Abicipar 2Q8 (N = 314)**	**Abicipar 2Q12 (N = 313)**	**Rzb rQ4 (N = 312)**	**Total (N = 939)**	**Abicipar 2Q8 (N = 316)**	**Abicipar 2Q12 (N = 315)**	**Rzb rQ4 (N = 318)**	**Total (N = 949)**
Age (years)								
Mean	75.5 (8.4)	76.9 (8.0)	77.1	76.5	75.9 (8.6)	76.2 (8.3)	75.9	76.0
(SD)			(8.4)	(8.3)			(8.4)	(8.4)
Min, max	51, 93	54, 98	50, 98	50, 98	50, 95	51, 99	52, 98	50, 99
Sex, n (%)								
Male	152 (48.4)	130 (41.5)	143 (45.8)	425 (45.3)	137 (43.4)	141 (44.8)	133 (41.8)	411 (43.3)
Female	162 (51.6)	183 (58.5)	169 (54.2)	514 (54.7)	179 (56.6)	174 (55.2)	185 (58.2)	538 (56.7)

Parameter	Study 150998-005				Study 150998-006			
	Abicipar 2Q8 (N = 314)	**Abicipar 2Q12 (N = 313)**	**Rzb rQ4 (N = 312)**	**Total (N = 939)**	**Abicipar 2Q8 (N = 316)**	**Abicipar 2Q12 (N = 315)**	**Rzb rQ4 (N = 318)**	**Total (N = 949)**
Race, n (%)								
White	249 (79.3)	248 (79.2)	243 (77.9)	740 (78.8)	266 (84.2)	266 (84.4)	264 (83.0)	796 (83.9)
Black	2 (0.6)	1 (0.3)	1 (0.3)	4 (0.4)	2 (0.6)	4 (1.3)	3 (0.9)	9 (0.9)
Asian	49 (15.6)	44 (14.1)	45 (14.4)	138 (14.7)	39 (12.3)	35 (11.1)	41 (12.9)	115 (12.1)
Hispanic	12 (3.8)	12 (3.8)	11 (3.5)	35 (3.7)	7 (2.2)	8 (2.5)	9 (2.8)	24 (2.5)
Other	0	0	0	0	2 (0.6)	0	0	2 (0.2)
NR	2 (0.6)	8 (2.6)	12 (3.8)	22 (2.3)	0	1 (0.3)	1 (0.3)	2 (0.2)
Unknown	0	0	0	0	0	1 (0.3)	0	1 (0.1)

NR – not reported

- *Baseline disease characteristics*

Overall, in Studies 150998-005 and 150998-006 combined, the mean baseline BCVA was 57 letters and the mean baseline CRT was 380 µm. There were no important differences with regard to baseline disease characteristics, neither between treatment arms, nor between studies.

The key disease characteristics for the individual studies are summarised in the below table.

Table 9: Key Baseline Disease Characteristics –Studies 150998-005 and 150998-006 (ITT)

Parameter	Study 150998-005				Study 150998-006			
	Abicipar 2Q8 (N = 314)	**Abicipar 2Q12 (N = 313)**	**Rzb rQ4 (N = 312)**	**Total (N = 939)**	**Abicipar 2Q8 (N = 316)**	**Abicipar 2Q12 (N = 315)**	**Rzb rQ4 (N = 318)**	**Total (N = 949)**
BCVA (letters)								
Mean (SD)	56.4 (13.4)	56.5 (12.9)	56.5 (12.5)	56.5 (12.9)	57.2 (12.3)	56.4 (12.5)	57.1 (12.3)	56.9 (12.4)
Min, max	24, 73	23, 75	19, 84	19, 84	23, 84	21, 81	24, 78	21, 84
≤ 55	122 (38.9)	121 (38.7)	128 (41.0)	371 (39.5)	126 (39.9)	130 (41.3)	122 (38.4)	378 (39.8)
> 55	192 (61.1)	192 (61.3)	184 (59.0)	568 (60.5)	190 (60.1)	185 (58.7)	196 (61.6)	571 (60.2)
CRT, µm								
Mean (SD)	384 (142.7)	378 (119.1)	378 (120.5)	380 (127.8)	380 (117.9)	378 (123.8)	382 (130.3)	380 (124.0)
Min, max	153, 1347	145, 789	179, 967	145, 1347	157, 898	111, 880	147, 954	111, 954

Numbers analysed

Analysis populations are summarised in the below table.

Table 10: Datasets analysed

	Study 150998-005			Study 150998-006		
	Abicipar 2Q8 N = 314 n (%)	**Abicipar 2Q12** N = 313 n (%)	**Rzb Q4** N = 312 n (%)	**Abicipar 2Q8** N=316 n (%)	**Abicipar 2Q12** N=315 n (%)	**Rzb Q4** N=318 n (%)
Randomised	314	313	312	316	315	318
ITT	314 (100.0)	313 (100.0)	312 (100.0)	316 (100.0)	315 (100.0)	318 (100.0)

PP week 52	265 (84.4)	262 (83.7)	290 (92.9)	267 (84.5)	265 (84.1)	299 (94.0)
Completers population week 104[a]	224 (71.3)	221 (70.6)	255 (81.7)	219 (69.3)	221 (70.2)	265 (83.3)
Safety set	312 (99.4)	312 (99.7)	310 (99.4)	313 (99.1)	314 (99.7)	315 (99.1)

[a] The completers population for analysis of efficacy was introduced after the primary database lock. It was defined as patients within the ITT population who completed the study without escaping to standard of care by Week 104 and the analyses were based on observed data and on LOCF.

As detailed in **Statistical methods**, the ITT population included all randomised patients. The PP set, which was the primary analysis set, included subjects that received ≥9 study treatments (incl. sham), not missing ≥3 consecutive treatments, and had no major protocol violation that affected the primary efficacy variable. The PP set further included treatment failures and subjects who received rescue were regarded as failures.

In both studies, the most common reason for being excluded from the PP set were missed treatments, which occurred more commonly in the abicipar treatment groups. In Study 150998-005, 16%, 17% and 7% of patients from the 2Q8, 2Q12 and ranibizumab treatment groups, respectively were excluded from the PP set due to this reason. The corresponding figures for Study 150998-005 were 15%, 16% and 6% in the three treatment groups.

Outcomes and estimation

- *Primary endpoint*

In both studies, the primary efficacy endpoint was the proportion of patients that lost < 15 letters in BCVA from baseline at week 52 using the ETDRS chart. The non-inferiority margin was 10% for the primary analysis in the PP set.

When analysed according to the protocol (PP set, 10% non-inferiority margin), both studies met their primary objective. However, in the ITT set, the protocol-defined non-inferiority margin was not met for the 2Q12 treatment arm in any of the studies.

Table 11: Primary efficacy evaluation. Number (Percent) of Patients that lost <15 letters in the Study Eye at Week 52, Studies 150998-005, 150998-006

	Study 150998-005			**Study 150998-006**		
	Abicipar 2Q8	**Abicipar 2Q12**	**Ranibizumab rQ4**	**Abicipar 2Q8**	**Abicipar 2Q12**	**Ranibizumab rQ4**
PP Population	**(N = 265)**	**(N = 262)**	**(N = 290)**	**(N = 267)**	**(N = 265)**	**(N = 299)**
Loss of < 15 letters at Week 52, n (%)	243 (91.7)	239 (91.2)	277 (95.5)	253 (94.8)	242 (91.3)	287 (96.0)
Difference vs. ranibizumab 95.1% CI[a]	-3.8 (-8.2, 0.3)	-4.2 (-8.7, 0.0)		-1.2 (-5.0, 2.4)	-4.6 (-9.0, -0.5)	
ITT Population	**(N = 314)**	**(N = 313)**	**(N = 312)**	**(N = 316)**	**(N = 315)**	**(N = 318)**
Loss of < 15 letters at Week 52, n (%)	283 (90.1)	276 (88.2)	298 (95.5)	292 (92.4)	280 (88.9)	303 (95.3)
Difference vs. ranibizumab 95.1% CI[a]	-5.4 (-9.6, -1.3)	-7.3 (-11.8, -3.1)		-2.9 (-6.8, 0.9)	-6.4 (-10.8, -2.2)	

CI = confidence interval

Stable vision was defined as a loss of < 15 letters in BCVA compared to baseline. Missing data and data after the first standard-of-care treatment were replaced by the last observation carried forward. Patients who escaped to standard of care by meeting the protocol criteria were considered failures.

a The 95.1% CIs for the weighted difference were calculated based on the Newcombe method using CMH weights and baseline BCVA (≤ 55 versus > 55 letters) as the stratification factor.

Sensitivity analyses included a tipping point analysis and an analysis excluding BCVA values collected after the onset of IOI or completely excluding patients with IOI. The latter improved the outcomes for abicipar in the PP and ITT populations, see **Table 13**. In addition, a supplementary analysis for the proportion of patients losing <15 letters in BCVA excluding subjects with IOI is summarised in **Table 21**.

- *Key secondary endpoint*

The key secondary efficacy endpoint would have been the preferred primary endpoint.

This efficacy variable of mean change from baseline in BCVA at week 52, non-inferiority was defined as a lower limit of the 95.1% CI for the difference between an abicipar group and ranibizumab of > -5.0 letters in the PP set.

When analysed according to the protocol (PP set, non-inferiority margin < 5 letters), only study -006 met its key secondary objective while in study -005, the lower 95% CI was -6.0 letters for the 2Q12 regimen of abicipar. In the ITT set, non-inferiority for the key secondary endpoint when evaluated as per protocol (< 5 letters) was demonstrated only for the 2Q8 treatment arm in study -006.

Table 12: Key secondary efficacy evaluation. Mean Change from Baseline in Best-corrected Visual Acuity in the Study Eye at Week 52, Studies 150998-005, 150998-006 (MMRM)

	Study 150998-005			Study 150998-006		
	Abicipar 2Q8	**Abicipar 2Q12**	**Ranibizumab rQ4**	**Abicipar 2Q8**	**Abicipar 2Q12**	**Ranibizumab rQ4**
PP Population	**(N = 265)**	**(N = 262)**	**(N = 290)**	**(N=267)**	**(N=265)**	**(N=299)**
n[a]	241	239	272	248	251	287
Mean (SD) change from baseline at Week 52	6.7 (12.9)	5.6 (13.3)	8.5 (13.6)	8.3 (14.3)	7.3 (13.8)	8.3 (11.8)
LS mean (SE) change from baseline	6.2 (0.9)	5.0 (0.9)	8.6 (0.9)	8.2 (0.9)	6.8 (0.9)	8.4 (0.8)
LS mean (SE) difference versus rQ4	-2.4 (1.2)	-3.7 (1.2)		-0.2 (1.1)	-1.6 (1.1)	
95.1% CI[b]	(-4.7, -0.1)	(-6.0, -1.3)		(-2.4, 2.0)	(-3.8, 0.6)	
ITT Population	**(N = 314)**	**(N = 313)**	**(N = 312)**	**(N=316)**	**(N=315)**	**(N=318)**
n[a]	249	244	272	252	259	289
Mean (SD) change from baseline at Week 52	5.9 (14.3)	5.5 (13.4)	8.5 (13.6)	8.2 (14.4)	7.0 (14.2)	8.3 (11.8)
LS mean (SE) change from baseline	5.2 (0.9)	3.6 (0.9)	8.7 (0.9)	6.8 (0.9)	5.3 (0.9)	8.3 (0.9)
LS mean (SE) difference versus rQ4	-3.5 (1.2)	-5.0 (1.2)		-1.5 (1.2)	-3.0 (1.2)	
95.1% CI[b]	(-5.9, -1.1)	(-7.5, -2.6)		(-3.7, 0.8)	(-5.3, -0.7)	

CI = confidence interval, LS = least squares, SD = standard deviation, SE = standard error

a This n is the number of patients with data at baseline and Week 52.

b The 95.1% CIs were based on observed data using an MMRM, which included the treatment, region, baseline BCVA in the study eye, baseline CRT (≤ 400 or > 400) in the study eye, lesion type of CNV, visit, visit-by-baseline BCVA interaction, and treatment-by-visit interaction term as covariates using an unstructured covariance matrix.

Sensitivity analyses applied included ANCOVA with LOCF or multiple imputation for missing data as well as an analysis excluding patients that experienced an AE of IOI (the latter *post hoc*).

In Study 150998-005, using ANCOVA with multiple imputation the 2Q8 group, but not the 2Q12 group demonstrated non-inferiority (<5 letter) vs. ranibizumab group at Week 52 in the PP population, while in the ITT set, neither abicipar group was non-inferior to ranibizumab at Week 52. In Study 150998-006, both abicipar treatment groups were non-inferior to ranibizumab in the PP set and the 2Q8, but not the 2Q12, abicipar treatment group was non-inferior to ranibizumab in the ITT set.

A supplementary analysis for the change in BCVA excluding subjects with IOI is presented in **Table 22**. Briefly, in the PP set, for the 2Q8 regimen, the point estimates (95.1% CIs) for the difference vs. ranibizumab were -0.8 (-3.1, 1.4) and 0.5 (-1.7, 2.8) letters in Studies -005 and -006, respectively. In the ITT sets for the 2Q8 regimen, the corresponding figures were -1.0 (-3.2, 1.3) and 0.5 (-1.8, 2.7). For the 2Q12 regimens in the PP set, the point estimates for the differences (95.1% CIs) vs. ranibizumab were -2.7 (-4.9, -0.4) and -1.2 (-3.4, 1.0) in Studies -005 and -006, respectively, while in the ITT sets the outcomes were -2.7 (-5.0, -0.5) and -1.2 (-3.4, 1.0).

Table 13: Sensitivity analyses of the secondary efficacy evaluation. Mean Change from Baseline in Best-corrected Visual Acuity in the Study Eye at Week 52, Studies 150998-005, 150998-006 (LOCF)

	Study 150998-005			Study 150998-006		
	Abicipar 2Q8	**Abicipar 2Q12**	**Ranibizumab rQ4**	**Abicipar 2Q8**	**Abicipar 2Q12**	**Ranibizumab rQ4**
Exclusion of subjects with intraocular inflammation [2]						
PP Population	**(N = 244)**	**(N = 242)**	**(N = 290)**	**(N=267)**	**(N=265)**	**(N=299)**
n	**226**	**225**	**272**	**229**	**234**	**287**
LS square mean (SE) change from baseline	7.7 (0.9)	5.8 (0.9)	8.5 (0.8)	9.0 (0.9)	7.2 (0.9)	8.4 (0.8)
LS mean (SE) difference vs. rQ4	-0.8 (1.1)	-2.7 (1.1)		0.5 (1.1)	-1.2 (1.1)	
95.1% CI	(-3.1, 1.4)	(-4.9, -0.4)		(-1.7, 2.8)	(-3.4, 1.0)	
ITT Population	**(N = 267)**	**(N = 265**	**(N = 312)**	**(N=267)**	**(N=267)**	**(N=316)**
n	**228**	**227**	**272**	**231**	**236**	**289**
LS square mean (SE) change from baseline	7.4 (0.9)	5.6 (0.9)	8.4 (0.8)	8.7 (0.9)	7.0 (0.9)	8.2 (0.8)
LS mean (SE) difference vs. rQ4	-1.0 (1.1)	-2.7 (1.1)		0.5 (1.1)	-1.2 (1.1)	
95.1% CI	(-3.2, 1.3)	(-5.0, -0.5)		(-1.8, 2.7)	(-3.4, 1.0)	

[1] Missing data and data after the first standard-of-care treatment are replaced by LOCF. Treatment difference in LS means and the corresponding 95.1% CIs are based on an ANCOVA model.

[2] Analysis is based on observed data. Patients with intraocular inflammation AE are excluded. The corresponding 95.1% CIs are based on a MMRM.

- *Secondary efficacy*

Selected secondary endpoints and the 104-week key outcomes are summarised below.

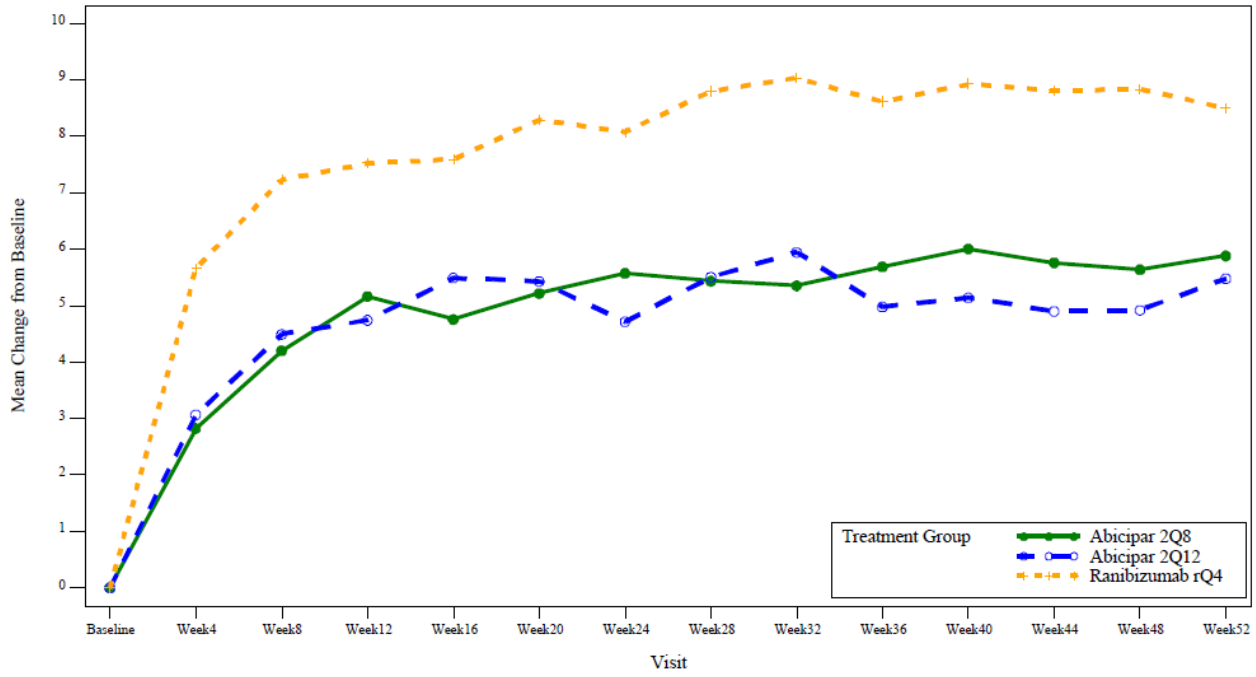
Mean change in BCVA over time

In Study 150998-05, ranibizumab was consistently favoured over both regimens of abicipar in the analyses of the mean BCVA vs. baseline over time with the upper bound 95.1% CI below zero (ANCOVA with LOCF and MMRM, PP and ITT set) at all time points except for week 16 for the 2Q12 regimen (PP set, both analyses). In Study 150998-06, BCVA with the 2Q8 regimen of abicipar was similar to that of ranibizumab at all time points. From week 20, the 2Q12 regimen of abicipar was

disfavoured vs. the 2Q8 regimen and ranibizumab at essentially all time points in the ITT set with the upper bound 95% CI below zero.

Figure 7: Mean change from Baseline in BCVA (letters) over time in the Study Eye, Studies 150998 005 and 150998-006 (ITT population).

Study 150998−005



Study 150998−006

Categorised BCVA change from baseline

Table 14: Secondary endpoints. Categorised change from baseline at Week 52 BCVA (letters) in Study eye, Studies 150998-005, 150998-006 (ITT set, LOCF)

	Study 150998-005			Study 150998-006		
	Abicipar 2Q8	Abicipar 2Q12	Rzb rQ4	Abicipar 2Q8	Abicipar 2Q12	Rzb rQ4
	(N = 314)	(N = 313)	(N = 312)	(N = 316)	(N = 315)	(N = 318)
Gain of ≥15 letters, n (%)	71 (22.6)	60 (19.2)	85 (27.2)	89 (28.2)	77 (24.4)	85 (26.7)
Difference vs. ranibizumab	-4.7	-8.2		1.4	-2.3	
95.1% CI[a]	(-11.5, 2.1)	(-14.7, -1.5)		(-5.5, 8.4)	(-9.1, 4.5)	
Gain of ≥10 letters, n (%)	116 (36.9)	111 (35.5)	157 (50.3)	135 (42.7)	123 (39.0)	146 (45.9)
Difference vs. ranibizumab	-13.4%	-14.9%		-3.2%	-6.9%	
95.1% CI[a]	(-21.0%, -5.6%)	(-22.4%, -7.1%)		(-10.9%, 4.6%)	(-14.5%, 0.8%)	
BCVA ≥ 70 letters	127 (40.4)	112 (35.8)	149 (47.8)	143 (45.3)	131 (41.6)	147 (46.2)
Difference vs. ranibizumab	-7.2%	-11.8%		-1.0%	-4.5%	
95.1% CI[a]	(-14.9%, 0.7%)	(-19.4%, -4.0%)		(-8.7%, 6.8%)	(-12.2%, 3.3%)	
Loss of ≥30 letters, n (%)[b]	7 (2.8)	7 (2.9)	4 (1.5)	5 (2.0)	5 (1.9)	2 (0.7)
Loss 15-30 letters, n (%)[b]	11 (4.4)	10 (4.1)	9 (3.3)	6 (2.4)	14 (5.4)	9 (3.1)
Loss 10-15 letters, n (%)[b]	10 (4.0)	14 (5.7)	12 (4.4)	11 (4.4)	6 (2.3)	6 (2.1)
Loss of 5-10 letters, n (%)[b]	17 (6.8)	24 (9.8)	17 (6.3)	14 (5.6)	14 (5.4)	13 (4.5)

[a] The 95.1% CIs for the weighted difference were calculated based on the Newcombe method using CMH weights and baseline BCVA (≤ 55 versus > 55 letters) as stratification factor.
[b] Table 14.3-8.1 CSR, see further Safety

In Study 150998-005, the percentage of patients with a ≥ 15 letter gain was numerically highest in the ranibizumab treatment group at all time points (ITT and PP set).

In Study 150998-006, the largest proportion of patients with a ≥15 letter gain was numerically highest in the abicipar 2Q8 treatment arm at 8/13 time points (ITT and PP set).

Central retinal thickness

The changes in CRT at week 52 were similar in all treatment groups in both studies.

Table 15: Secondary endpoint. Mean Change from Baseline in Central Retinal Thickness (µm) in the Study Eye at Week 52, Studies 150998 005, 150998-006 (Observed data)

	Study 150998-005			Study 150998-006		
	Abicipar 2Q8	Abicipar 2Q12	Rzb rQ4	Abicipar 2Q8	Abicipar 2Q12	Rzb rQ4
	(N = 314)	(N = 313)	(N = 312)	(N = 316)	(N = 315)	(N = 318)
n[a]	242	235	269	248	256	286
Mean (SD) change from baseline at Week 52	-142 (136.4)	-150 (127.4)	-141 (122.0)	-147 (118.1)	-142 (127.1)	-147 (126.2)
LS mean (SE) difference versus rQ4	8.6 (6.3)	2.3 (6.3)		3.5 (5.4)	5.9 (5.4)	
95.1% CI[b]	(-3.8, 20.9)	(-10.1, 14.7)		(-7.1, 14.0)	(-4.7, 16.5)	

[a] The number of patients with baseline and week 52 data.

[b] The 95.1% CIs were based on a MMRM, which included the treatment, region, baseline BCVA in the study eye, baseline CRT in the study eye, lesion type of choroidal neovascularization, visit, visit-by-baseline CRT interaction, and treatment-by-visit interaction term as covariates using an unstructured covariance matrix.

When evaluating the CRT over time, in the abicipar treatment arms, CRT increased between injections with larger such increases (up to approximately 40µm) in the 2Q12 treatment arm.

NEI-VFQ-25

In Study 150998-005, ranibizumab was numerically favoured in the composite score (LS mean change week 52: 2.7, 3.7 and 4.6 for 2Q8, 2Q12 and ranibizumab, respectively) and in the majority of

subscores followed by the 2Q12 abicipar groups. The differences were generally small, and only in the LS mean subscore of Driving difficulties, the 2Q8 regimen of differed abicipar markedly vs. ranibizumab (-2.60 vs. +2.46, 95.1% CI: -9.76, -0.36).

Also in Study 150998-006, ranibizumab was numerically favoured in the composite score (LS mean change week 52: 2.8, 2.4 and 4.4 for 2Q8, 2Q12 and ranibizumab, respectively) and in the majority of subscores followed by the 2Q8 abicipar groups. The differences were generally small, and only in the LS mean subscore of General vision, the 2Q12 regimen of differed abicipar markedly vs. ranibizumab (5.85 vs. 8.09, 95.1% CI: -4.33, -0.14).

SD-OCT analyses (evaluated by CRC)

Intraretinal fluid: In both studies, clearance of subretinal fluid occurred early with the time to first absence of fluid shortest for both abicipar groups compared with ranibizumab. At Week 52, the percentage of patients with absence of subretinal fluid was similar in the 3 treatment groups in Study 150998-005 were 61% in the 2Q8 group, 66 in the 2Q12 group, and 63% in the ranibizumab group. In Study 150998-006, the corresponding figures were 67%, 61% and 69% in the 3 groups.

In both studies, clearance of intraretinal thickening occurred early with the time to first absence of fluid shortest for both abicipar groups compared with ranibizumab. Similarly, in both studies, the time to all dry of the fluids occurred early with the time clearance of fluids shortest for both abicipar groups compared with ranibizumab.

Summary of key efficacy data at 104 weeks

The proportion of patients losing >15 letters in BCVA, the mean change from baseline and the proportion of patients gaining ≥15 letters in BCVA, all at week 104 are displayed in the below tables.

Table 16: Number (Percent) of Patients that lost <15 letters in the Study Eye at Week 104, using Observed Data, Completer Population, Studies 150998-005 and 150998-006

Analysis Visit Statistics[a]	Study 150998-005			Study 150998-006		
	Abicipar 2Q8 (N=224)	Abicipar 2Q12 (N=221)	Ranibizumab rQ4 (N=255)	Abicipar 2Q8 (N=219)	Abicipar 2Q12 (N=221)	Ranibizumab rQ4 (N=265)
Week 104, N1	215	210	242	211	212	256
<15 letter loss at Week 104, n (%)	200 (93.0)	191 (91.0)	227 (93.8)	196 (92.9)	188 (88.7)	243 (94.9)
Difference vs. rQ4 (%)	-0.8	-2.9		-2.1	-6.2	
95.1% CI (%)b	(-5.7, 3.9)	(-8.2, 2.1)		(-6.9, 2.3)	(-11.6, -1.2)	

CI = confidence interval; N1 = Patients with nonmissing values; n (%) = number (percent) patients with event
Stable vision was defined as a loss of < 15 letters in BCVA compared to baseline.
a Included patients who completed the study without escaping to standard of care. No missing value was imputed.
b The 95.1% CIs for the weighted differences were calculated based on the Newcombe method using Cochran-Mantel- Haenszel weights and baseline BCVA (≤ 55 versus > 55 letters) as the stratification factor.

Table 17: Change from Baseline in BCVA in Number of Letters Week 104 Completer Population, Studies 150998-005 and 150998-006

Analysis Visit Statistics	Study 150998-005			Study 150998-006		
	Abicipar 2Q8 (N=224)	Abicipar 2Q12 (N=221)	Ranibizumab rQ4 (N=255)	Abicipar 2Q8 (N219)	Abicipar 2Q12 (N=221)	Ranibizumab rQ4 (N=265)
Week 104 results						
n[a]	215	210	242	211	212	256
Change from baseline to Week 104						
Mean (SD)	6.4 (15.2)	5.0 (14.1)	8.8 (14.3)	7.9 (14.6)	6.0 (15.0)	7.5 (12.8)
LS mean (SE)	7.0 (1.0)	5.6 (1.0)	8.8 (0.9)	8.5 (1.0)	6.6 (1.0)	8.2 (0.9)
LS mean (SE) difference vs rQ4	-1.8 (1.3)	-3.2 (1.3)		0.3 (1.3)	-1.6 (1.3)	
95.1% CI [b]	(-4.4, 0.8)	(-5.8, -0.6)		(-2.2, 2.9)	(-4.1, 0.9)	

a Analysis is based on observed data for the patients who completed the study; n is the number of patients with data at baseline and Week 104.

b The 95.1% CIs were based on observed data using a mixed model for repeated measures, which included the treatment, region, baseline BCVA in the study eye, baseline CRT (≤ 400 or > 400) in the study eye, lesion type of choroidal neovascularization, visit, visit-by-baseline BCVA interaction, and treatment-by-visit interaction term as covariates using an unstructured covariance matrix.

Table 18: Secondary endpoints. Categorised change from baseline at Week 104 BCVA (letters) in Study eye, Completer Population, Studies 150998-005, 150998-006

Statistics[a]	Study 150998-005			Study 150998-006		
	Abicipar 2Q8	Abicipar 2Q12	Rzb rQ4	Abicipar 2Q8	Abicipar 2Q12	Rzb rQ4
	(N = 224)	(N = 221)	(N = 255)	(N = 219)	(N = 221)	(N = 265)
N1	215	210	242	211	212	256
Gain of ≥15 letters, n (%)	66 (30.7)	48 (22.9)	79 (32.6)	67 (31.8)	62 (29.2)	72 (28.1)
Difference vs. ranibizumab	-3.5	--14.0		7.4	2.6	
95.1% CI[a]	(-12.6, 5.7)	(-22.9, -4.8)		(-1.8, 16.3)	(-6.5, 11.6)	

N1 = patients with nonmissing values; n (%) = number (percent) of patients

[a] No missing value was imputed and included patients who completed the study.

[b] The 95.1% CIs for the weighted differencse were calculated based on the Newcombe method using Cochran-Mantel- Haenszel weights and baseline best-corrected visual acuity (≤ 55 versus > 55 letters) as the stratification factor.The mean reduction in CRT was fairly consistent between treatment arms and studies and the reduction observed at 12 months was maintained. Generally, the proportion of patients with intraretinal fluid decreased up to the 1st treatment year (in brackets below), and increased during the 2nd year, more so in the abicipar treatment groups. The average number of subjects (pooled data) with no intraretinal fluids at week 104 (week 52) were approximately 52% (62%), 50% (61%) and 55% (61%) in the 2Q8, 2Q12 and ranibizumab treatment arms, respectively.

Ancillary analyses

Subgroup analyses

- *BCVA*

The below Forest Plot summarises the mean change in BCVA in the subgroups at week 52.

Figure 8: BCVA, mean change from baseline treatment difference between abicipar 2Q8 and ranibizumab by subgroups, Pooled Studies 150998-005 and 150998-006, (PP set)

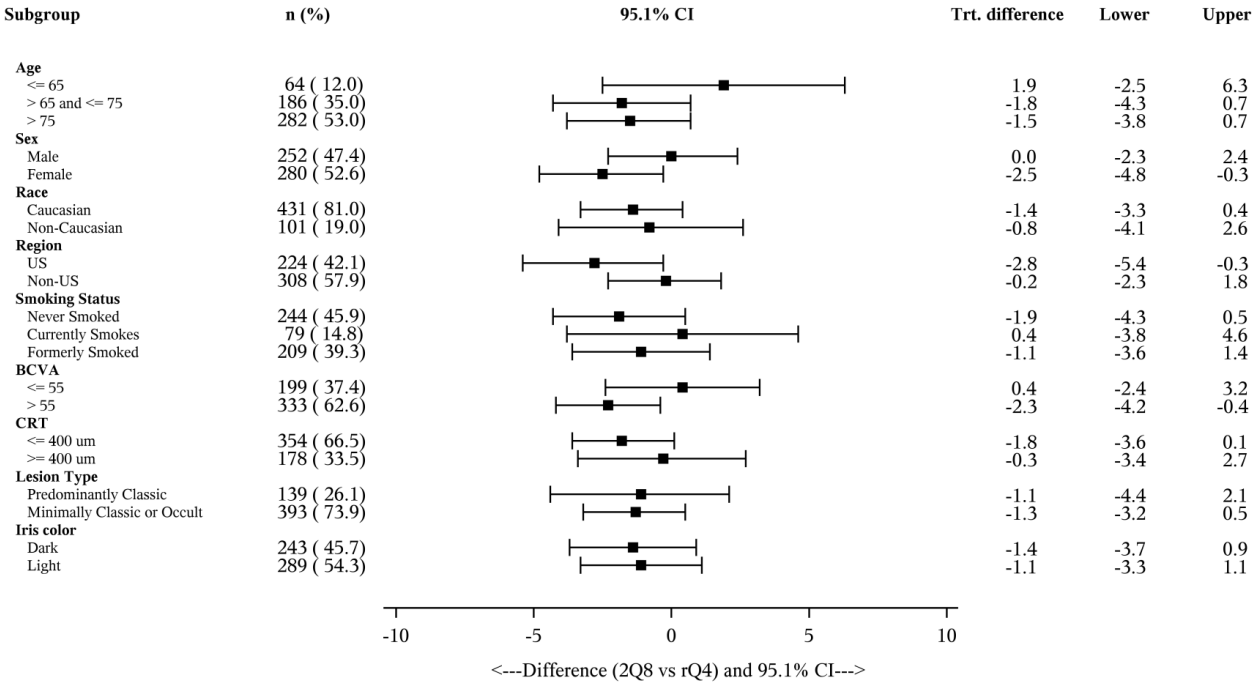
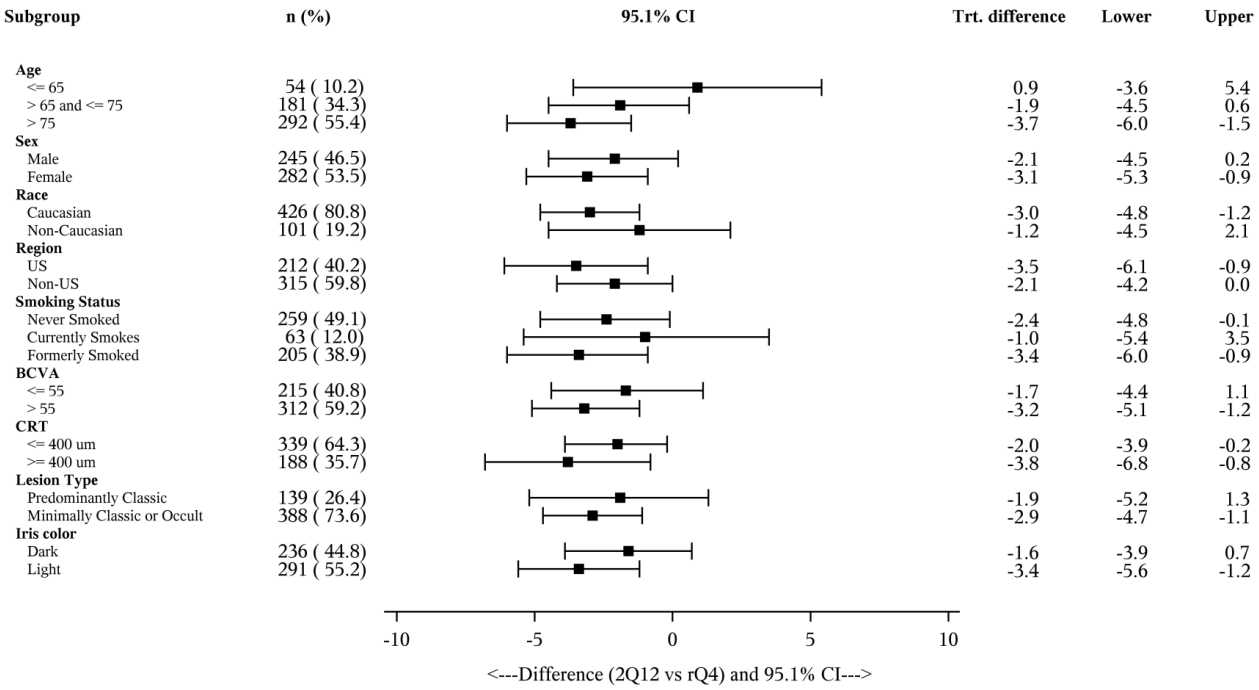


Figure 9: BCVA, mean change from baseline treatment difference between abicipar 2Q12 and ranibizumab by subgroups, Pooled Studies 150998-005 and 150998-006, (PP set)



- *Fluctuations in central retinal thickness (CRT) and intraretinal fluids (IRF) – impact on BCVA*

A potential impact of CRT fluctuations on BCVA was analysed by calculating the standard deviation of CRT measurements for each individual abicipar-treated patient and by separating the ITT population of the 2Q8 and 2Q12 treatment arms (pooled 150998-005/-006 data) into quartiles based on the extent

of CRT fluctuation between visits in the abicipar treatment arms. BCVA outcomes at Week 52 and Week 104 were subsequently divided into quartiles according to baseline CRT. The results suggest that patients with higher CRT fluctuation have a less favourable visual acuity outcome on both abicipar regimens. In the quartile with the highest fluctuations in both the 2Q8 and 2Q12 treatment groups at week 104, there was a loss of 6-8 letters in BCVA compared to the maximal gain achieved after the three initial monthly injections.

Also with regard to IRF, on both abicipar regimens, there was a pronounced fluctuation in the proportion of patients with fluid between visits. The pooled Phase III data indicate that the predominant manifestation on abicipar was recurrence of IRF between injections whereas on monthly ranibizumab a higher level of disease activity apparently translated into a higher proportion of patients with persistent IRF. Both recurrent and persistent IRF had a negative impact on visual acuity outcomes. At week 104, there was no mean gain in BCVA in abicipar-treated patients with a higher proportion of visits with IRF, while in this subgroup, ranibizumab-treated subjects gained a mean of 4 letters. In the subgroups with lower proportion of visits with IRF, the corresponding gains in BCVA were 6, 6 and 10 letters in the 2Q8, 2Q12 and rQ4 treatment arms, respectively.

- *Impact on immunogenicity and intraocular inflammation*

Impact of immunogenicity on patient disposition

Even though a slightly higher proportion of subjects developed antibodies towards abicipar in Study 150998-005, at week 52, there were no major differences between studies with the maximum number of patients developing BABs at any visit being 32% and 36.3% in the abicipar 2Q8 and 2Q12 dose groups. After repeat injections, the incidence of NABs increased to a maximum of 24% and 30% in the pooled 2Q8 and 2Q12 dose groups from both studies

A total of 69.2% (231/334) of NAB positive [NAB(+)] patients completed the studies through Week 52 as compared to 88.8% (780/878) of NAB negative [NAB(-)] patients. A higher percentage of NAB(+) patients as compared to NAB(-) patients discontinued due to ocular adverse events: 23.1% (77/334) vs. 3.4% (30/878), see further Safety.

Impact of Immunogenicity on efficacy

As summarised in the below table, for patients who were NAB negative, a numerically lower percentage lost <15 letters in BCVA as compared to NAB positive patients by Week 52. Similarly, the mean change in BCVA from baseline was smaller in NAB positive vs. NAB negative patients. Results for BAB positive patients were similar to those of NAB positive patients. Antibody titres appeared to have a limited impact on the outcomes.

Table 19: BCVA outcomes in NAB and BAB positive vs. NAB negative patients at Week 52. Pooled studies 150998-005 and 150998-006 (PP set)

	Abicipar				**Abicipar**			
	2Q8 NAB+	**2Q8 NAB-**	**2Q12 NAB+**	**2Q12 NAB-**	**2Q8 BAB+**	**2Q8 BAB-**	**2Q12 BAB+**	**2Q12 BAB-**
All treated patients	*57*	*208*	*70*	*191*	*48*	*219*	*62*	*203*
Loss of < 15 letters, %	82.5	94.2%	82.9	94.2	87.5	96.3	85.5	93.1
All treated patients	*92*	*397*	*118*	*372*	*129*	*360*	*151*	*339*
Mean (SD) change from baseline (letters)	2.0 (14.9)	8.8 (12.9)	1.5 (14.9)	8.0 (12.7)	3.3 (14.9)	9.0 (12.9)	2.4 (14.2)	8.3 (12.8)

All treated patients	*97*	*397*	*118*	*372*	*129*	*360*	*151*	*339*
Gain of ⩾15 letters, %	19.6	31.5	16.9	28.2	21.7	31.9	17.9	28.9

Source: Tables 4-12 to 4-15, Summary of Clinical Pharmacology Studies

Impact of intraocular inflammation (IOI) on efficacy

The subgroup analyses by IOI in NAB and BAB positive subjects treated with abicipar indicated that subjects with IOI had inferior BCVA outcomes.

The adverse effect on BCVA in subjects with IOI was more pronounced in Study 150998-005; however, marked also in Study 150998-006.

Table 20: BCVA outcomes in NAB and BAB positive patients with (IOI+) and without intraocular inflammation (IOI-) at Week 52. Pooled studies 150998-005 and 150998-006 (PP set)

	Abicipar NAB positive				**Abicipar BAB positive**			
	2Q8 IOI+	**2Q8 IOI-**	**2Q12 IOI+**	**2Q12 IOI-**	**2Q8 IOI+**	**2Q8 IOI-**	**2Q12 IOI+**	**2Q12 IOI-**
All treated patients	*32*	*73*	*33*	*99*	*33*	*111*	*36*	*131*
Loss of < 15 letters, %	62.5	94.5	78.8	85.9	63.6	94.6	75.0	87.8
All treated patients	*25*	*67*	*26*	*92*	*26*	*103*	*28*	*123*
Mean (SD) change from baseline (letters)	-6.9 (19.9)	5.3 (11.9)	-0.8 (10.4)	2.1 (15.9)	-6.0 (20.0)	5.6 (12.3)	-1.5 (10.5)	3.3 (14.8)
All treated patients	*25*	*67*	*26*	*92*	*26*	*103*	*28*	*123*
Gain of ⩾15 letters, %	12.0	22.4	3.8	20.7	15.4	23.3	3.6	21.1

Source: Tables 4-12 to 4-15, Summary of Clinical Pharmacology Studies

The overall impact on efficacy at Week 52 (pooled Phase 3 studies) when excluding subjects with IOI is summarised in the below tables.

Table 21: Proportion of subjects losing<15 letters in BCVA excluding patients with IOI at Week 52. Study 150998-005 (PP and ITT set)

	Study 150998-005			**Study 150998-006**		
	2Q8	**2Q12**	**rQ4**	**2Q8**	**2Q12**	**rQ4**
PP population	**N=265**	**N=262**	**N=290**	**N=267**	**N=265**	**N=299**
PP Population Excluding IOI	**(N = 244)**	**(N = 242)**	**(N = 290)**	**(N = 247)**	**(N = 246)**	**(N = 299)**
n (%)	231 (94.7)	226 (93.4)	227 (95.5)	237 (96.0)	225 (91.5)	287 (96.0)
Difference vs. rQ4	-0.8	-2.1		0.0	-4.4	
95.1% CI [a]	(-4.9, 2.9)	(-6.4, 1.9)		(-3.7, 3.4)	(-9.0, -0.4)	
ITT Population Excluding IOI	**N = 267)**	**N = 265**	**N = 312**	**N = 267**	**N = 267**	**N = 316**
n (%)	251 (94.0)	245 (92.5)	298 (95.5)	254 (95.1)	246 (92.1)	302 (95.6)
Difference vs. rQ4	-1.5	-3.0		-0.4	-3.3	
95.1% CI [a]	(-5.5, 2.2)	(-7.3, 0.9)		(-4.2, 3.1)	(-7.6, 0.6)	

Missing data and data after the first standard-of-care treatment were replaced by LOCF. Patients who escaped to standard of care by meeting the protocol criteria were set to failures.

[a] 95.1% CIs for the weighted difference were calculated based on the Newcombe method using CMH weights and baseline BCVA (≤ 55 vs. > 55 letters) as the stratification factor.

Table 22: Mean change from baseline in BCVA excluding patients with IOI at Week 52. Pooled studies 150998-005 and 150998-006 (PP and ITT set)

	Study 150998-005			Study 150998-006		
	2Q8	**2Q12**	**rQ4**	**2Q8**	**2Q12**	**rQ4**
PP population	**N=265**	**N=262**	**N=290**	**N=267**	**N=265**	**N=299**
n[a]	226	225	272	229	234	287
LS mean (SE) change from baseline	7.7 (0.9)	5.8 (0.9)	8.5 (0.8)	9.0 (0.9)	7.2 (0.9)	8.4 (0.8)
LS mean (SE) Difference vs. rQ4	-0.8 (1.1)	-2.7 (1.1)		0.5 (1.1)	-1.2 (1.1)	
95.1% CI[b]	(-3.1, 1.4)	(-4.9, -0.4)		(-1.7, 2.8)	(-3.4, 1.0)	
ITT Population Excluding IOI	**N = 267**	**N = 265**	**N = 312**	**N = 267**	**N = 267**	**N = 316**
n[a]	228	227	272	231	236	289
LS mean (SE) change from baseline	7.4 (0.9)	5.6 (0.9)	8.4 (0.8)	8.7 (0.9)	7.0 (0.9)	8.2 (0.8)
LS mean (SE) Difference vs. rQ4	-1.0 (1.1)	-2.7 (1.1)		0.5 (1.1)	-1.2 (1.1)	
95.1% CI[b]	(-3.2, 1.3)	(-5.0, -0.5)		(-1.8, 2.7)	(-3.4, 1.0)	

[a] This n is the number of patients with data at baseline and Week 52. Analysis was based on observed data

[b] The 95.1% CIs were based on observed data using a mixed model for repeated measures, which included the treatment, region, baseline BCVA in the study eye, baseline CRT (≤ 400 or > 400) in the study eye, lesion type of choroidal neovascularization, visit, visit-by-baseline BCVA interaction, and treatment-by-visit interaction term as covariates using an unstructured covariance matrix.

Impact of Immunogenicity on Long-Term Efficacy

The impact of NABs on long-term efficacy (<15 letter loss in BCVA, mean change from baseline in BCVA and CRT) was evaluated based by week 104 (150998-005 and 150998-006) was evaluated.

Because IOI may negatively affect vision, to determine the effect of NABs on efficacy in the absence of intraocular inflammation as a confounder, NAB+ patients (excluding those with IOI) were also compared to NAB- patients, see below table.

For the completer populations of Studies 150998-005 and 150998-006 at Week 104, the rates of subjects losing <15 letters in BCVA were similar as Week 52 in NAB+, NAB+ excluding patients with IOI, and NAB- patients in both abicipar 2Q8 and abicipar 2Q12 treatment groups.

When excluding patients with IOI, the rates of subjects losing <15 letters in BCVA for NAB+ patients were similar to those of NAB- patients (94.3% vs. 94.9%) for abicipar 2Q8 in Study 150998-005 but numerically lower (89.3% vs. 94.0%) for Study 150998-006. Also for abicipar 2Q12, the rates in NAB+ patients excluding those with IOI were similar to those of NAB- patients (97.6% vs. 90.5%) in Study 150998-005, but numerically lower (82.8% vs. 90.2%) for Study 150998-006.

Summary of main efficacy results

Table 23: Summary of efficacy for trial 150998-005

Title: Safety and Efficacy of Abicipar Pegol (AGN-150998) in Patients With Neovascular Age-related Macular Degeneration (CEDAR Study)			
Study identifier	150998-005 EudraCT Number: 2014-004579-22		
Design	Multicentre, double-masked, randomized, parallel-group, active controlled, non-inferiority studies to evaluate the safety and efficacy of abicipar compared with ranibizumab in treatment-naive patients with nAMD.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks not applicable 52 weeks
Hypothesis	Non-inferiority		
Treatments groups	2Q8		Abicipar 2.0 mg: 3 monthly intravitreal injections followed by injections at 8 weeks interval for 52 weeks. Randomized N=314
	2Q12		Abicipar 2.0 mg: 2 monthly intravitreal injections followed by injections at 12 weeks interval for 52 weeks. Randomized N=312
	rQ4		Ranibizumab 0.5 mg: Monthly intravitreal injections for 52 weeks Randomized N=310
Endpoints and definitions	Primary endpoint	%<15 letter loss	The proportion of patients that lost < 15 letters in best corrected visual acuity (BCVA) from baseline at week 52. Pre-defined non-inferiority margin: 10 %
	Key secondary endpoint	BCVA - Mean change	The mean change from baseline in BCVA at week 52 Pre-defined non-inferiority margin: 5 letters
	Secondary endpoint	% ≥15 letter gain	The proportion of patients that gained ≥ 15 letters in best corrected visual acuity (BCVA) from baseline at week 52.
	Secondary endpoint	CRT	Mean change from baseline in central retinal thickness (µm) at Week 52
	Subgroup analysis	% <15 letter loss IOI-	The proportion of patients that lost < 15 letters in best corrected visual acuity (BCVA) from baseline at week 52 excluding subjects with intraocular inflammation (IOI)
	Subgroup analysis	BVCA – mean change IOI-	The mean change from baseline in BCVA at week 52 excluding subjects with intraocular inflammation (IOI)
Database lock	The primary database lock occurred on 18 Jun 2018 and a database unlock and relock occurred on 29 Jun 2018 to correct identified data errors. On 04 Dec 2018, another data correction was made in the database.		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol: Received ≥9 treatments (incl. sham), not missed ≥3 consecutive injections (incl. sham), had no major protocol deviations, discontinued study due to treatment failure. Patients who escaped to standard of care by meeting		

	the protocol criteria were considered failures. 52 weeks			
Descriptive statistics and estimate variability Effect estimate per comparison (CMH, LOCF)	**Treatment group**	**2Q8**	**2Q12**	**rQ4**
	Number of subject	265	262	290
	% <15 letter loss	91.7%	91.2%	95.5%
	Difference vs. rQ4	-3.8%	-4.2%	
	95.1% CI	-8.2, 0.3	-8.7, 0.0	
Analysis population and time point description Descriptive statistics and estimate variability Effect estimate per comparison (CMH, LOCF)	Intention to treat: All randomised subjects 52 weeks			
	Number of subject	314	313	312
	% <15 letter loss	90.1%	88.2%	95.5%
	Difference vs. rQ4	-5.4	-7.3	
	95.1% CI	-9.6, -1.3	-11.8, -3.1	
Analysis description	**Key secondary endpoint** BCVA - Mean change, letters (SD), PP set	**2Q8**	**2Q12**	**rQ4**
		6.7 (12.9)	5.6 (13.3)	8.5 (13.6)
		-2.4	-3.7	Difference LS mean vs. rQ4
		-4.7, -0.1	-6.0, -1.3	95.1% CI (MMRM)
	Key secondary endpoint BCVA - Mean change, letters (SD), ITT set	5.9 (14.3)	5.5 (13.4)	8.5 (13.6)
		-3.5 (1.2)	-5.0 (1.2)	LS mean vs. rQ4
		-5.9, -1.1	-7.5, -2.6	95.1% CI (MMRM)
	Secondary endpoint: % ≥15 letter gain, ITT set	**2Q8**	**2Q12**	**rQ4**
		22.6%	19.2%	27.2
		-4.7	-8.2	Difference vs. rQ4
		-11.5, 2.1	-14.7, -1.5	95.1% CI (CMH, LOCF)
	Secondary endpoint: CRT, observed data Change from baseline (µm)	n=242	n=235	n=269
		-142	-150	-141
		8.6	2.3	Difference LS mean vs. rQ4
		-3.8, 20.9	-10.1, 14.7	95.1% CI (MMRM)
	Subgroup analysis: % <15 letter loss IOI**- PP set** Difference vs. rQ4, 95.1% CI	**2Q8 IOI-**	**2Q12 IOI-**	**rQ4 IOI-**
		n=231	n=223	n=224
		94.7% -0.8 (-4.9, 2.9)	93.4% -2.1 (-6.4, 1.9)	95.5%
	Subgroup analysis: % <15 letter loss IOI**- ITT set** Difference vs. rQ4, 95.1% CI	n=251	n=246	n=298
		94.0%	92.5%	95.5%
		-1.5 (-5.5, 2.2)	-3.0 (-7.3, 0.9)	
	Subgroup analysis: BVCA – mean change	**2Q8 IOI-**	**2Q12 IOI-**	**rQ4 IOI-**
		n=226	n=225	n=272
		7.7 (0.9)	5.8 (0.9)	8.5 (0.8)

	(SE) IOI-. **PP set** Difference vs. rQ4, 95.1% CI	 -0.8 (1.1) (-3.1, 1.4)	 -2.7 (1.1) (-4.9, -0.4)	
	Subgroup analysis: BVCA – mean change (SE) IOI-. **ITT set** Difference vs. rQ4, 95.1% CI	n=228 **2Q8 IOI-** 7.4 (0.9) -1.0 (1.1) (-3.2, 1.3)	n=227 **2Q12 IOI-** 5.6 (0.9) -2.7 (1.1) (-5.0, -0.5)	n=272 **rQ4 IOI-** 8.4 (0.8)
Notes	Consider amongst others the following information: In the pooled studies -005 and -006, a large proportion (23%) of NAB+ subjects in the abicipar treatment arms discontinued due to ocular AEs compared to NAB- subjects (3.4%). In the CHMP advice (EMEA/H/SA/3303/1/2016/III), the selected primary endpoint (% <15 letter loss) was not supported and the selected key secondary endpoint (BCVA – Mean change) was recommended as the primary endpoint. Similarly, the preferred non-inferiority margins were 7% in the primary responder analysis and 3-4 letters for BCVA - Mean change, at least in the pooled studies. Exclusion of subjects from the PP set is to an important extent due to the development of intraocular inflammation (leads to withholding treatment) that in turn had an adverse impact on BCVA. Excluding subjects with IOI from the analyses of efficacy improves BCVA outcomes for abicipar, at least for the 2Q8 regimen. For the 2Q8 regimen, the lower CIs ended up well within the recommendations given in the CHMP advice.			

Table 24: Summary of efficacy for trial 150998-006

Title: Safety and Efficacy of Abicipar Pegol (AGN-150998) in Patients With Neovascular Age-related Macular Degeneration (SEQUOIA Study)		
Study identifier	150998-005 EudraCT Number: 2014-004580-20	
Design	Multicentre, double-masked, randomized, parallel-group, active controlled, non-inferiority studies to evaluate the safety and efficacy of abicipar compared with ranibizumab in treatment-naive patients with nAMD.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks not applicable 52 weeks
Hypothesis	Non-inferiority	
Treatments groups	2Q8	Abicipar 2.0 mg: 3 monthly intravitreal injections followed by injections at 8 weeks interval for 52 weeks. Randomized N=316
	2Q12	Abicipar 2.0 mg: 2 monthly intravitreal injections followed by injections at 12 weeks interval for 52 weeks. Randomized N=315
	rQ4	Ranibizumab 0.5 mg: Monthly intravitreal injections for 52 weeks Randomized N=318

Endpoints and definitions	Primary endpoint	%<15 letter loss	The proportion of patients that lost < 15 letters in best corrected visual acuity (BCVA) from baseline at week 52. Pre-defined non-inferiority margin: 10 %
	Key secondary endpoint	BCVA - Mean change	The mean change from baseline in BCVA at week 52 Pre-defined non-inferiority margin: 5 letters
	Secondary endpoint	% ≥15 letter gain	The proportion of patients that gained ≥ 15 letters in best corrected visual acuity (BCVA) from baseline at week 52.
	Secondary endpoint	CRT	Mean change from baseline in central retinal thickness (µm) at Week 52
	Subgroup analysis	% <15 letter loss IOI-	The proportion of patients that lost < 15 letters in best corrected visual acuity (BCVA) from baseline at week 52 excluding subjects with intraocular inflammation (IOI)
	Subgroup analysis	BVCA – mean change IOI-	The mean change from baseline in BCVA at week 52 excluding subjects with intraocular inflammation (IOI)
Database lock	May 30, 2018		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	**Per protocol**: Received ≥9 treatments (incl. sham), not missed ≥3 consecutive injections (incl. sham), had no major protocol deviations, discontinued study due to treatment failure. Patients who escaped to standard of care by meeting the protocol criteria were considered failures. 52 weeks			
Descriptive statistics and estimate variability Effect estimate per comparison (CMH, LOCF)	**Treatment group**	**2Q8**	**2Q12**	**rQ4**
	Number of subject	267	265	299
	% <15 letter loss	94.8%	91.3%	96.0%
	Difference vs. rQ4	-1.2	-4.6	
	95.1% CI	(-5.0, 2.4)	(-9.0, -0.5)	
Analysis population and time point description Descriptive statistics and estimate variability Effect estimate per comparison (CMH, LOCF)	**Primary analysis** **Intention to treat**: All randomised subjects 52 weeks			
	Number of subject	316	315	318
	% <15 letter loss	92.4%	88.9%	95.3%
	Difference vs. rQ4	-2.9%	-6.4%	
	95.1% CI	-6.8, 0.9	-10.8, -2.2	

Analysis description				
	Key secondary endpoint	**2Q8**	**2Q12**	**rQ4**
	BCVA - Mean change, letters (SD), PP set	8.3 (14.3)	7.3 (13.8)	8.3 (11.8)
		-0.2 (1.1)	-1.6 (1.1)	Difference (SE) LS mean vs. rQ4
		(-2.4, 2.0)	(-3.8, 0.6)	95.1% CI (MMRM)
	Key secondary endpoint	8.2 (14.4)	7.0 (14.2)	8.3 (11.8)
	BCVA - Mean change, letters (SD), ITT set	-1.5 (1.2)	-3.0 (1.2)	LS mean vs. rQ4
		(-3.7, 0.8)	(-5.3, -0.7)	95.1% CI (MMRM)
	Secondary endpoint:	**2Q8**	**2Q12**	**rQ4**
	% ≥15 letter	28.2%	24.4%	26.7%
		1.4	-2.3	Difference vs.

	gain, ITT set			rQ4
		-5.5, 8.4	-9.1, 4.5	95.1% CI (CMH, LOCF)
	Secondary endpoint: CRT, observed data	n=248	n=256	n=289
	Change from baseline (µm)	-147	-142	-147
		3.5	5.9	Difference LS mean vs. rQ4
		-7.1, 14.0	-4.7, 16.5	95.1% CI (MMRM)
	Subgroup analysis: % <15 letter loss IOI- **PP set** Difference vs. rQ4, 95.1% CI	**2Q8 IOI-**	**2Q12 IOI-**	**rQ4 IOI-**
		n=237	n=225	n=287
		96.0% 0.0 (-3.7, 3.4)	91.5% -4.4 (-9.0, -0.4)	96.0%
	Subgroup analysis: % <15 letter loss IOI- **ITT set** Difference vs. rQ4, 95.1% CI	**2Q8 IOI-**	**2Q12 IOI-**	**rQ4 IOI-**
		n=254	n=246	n=302
		95.1% -0.4 (-4.2, 3.1)	92.1% -3.3 (-7.6, 0.6)	95.6%
	Subgroup analysis: BVCA – mean change (SE) IOI-. **PP set** Difference vs. rQ4, 95.1% CI	**2Q8 IOI-**	**2Q12 IOI-**	**rQ4 IOI-**
		n=229	n=234	n=287
		9.0 (0.9) 0.5 (1.1) (-1.7, 2.8)	7.2 (0.9) -1.2 (1.1) (-3.4, 1.0)	8.4 (0.8)
	Subgroup analysis: % <15 letter loss IOI- **ITT set** Difference vs. rQ4, 95.1% CI	**2Q8 IOI-**	**2Q12 IOI-**	**rQ4 IOI-**
		n=231	n=236	n=289
		8.7 (0.9) 0.5 (1.1) (-1.8, 2.7)	7.0 (0.9) -1.2 (1.1) (-3.4, 1.0)	8.2 (0.8)
Notes	Consider amongst others the following information: In the pooled studies -005 and -006, a large proportion (23%) of NAB+ subjects in the abicipar treatment arms discontinued due to ocular AEs compared to NAB- subjects (3.4%). In the pooled comparator arms, 0.6% of patients discontinued due to ocular AEs. In the CHMP advice (EMEA/H/SA/3303/1/2016/III), the selected primary endpoint (% <15 letter loss) was not supported and the selected key secondary endpoint (BCVA – Mean change) was recommended as the primary endpoint. Similarly, the preferred non-inferiority margins were 7% in the primary responder analysis and 3-4 letters for BCVA - Mean change, at least in the pooled studies. Exclusion of subjects from the PP set is to an important extent due to the development of intraocular inflammation (leads to withholding treatment) that in turn had an adverse impact on BCVA. Excluding subjects with IOI from the analyses of efficacy improves BCVA outcomes for abicipar, at least for the 2Q8 regimen. For the 2Q8 regimen, the lower CIs ended up well within the recommendations given in the CHMP advice.			

Analysis performed across trials (pooled analyses and meta-analysis)

A separate statistical analysis plan was prepared for the integrated summary of effectiveness (ISE). Integrated analysis was planned to be based on the pooled data from the 2 pivotal Phase 3 Studies 150998-005 and 150998-006 collected during the first year up to Week 52 visit. Analyses for the ISE was planned to be based on the ITT and PP populations as defined in the individual analysis plans with the PP population to be used for the primary analysis for non-inferiority tests of the primary and the key secondary endpoints, whereas the ITT population was planned to be used for superiority tests of secondary efficacy variables. A non-inferiority margin of 7% was planned to be used for the non-inferiority test of "loss of <15 letters ("stable" vision) at Week 52, and a non-inferiority margin of 4 letters was planned to be used for the non-inferiority test of mean change from baseline in BCVA at Week 52.

The key efficacy outcomes of the pooled studies are summarised in the below tables.

Table 25: Number (Percent) of Patients that lost <15 letters in the Study Eye at Week 52, Studies 150998-005, 150998-006 Pooled

	Pooled Studies 150998-005 and 150998-006		
	Abicipar 2Q8	**Abicipar 2Q12**	**Ranibizumab rQ4**
Per-protocol Population	**(N = 532)**	**(N = 527)**	**(N = 589)**
Loss of < 15 letters at Week 52, n (%)	496 (93.2)	481 (91.3)	564 (95.8)
Difference versus rQ4	-2.5	-4.5	
95.1% CI[a]	(-5.3, 0.2)	(-7.5, -1.6)	
Intent-to-treat Population	**(N = 630)**	**(N = 628)**	**(N = 630)**
Loss of < 15 letters at Week 52, n (%)	575 (91.3)	556 (88.5)	601 (95.4)
Difference versus rQ4	-4.1	-6.9	
95.1% CI[a]	(-7.0, -1.4)	(-9.9, -3.9)	

Table 26: Mean Change from Baseline in Best-corrected Visual Acuity in the Study Eye at Week 52, Studies 150998-005, 150998-006 Pooled

	Pooled Studies 150998-005 and 150998-006		
	Abicipar 2Q8	**Abicipar 2Q12**	**Ranibizumab rQ4**
Per-protocol Population	**(N = 532)**	**(N = 527)**	**(N = 589)**
n[a]	489	490	559
Mean (SD) change from baseline at Week 52	7.5 (13.7)	6.4 (13.5)	8.4 (12.7)
LS mean (SE) change from baseline	7.2 (0.6)	5.9 (0.6)	8.5 (0.6)
LS mean (SE) difference versus rQ4	-1.3 (0.8)	-2.6 (0.8)	
95.1% CI[b]	(-2.9, 0.3)	(-4.2, -1.0)	
Intent-to-treat Population	**(N = 630)**	**(N = 628)**	**(N = 630)**
n[a]	501	503	561
Mean (SD) change from baseline at Week 52	7.0 (14.4)	6.3 (13.8)	8.4 (12.7)
LS mean (SE) change from baseline	6.0 (0.6)	4.4 (0.6)	8.5 (0.6)
LS mean (SE) difference versus rQ4	-2.5 (0.8)	-4.0 (0.8)	
95.1% CI[b]	(-4.2, -0.8)	(-5.7, -2.4)	

Clinical studies in special populations

nAMD is a disease in the elderly to very elderly population and the mean and median ages in the confirmatory trials was 76 and 77 years, respectively.

Table 27: Age distribution

	Age <65	Age 65-74	Age 75-84	Age 85+	Total
Overall	196	715	1063	435	2409
Controlled trials	181 (8.3%)	663 (30.3%)	953 (43.6%)	388 (17.8%)	2185 (100.0%)
Uncontrolled trials	15 (6.7%)	52 (23.2%)	110 (49.1%)	47 (21.0%)	224 (100.0%)

Supportive study(ies)

Study 1771-201-008 is a 28-week multicenter, single arm, open label, Phase II study to evaluate the safety and treatment effects of abicipar. The study evaluates a modified drug substance manufacturing process, where residual *E. coli* host cell protein (HCP) has been reduced. In this study, 5 intravitreal injections of 2 mg abicipar were administered into the study eye at Day 1, and Weeks 4, 8, 16, and 24. See further safety.

3.3.6. Discussion on clinical efficacy

To support the MAA for abicipar in the treatment of neovascular (wet) age-related macular degeneration (AMD), the applicant has provided efficacy data from two identical, pivotal Phase III studies, Studies 150998-005 and 150998-006. The studies were randomised, double-masked, multicentre, active-controlled in treatment-naïve subjects with CNV secondary to AMD. The studies evaluated 2Q8 and 2Q12 dosing schedules of 2.0 mg abicipar compared to 0.5 mg ranibizumab Q4.

The studies are 2-year in duration and the full 2-year study data have been provided with response to the LoQ.

In addition, Studies 150998-001, -002 and -003 have evaluated different doses of abicipar in terms of efficacy.

The applicant received CHMP scientific advice in 2016 (EMEA/H/SA/3303/1/2016/III).

Design and conduct of clinical studies

- Dose selection

Single and repeat monthly injections with 1.0, 2.0, 3.0, and 4.2 mg (Study 150998-001) abicipar vs. 0.5 mg ranibizumab, 1.0 or 2.0 mg of abicipar vs. 0.5 mg ranibizumab (Studies 150998-002 and 150998-003) were evaluated to support the proposed dose of abicipar.

Study 150998-001 supported a treatment effect of abicipar that is in line with that of ranibizumab. In Stage 1, the median time to escape to SOC after a single injection of abicipar was around 8 to 12 weeks, and BCVA improved by 3 - 13 letters without any clear dose response relationship. In Stage 2, the median time to recurrence of active disease was similar between treatment arms (57-59 days), the initial improvement in BCVA was largest in the 3.0 mg abicipar group, but without any significant differences between treatment arms. The reduction in CRT was most pronounced with the highest 4.2

mg dose of abicipar. In Stage 3, the 2.0 mg dose of abicipar was numerically favoured in terms of the mean change in BCVA vs. baseline and the largest proportion in this dose group gained ≥ 15 letters. The lower 1 mg dose was numerically favoured with regard to reduction of CRT. Thus, there was no consistent dose response relationship seen and no conclusions on the choice of the most effective dose can be drawn.

In the identically designed Studies 150998-002 (Japanese) and 150998-003 (Caucasians), the 2 mg dose of abicipar appeared to result in a higher gain in BCVA compared to the 1 mg dose, but indicated that the 2.0 mg abicipar was inferior compared to ranibizumab. However, the studies were limited in size and not formally evaluated. As from Study 150998-001, these studies do not provide support to conclude on the optimal dose or regimen of abicipar.

Taken together, none of the Phase II studies provides consistent support for the choice of the 2.0 mg dose of abicipar or the proposed 2Q12 regimen and it is unclear why a higher dose of abicipar wasn't evaluated. Nevertheless, the pivotal studies evaluated the 2 mg dose of abicipar and it is not considered meaningful to request further justification on the choice of dose.

The 2Q8 and 2Q12 regimens of abicipar were evaluated in the pivotal Phase III studies discussed below.

- Pivotal studies 150998-005 and 150998-006

Patient population

Treatment-naïve patients older than 50 years with active CNV lesions secondary to AMD that affected the central or juxtafoveal subfield, and visual impairment (BCVA 73-24 letters) were included in the studies. The patient selection criteria were in line with those applied in previous trials and acceptable for the targeted population. In the overall development programme, essentially all patients have been treatment-naïve. While acknowledged that this is a preferable population to render a sensitive trial in a non-inferiority setting, there is consequently no information on the efficacy (or safety) of abicipar in a treatment-experienced population. This remains to be addressed in the SmPC section 5.1 (**SmPC**).

Treatment regimen

After 3 initial intravitreal (IVT) monthly injections, 2.0 mg of abicipar was administered every 8 weeks (2Q8), or after 2 initial monthly injections, 2.0 mg of abicipar was administered every 12th week (2Q12). Ranibizumab was given every 4 weeks (rQ4). The applicant justifies the 2Q8 and 2Q12 dosing regimens with the longer half-life compared to ranibizumab together with the results of Stage 3 from Study 150998-001.

The choice of an active comparator is fully supported since without treatment, patients with nAMD are expected to experience a rapid and irreversible loss of vision. The studies were conducted versus monthly ranibizumab (Lucentis). This is an effective and widely used treatment in this indication and considered a reasonable comparator. Also the monthly dosing regimen for ranibizumab is agreed as from an efficacy view, this would be expected to be an effective regimen without any concerns of a potentially suboptimal regimen.

Due to the differences in regimens between treatment arms, to maintain masking, subjects not scheduled for an active treatment at the monthly visit received a sham injection where a blunt end of a needleless syringe is pressed against the conjunctiva. Due to the risk associated with IVT injections, administrating true, placebo injections are not considered ethically justified and sham injections aims to mimic a true injection to preserve masking. Although not ideal when a subject receives both a sham and a true injection, this is standard in a setting where IVT injections are administered and the best that can be done.

The applicant has chosen to maintain the treatment schedules throughout the 2 years. It is considered a lost opportunity not to explore an individualised dosing regimen applying a PRN (pro re nata – as needed) or a treat-and-extend regimen in at least one of the studies. Currently, no further questions are raised on this topic as there are concerns related to the efficacy of abicipar, notably the 2Q12 regimen, see further below.

Efficacy endpoints

The overall selection of efficacy endpoints is in line with what would be expected and anticipated to provide a reasonable view of a treatment effect of abicipar. The evaluation of key efficacy was based on effects on BCVA. This is appropriate in patients with nAMD and has been used in the clinical development of other medicinal products for the intended indication. The choice of efficacy endpoints was discussed in the CHMP scientific advice (EMEA/H/SA/3303/1/2016/III).

The primary efficacy comparison was made in a non-inferiority setting and evaluated the proportion of patients who lost fewer than 15 letters in BCVA ("stable BCVA") from baseline at Week 52 applying a non-inferiority margin of 10%. In the aforementioned advice, it was advised against evaluating the proportion of patients losing < 15 letters BCVA from baseline. Although this is a measure used in earlier registration studies in the current indication, today, patient and clinician expectation in nAMD is for improvement in vision. Consequently, it was advised to set focus on an evaluation of the mean change in BCVA from baseline, alternatively an evaluation of the proportion of patients gaining ≥ 15 letters in BCVA. Although the 10% non-inferiority margin is expected to preserve more than 50% of the treatment effect of ranibizumab observed in the MARINA study, a non-inferiority margin solely justified based on "effect-retention" is not generally accepted and no clinical justification has been provided. To note is that for pegaptanib (Macugen), the first VEGF-inhibitor authorised in 2006 for the current indication, the difference in response rate versus placebo at 1 year was about 14%. As the CHMP considered this difference was considered acceptable from a licensure perspective (also taking risk into account), the proposed non-inferiority margin of 10% seems somewhat wide. It was however advised that a margin in the range of 7% that is met through the totality of evidence, i.e. from the pooled studies, would be considered acceptable for the assessment of non-inferiority. Such analyses were pre-planned and have been presented.

The key secondary endpoint is the mean change from baseline in BCVA at Week 52 applying a non-inferiority margin of 5.0 letters. From an assessment perspective, this is the preferred primary evaluation and will be regarded as such. However, the choice of a margin of 5.0 letters for an evaluation of the mean change from baseline has also not been justified and is again considered wide. Before the era of optical coherence tomography (OCT), the widely accepted re-treatment criterion for Lucentis was based on a BCVA loss of 5 letters. Such loss can thus not be excluded to be of relevance for a patient. A 3-4 letter margin was consequently recommended in the advice. The 4 letter margin proposed by the applicant in the pooled studies was tentatively accepted for the assessment of non-inferiority. Such analyses have been conducted.

Since the studies have been concluded up to the 52-week time point for evaluation of primary efficacy, it is not considered meaningful to request additional clarifications on the above issues concerning choice of primary endpoints and equivalence margins. The efficacy outcomes have been reviewed with focus on the mean BCVA change from baseline scrutinising the (lower bounds) of 95.1% CIs.

Responder analyses (e.g. gain of ≥15 and 10 letters) were defined among the additional secondary endpoints. These will inform on the magnitude of the treatment effect and are endorsed. Anatomical outcomes such as retinal thickness and retinal fluid status measured by OCT by masked central reading provide objective and supportive data. The impact of the changes in the quality of life has also been addressed.

Statistical analysis

Each study aimed to enroll approximately 900 subjects assuming a 90% response rate and an anticipated dropout rate of approximately 20% during a 52-week period. The sample size calculation can be followed; however, the efficacy objective of the trial was to demonstrate non-inferiority for at least one of the two tested abicipar regimens. Against this background, the sample size calculations done do not fully reflect this objective, and the actual power beforehand to show at least one of the regimens non-inferior to ranibizumab, was not calculated. However, no further issues arise in this context.

For both studies, the randomisation was performed 1:1:1 to three different groups: abicipar 2Q8, abicipar 2Q12 and ranibizumab monthly. The randomisation was stratified by region (North America, Asia, and rest of the world). Within each region, randomisation was stratified according to BCVA at baseline (BCVA ≤55 versus >55 ETDRS letters) and CRT (CRT ≤400 vs >400 microns). The randomisation strategy is generally considered adequate and the stratification factors are clinically relevant.

According to protocols, the PP population was to be used for analyses of the primary and secondary efficacy variables with the ITT population as secondary analysis population. The PP set included patients who received ≥ 9 study treatments (including sham), had not missed ≥3 consecutive treatments (including sham) and did not have any major protocol deviation, all up to week 52. In addition, the PP set also included patients who discontinued from the study due to treatment failure, but without a major protocol deviations that impacted efficacy outcomes, while patients who escaped to SOC according to protocol criteria were considered as treatment failures. In principle, the definitions of the analysis sets is considered adequate; however, this has implications for the analyses. In a non-inferiority setting, it would be expected that both the PP and the ITT sets should considered for the primary efficacy evaluation since the PP and ITT results could potentially deviate concerning the non-inferiority conclusion, usually under an expectation that ITT would reveal evidence for non-inferiority and the PP analysis would not. As discussed below, the situation for the interpretation of the 005/006 trial results would be opposite to the usual expectation, namely the PP analyses more likely to allow the conclusion of non-inferiority than the ITT analyses. This issue required further exploration in context of deriving unbiased effect estimates, see below.

The sequential testing approach having the test of 2Q8 as gatekeeper for the evaluation of 2Q12 cannot be seen fully suitable to reflect the wording in the hypotheses stated, namely to show at least one of the two abicipar regimens non-inferior to ranibizumab. Thus , the applicant was requested to justify the adequacy of the proposed sequential testing. The applicant clarified that there was obviously the intention to reflect at planning stage the assumption of a higher probability of treatment success for the 2Q8 regimen. This fact needs to be taken forward to B/R assessment for the two Abicipar regimens investigated.

Testing the binary outcome variable "<15 letters loss in BCVA" via stratified method with CMH weights is a reasonable approach. However, the missing data imputation approach via LOCF might not be conservative in this non-inferiority setting since there is a risk that the study could be declared successful with respect to non-inferiority even if in fact abicipar would be considerably worse than ranibizumab. Hence, the alternative suggested in the CHMP advice to switch to change to baseline analysis in BCVA and to analyse via MMRM becomes highly relevant in this context.

For the key secondary endpoint, the choice of the MMRM is endorsed; however, given the importance of the change to baseline analysis (ref to CHMP Scientific Advice), altering the hierarchy of endpoints for statistical testing might eventually inflict an issue of multiplicity. However, post-hoc this might be difficult to handle and this question actually remains an assessment issue. No further clarification is required from the applicant.

No major changes that could have affected the study outcomes were made in Protocol Amendments 1 to 3. The changes in Protocol Amendment 4 were made after the last patient had completed week 52 (April 18, 2018), but before the primary database lock (June 18, 2018). These changes concerned the primary analysis population (from ITT to PP) and replacement of the ANCOVA with MMRM for continuous variables. During the first round of assessment this timing of decision making to amend the primary efficacy analysis methods within the last amendment after last-patient-last-visit (but before data base lock) triggered a concern regarding premature access to study outcome information before data base lock. However, the applicant provided additional clarification that there was no unplanned access/review of unmasked efficacy data under both protocols, which could have influenced the decision for amendments of the ongoing trials.

Efficacy data and additional analyses

In both pivotal studies, patients were recruited from 6 different continents including Europe and North America. A total of 13 European countries were included thereby ensuring a broad European representation, which is endorsed.

A total of 939 and 949 patients were randomised to abicipar and ranibizumab in the controlled trials – 005 and -006, respectively. Subject retention and pattern of discontinuations were similar between studies. Across the studies, 80% to 84% of patients in the abicipar treatment arms completed Week 52, while 91.3% to 93.7% of subjects completed the first treatment year in the ranibizumab treatment arms. The higher dropout rates in the abicipar treatment arms were mainly due to a higher proportion of subjects discontinuing treatment due to ocular adverse events (AEs), mainly IOIs, in the abicipar treatment arms (8%-11%) compared to ranibizumab (<1%).

Baseline demographics and disease characteristics were well balanced within studies and similar between studies. No concerns are raised. Subjects received the majority of the planned injections and the extent of exposure was similar between studies.

In both studies, the most common reason for being excluded from the PP set were missed treatments. However, the reasons for missing treatment are not easy to disentangle. It is anyway clear that several subjects in the abicipar treatment arms were excluded from the PP set as treatment was withheld or since patients discontinued due to ocular AEs. The majority of there were IOI.

The applicant has chosen the PP set as the primary analysis population. While reasonable to account subjects with "lack of efficacy" as failures, it does not seem reasonable to exclude subjects withholding/discontinuing treatment due to AEs that, at least, cannot be excluded to be related to treatment (drug or injection) from the primary analysis population. Rather, these would be included and regarded as failures in the primary responder analysis independently whether defined as an ITT or a PP set. Similarly, in the key secondary analysis (that is of principal interest), missing data due to AEs should be imputed by an appropriate and conservative method.

During the 1st treatment year, the number of patients who discontinued treatment in the abicipar arm is approximately 17-20 % for the abicipar arms and approximately 6-9 % for the ranibizumab arm. Patients discontinued mainly due to AE (abicipar: ≈ 10-13 %, ranibizumab: ≈ 2 -5 %) and withdrawal by patients (abicipar: ≈ 4-6 %, ranibizumab: ≈ 2 %). By definition, the per-protocol population only include subjects who complied to treatment to a large extent. The number of discontinuation and the difference in discontinuation pattern may have biased the PP population, and therefore the interpretation of the results based on the PP-population could be hampered. The applicant was asked to explore options to investigate the outcome of patients who start treatment with abicipar and then switch to other treatments; however, follow-up post discontinuation was very limited. This is highly unfortunate as information on the final impact on BCVA will not be possible to obtain. .

The applicant has explained that the majority of patients who were excluded from the PP analysis were due to missed study treatments as a consequence of IOI.

In addition, a higher proportions of drop outs were due to "Withdrawal by patient" in the abicipar treatment groups (6.1%-3.5%) vs. the ranibizumab treatment groups (1.9%-2.2%). Unfortunately, the applicant has not collected data to inform on reasons behind the higher rate of withdrawal by patient in the abicipar treatment groups.

With response to the LoI, the 2nd year study outcomes have been provided and discussed below.

Primary efficacy

Although ranibizumab was consistently favoured with regard to the point estimates, more than (PP set) or close to (ITT set) 90% of subjects in the abicipar treatment groups lost <15 letters in BCVA. Maintaining BCVA in around 90% of subjects is per se considered of clear relevance compared to no treatment; however, when put in context with the outcome of the comparator, there are concerns.

As previously discussed, the selected primary endpoint is outdated as it is now an expectation of a gain in BCVA rather than maintaining or losing up to 14 letters of BCVA. Further, the high response rates in all treatment arms together with the 10% non-inferiority margin indicate that this is also not a sensitive measure to detect potential differences between treatment arms.

When analysed according to the protocol-defined non-inferiority margin of 10%, Study 150998-005 met its primary objective for the PP population for both regimens (95.1% CIs -8.2, 0.3 and -8.7, 0.0) and for the 2Q8 regimen in the ITT set (95.1% CI -9.6, -1.3). However, turning around the planned superiority analyses for abicipar, in the latter analysis, the upper limit of the CI is below zero. This indicates that the effect of ranibizumab would be superior over that of abicipar. Similarly, in the ITT set for the 2Q12 regimen, abicipar failed to meet its objective and was inferior to ranibizumab (95.1% CI -11.8, -3.1). In Study 150998-006, for the 2Q12 regimen, abicipar was inferior to ranibizumab in both the PP and the ITT set (-9.0, -0.5 and -10.8, -2.2, respectively), even if the CI lower bound was within 10% in the PP set. These results were confirmed by the sensitivity analysis of the PP population (using LOCF or MI with modified Wald method for CIs, or MI with Newcombe method for CIs).

Also when pooling the studies and thus expecting the 7% non-inferiority margin to be met, for the 2Q12 regimen the lower bound of the 95.1% CI was -7.5% (PP) and -9.9% (ITT) and borderline (-7%) in the ITT set for the 2Q8 regimen.

Considering the above criticism on the somewhat wide non-inferiority margin, the concerns regarding discontinuation and exclusion of subjects withholding treatment due to an IOI from the PP set, for the pre-defined primary endpoint, only Study -006 is considered truly positive (PP and ITT set, lower bound NI-margin at or above -7%), and this only in the 2Q8 abicipar treatment arm. This should be put in context of the proposed posology where a 2Q12 regimen is recommended and a major objection was raised.

The applicant presented several sensitivity analyses, which are overall acceptable. One analysis implemented MI. The imputation model included baseline BCVA in the study eye, age, and randomisation stratification factors of CRT and lesion type. This model assumed MAR when controlling for the mentioned variables. The variables included in the MI model are considered to be correlated with treatment outcome. However, the main reason for treatment discontinuation was AE. When potential predictors of AE are included in the multiple imputation model, the difference in the proportion of patients losing <15 letters in BCVA at Week 52 vs rQ4 turned out to increases for both abicipar treatment regimens.

In the original dossier, the applicant also performed a tipping point analysis to investigate departures from the MAR assumption. This was done for PP, and similar analyses were additionally requested for

ITT. For the endpoint proportion of patients losing <15 letters at Week 52 using MI with the ITT population, only abicipar 2Q8 would indicate non-inferiority to rQ4. The results of the tipping point analyses indicate that if non-missing at random is assumed, it is likely that abicipar would be inferior to rQ4 using the ITT population.

In addition, in response to a concern raised at the previous round, the applicant presented an analysis where all discontinuations are treated as treatment failures. The results are reported below and point to a wider difference between ranibizumab and abicipar.

Table 28

		Study 150998-005			Study 150998-006			Pooled		
		Abicipar 2Q8	Abicipar 2Q12	Ranibizu-mab rQ4	Abicipar 2Q8	Abicipar 2Q12	Ranibizumab rQ4	Abicipar 2Q8	Abicipar 2Q12	Ranibizumab rQ4
Primary analysis [LOCF] [1] [2]	**Per-protocol Population**	**(N = 265)**	**(N = 262)**	**(N = 290)**	**(N = 267)**	**(N = 265)**	**(N = 299)**	**(N = 532)**	**(N = 527)**	**(N = 589)**
	Stable vision at Week 52, n (%)	243 (91.7)	239 (91.2)	277 (95.5)	253 (94.8)	242 (91.3)	287 (96.0)	496 (93.2)	481 (91.3)	564 (95.8)
	Difference versus rQ4	-3.8	-4.2		-1.2	-4.6		-2.5	-4.5	
	95.1% CI [4]	(-8.2, 0.3)	(-8.7, 0.0)		(-5.0, 2.4)	(-9.0, -0.5)		(-5.3, 0.2)	(-7.5, -1.6)	
	Intent-to-treat Population	**(N = 314)**	**(N = 313)**	**(N = 312)**	**(N = 316)**	**(N = 315)**	**(N = 318)**	**(N = 630)**	**(N = 628)**	**(N = 630)**
	Stable vision at Week 52, n (%)	283 (90.1)	276 (88.2)	298 (95.5)	292 (92.4)	280 (88.9)	303 (95.3)	575 (91.3)	556 (88.5)	601 (95.4)
	Difference versus rQ4	-5.4	-7.3		-2.9	-6.4		-4.1	-6.9	
	95.1% CI [4]	(-9.6, -1.3)	(-11.8, -3.1)		(-6.8, 0.9)	(-10.8, -2.2)		(-7.0, -1.4)	(-9.9, -3.9)	
Patients who discontinued study before Week 52 set to non-responders [1] [3]	**Per-protocol Population**	**(N = 265)**	**(N = 262)**	**(N = 290)**	**(N = 267)**	**(N = 265)**	**(N = 299)**	**(N=532)**	**(N=527)**	**(N=589)**
	Stable vision at Week 52, n (%)	239 (90.2)	230 (87.9)	271 (93.4)	246 (92.1)	235 (88.7)	285 (95.3)	485 (91.2)	465 (88.2)	556 (94.4)
	Difference versus rQ4	-3.3	-5.6		-3.1	-6.6		-3.2	-6.2	
	95.1% CI [4]	(-8.1, 1.3)	(-10.7, -0.7)		(-7.5, 0.9)	(-11.4, -2.1)		(-6.4, -0.2)	(-9.6, -2.9)	
	Intent-to-treat Population	**(N = 314)**	**(N = 313)**	**(N = 312)**	**(N = 316)**	**(N = 315)**	**(N = 318)**	**(N=630)**	**(N=628)**	**(N=630)**
	Stable vision at Week 52, n (%)	244 (77.7)	235 (75.1)	272 (87.2)	251 (79.4)	244 (77.5)	288 (90.6)	495 (78.6)	479 (76.3)	560 (88.9)
	Difference versus rQ4	-9.5	-12.1		-11.1	-13.1		-10.3	-12.6	
	95.1% CI [4]	(-15.4, -3.5)	(-18.2, -6.0)		(-16.7, -5.6)	(-18.8, -7.4)		(-14.4, -6.2)	(-16.8, -8.4)	

Key secondary and secondary endpoints

Also for the efficacy endpoint of main interest, the key secondary endpoint evaluating the mean BCVA change from baseline to week 52, the non-inferiority margin of 5 letters is considered somewhat wide and a margin in a range of 3-4 would have been preferred. In Study 150998-005, abicipar was technically inferior to ranibizumab in both analysis sets and for both regimens since the upper bound 95.1% CIs were below zero. The lower bound margin was only within the pre-specified margin of -5 letters in the PP population for the 2Q8 regimen (-4.7 letters). From efficacy view, Study 150998-005 is regarded a failed study. When excluding subjects with IOI, the 95.1% CIs for the difference vs. ranibizumab is reassuring in both the PP and ITT sets for the 2Q8 regimen of abicipar. However, for the 2Q12 dosing regimens, the upper bound 95.1% CI in both analysis sets is still below zero in Study -005 and in the pooled studies. Again, even if a proportion of patients might well be managed with the 2Q12 regimen, on the overall population level, the efficacy of the 2Q12 regimen is not fully convincing.

In contrast to the analysis for the primary endpoint, patients who escaped to standard of care due to loss of more than 30 letters were not imputed as non-responder for the analysis of the key secondary endpoint. Upon request, the applicant explained that the imputation rules were defined in the SAP before database lock and study unmasking. Several sensitivity analyses were planned and the applicant argues that no post-baseline variables were included in the imputation model since they could be confounded by other factors such as ocular adverse events (IOI, RVO, etc) or progression of the underlying disease following study treatment.

Study 150998-006 came out better and in the PP set, the 95.1% CIs were -2.4, 2.0 and -3.8, 0.6 for the 2Q8 and 2Q12 regimens, respectively. For the 2Q8 regimen, abicipar is judged being non-inferior to ranibizumab. However, the outcomes of the 2Q12 regimen are less reassuring considering the differences between the ITT and the apparently anti-conservative analysis in the PP set. In the ITT population, abicipar was non-inferior to ranibizumab for the 2Q8 regimen (95.1% CI -3.7, 0.8), but not for the 2Q12 regimen (-5.3, -0.7). Taken together and considering the proposed 2Q12 dosing schedule, Study -006 is also not regarded fully convincing. Also when viewing the mean change in BCVA over time, ranibizumab was favoured over both abicipar regimens at all time-points in Study -005 while Study -006 is judged to be non-inferior to ranibizumab for the 2Q8 regimen.

Overall, consistency across between studies has not been demonstrated. Thus, the inconsistency in study conclusions between studies -005 and -006 questions the robustness of the efficacy data. The applicant argues that the results for the primary endpoint (proportion of patients losing <15 letters in BCVA) was similar between studies and that the differences between studies mainly were due to the smaller initial gain in Study -005, particular for the 2Q12 regimen where only 2 monthly injections are administered. Whilst this explanation of the source of heterogeneity is acknowledged, the finding described is seen as a non-negligible signal disfavouring the 2Q12 regimen and will be taken forward to B/R assessment for the two Abicipar regimens investigated. Unfortunately, the applicant has not sufficiently justified that both studies are truly positive. In the justification, the applicant has further not addressed that IOI resulted in a substantially higher proportion of patients with a ≥30 letter vision loss in Study -005 compared to Study -006 and approximately 2/3 of these events were reported during the initial treatment period (see Safety). This might explain the lower initial gain in BCVA in Study -005. In view of missing data for the primary analysis were imputed with the LOCF approach, this should reasonably affect the outcome of Study -005, at least in the ITT set. For the key secondary endpoint, it is however not clear to what extent the larger proportion of subjects with a loss of BCVA might have affected the outcomes in the ITT and PP sets. The issue is however not further pursued.

Also in the pooled analysis of the mean change from baseline in the two studies, only in the PP set for the 2Q8 regimen, the lower bound 95.1% CI was smaller than the 3-4 letters recommended in the CHMP advice while the upper bound 95.1% CI was below zero in the remaining analyses (PP set for 2Q12 and ITT sets for both regimen). This is also not convincing and, taken together, of major concern.

The applicant points to the efficacy of abicipar being confounded by IOI. In comparison with the results presented in **Table 12** the PP-population, the exclusion of patients who developed IOI changed the mean change from baseline for 2Q8 from 6.2 and 8.2 letters in study 005 and 006; to 7.7 and 9.0 letters and "improved" the confidence intervals. A similar pattern was observed for 2Q12 although the difference, albeit smaller, compared to ranibizumab remained. However, since the exclusion of patients who had IOI improved the results for abicipar it could be considered that IOI had an adverse impact on BCVA. The results for the ranibizumab arm remained unchanged, which is expected since those patients practically did not suffer IOI. The interpretation of this analysis is difficult given that a group of patients were excluded based on a post-randomization variable, and therefore randomization is broken. In other words, the comparison of abicipar with the ranibizumab arm is not straightforward because the patients are different. While the ranibizumab arm contains most of the patients randomized, the subjects included in the abicipar arm are only those who tolerated abicipar treatment, and therefore they are not necessarily comparable with the patients included in the randibizumab arm. It is not possible to forsee to the size of the bias in this analysis.

Also for the secondary analyses of gain in BCVA (≥10 and ≥15 letters) from baseline to week 52, ranibizumab was favoured over the two abicipar regimens in Study 150998-05 while Study 150998-06 is again more convincing, at least for the 2Q8 regimen.

The changes in CRT at week 52 were clinically meaningful and similar in all treatment groups in both studies. Of potential concern of an adverse impact on BCVA in the long term are however the fluctuations observed between injections in the abicipar treatment groups. Although the increases in CRT between injections were below the 50µm generally regarded to be of relevance, this implies that there is some disease activity between injectionsand further interpretation of these findings was asked for. The applicant has calculated the standard deviation of CRT measurements for each individual and separated the 2Q8 and 2Q12 treatment arms into quartiles (lowest to highest fluctuations). The results suggest that patients with higher CRT fluctuation have a less favourable visual acuity outcome on both abicipar regimens.

In both studies, abicipar cleared subretinal fluid, reduced intraretinal thickening and dried the retina faster than ranibizumab. However, the applicant has further identified that recurrences of intraretinal fluids (IRF) occurred between abicipar injections, while for ranibizumab, a higher level of disease activity translated into a higher proportion of patients with persistent IRF. Published data indicate that cumulative exposure to IRF appears to have an adverse impact on long-term BCVA outcomes of anti-VEGF treatment for AMD. Indeed, at week 104, there was no mean gain in BCVA in abicipar-treated patients with a higher proportion of visits with IRF while the corresponding ranibizumab-treated subjects gained a mean of 4 letters. In the subgroups with lower proportion of visits with IRF, the corresponding gains in BCVA were 6, 6 and 10 letters in the abicipar 2Q8, 2Q12 and ranibizumab treatment arms, respectively.

Taken together, an even more frequent injection interval than Q8 might be optimal for certain patients. However, neither a potential added benefit of more frequent injections, nor the safety profile abicipar has been explored and further discussion on this is not meaningful. However, as discussed below, the efficacy of the 2Q12 regimen is not fully convincing, especially in the long-term, and it seems likely that a proportion of patients are in need of more frequent dosing. Consequently, there is a request for a further update of the SmPC, section 4.2.

The outcomes of the VFQ-25 was largely similar between studies; however, again there were trends of a favour for ranibizumab even if the differences between treatment arms were small and at week 52, only for one of the subscales exceeded the 4-5 units generally regarded to of clinical relevance.

2-year data

Approximately 71% of abicipar-treated and 83% of ranibizumab-treated subjects completed the 2-year studies. The main reason for discontinuations were adverse events that were observed in approximately 16% for the abicipar and 7% for ranibizumab treatment groups. Most were ocular (12% and 2% for abicipar and ranibizumab, respectively) without any major differences between the studies or the two abicipar-treatment arms. It is apparent that the overall incidence of adverse events that led to study discontinuation was somewhat higher in the abicipar treatment groups also between the 1st and the 2nd year.

Efficacy at 2-years was evaluated in the completers population defined after the primary database lock. It was defined as patients within the ITT population who completed the study without escaping to standard of care by Week 104 and the analyses were based on observed data and on LOCF. Briefly, the proportions of subjects losing <15 letters were essentially maintained during the 2nd treatment year (approximately 93%, 90%, 94% for 2Q8, 2Q12 and ranibizumab, respectively). Also at 2-years the 2Q12 regimen is less convincing (95% CI for the differences vs. ranibizumab was -8.2, 2.1 and -11.6, -1.2 in Studies -005 and -006, respectively).

With regard to the informative key secondary endpoint, the mean change from baseline, in Study -005, the mean gains in BCVA vs. baseline (95% CI for difference) were 6.4 (-4.4, 0.8) and 5.0 (-5.8, -0.6) letters in the 2Q8 and 2Q12 abicipar treatment groups vs. 8.8 letters for ranibizumab. In Study -006,

the mean gains were 7.9 (-2.2, 2.9) and 6.0 (-4.1, 0.9) letters in the two abicipar treatment groups and for ranibizumab, the corresponding figure was 7.5 letters.

The observed data based on the completer population might not represent a conservative estimate and even if an absolute effect is demonstrated, the 2Q12 dosing regimen of abicipar on the primary and key secondary endpoint is not fully convincing. Further, in the 2Q12 abicipar treatment group, only 3 full "cycles" of treatment was administrated during the 1st treatment year and primary efficacy was evaluated one month after the most recent injection. It is possible that this might have been insufficient to address maintenance of efficacy for this regimen. Considering that the applicant presents data in support of fewer events of IOIs during the 2nd treatment year and that the estimates are based on observed data, for a subset of patients on the 2Q12 regimen, again, efficacy is not fully convincing and there is potential concern of maintenance of longer-term efficacy. This has impact on the wording of the SmPC, section 4.2 where the 2Q12 regimen is recommended and the 2Q12 regimen is only mentioned as one having similar efficacy. This is not acceptable and further rephrasing is requested and detailed comments will be provided pending the response to the LoOI. (**SmPC**). In addition, there is potential concern of accumulation of intraretinal fluids between the less frequent injections and an inferior BCVA outcome over time.

Subgroup analyses

In general, the 52-week change in BCVA vs. baseline was consistent between subgroups and followed the results observed in the overall study population.

Of interest are the subgroup analyses evaluating BCVA (the 52-week loss of <15 letters and mean change in BCVA relative to baseline) by development of anti-abicipar binding antibodies (BABs), neutralizing anti-abicipar antibodies (NABs) and IOI.

A large proportion, around one third of patients randomised to either 2Q8 or 2Q12 abicipar, developed NABs and/or BABs against abicipar. The applicant has discussed different potential reasons for the high incidence of NABs and BABs. Reasons may be related to the T-cell epitope causing abicipar to be more immunogenic than e.g. ranibizumab. Indeed, this is most likely based on the higher frequency of NABs and BABs related to abicipar compared to the reported frequency of NABs and BABs to ranibizumab. Nevertheless, the high frequency of NABs and BABs is of concern, see Safety. The majority of subjects that developed IOIs (around 80-90%) were positive for ADAs. The applicant concludes that "a causal relationship between AEs, including IOI, and ADA response could not be established". However, although acknowledging that ADAs might not be the only reason behind the IOI, a causal relationship cannot be excluded since when computing the relative risk for getting an IOI depending on the presence of BABs or not, it is evident that subjects being BAB positive has an approximately 10-fold higher risk of developing an IOI. In the analysis by IOI (yes/no), it is further demonstrated that the visual acuity outcomes are inferior in ADA positive subjects with IOI. This remains of major concern and will be taken into account when considering the overall benefit/risk of abicipar. The applicant has provided data on the impact of immunogenicity on long-term efficacy and also with these data at hand, the presence of NAB(+) affects the efficacy negatively. However, from the data presented it cannot be concluded whether efficacy might be directly affected in NAB(+) subjects or whether this is a consequence of the IOI. Therefore, the applicant is asked to present the results for the analysis evaluating impact of NABs on efficacy (proportion of patients losing <15 letters and mean change from baseline) conducted with the completer population and patients who discontinued due to ocular adverse events. **(OC)**

Since essentially all participants in the clinical development programme were treatment-naïve, it is unclear whether the immunogenicity profile will be similar in subjects previously treated with other anti-VEGFs and the absence of data in treatment-experienced subjects still needs to be addressed in the SmPC, section 5.1. (**SmPC**)

Taken together, the applicant claims that the efficacy of abicipar to improve visual acuity is confounded by IOI, reported by approximately 15 % of the patients. This is not agreed, the AE are caused by abicipar treatment, and it is a requirement in this disease to be able to receive treatment to delay the progression of the disease.

The applicant presented several analyses were patients who suffered IOI AE were excluded. The AE are post-baseline events and therefore the exclusion of such patients will give biased results. The analyses presented excluding those patients are not considered interpretable since a fair comparison would have been among those patients who would have never developed IOI AE regardless of the treatment arm they were assigned. If the applicant aims for such a comparison another methodological framework should be used (see for example Principal stratum estimand in E9 addendum).

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical efficacy

Not applicable.

Additional efficacy data needed in the context of a conditional MA/under exceptional circumstances

Not applicable.

3.3.7. Conclusions on clinical efficacy

Overall, the major objection on efficacy is not considered solved. There are still lack of convincing effect of abicipar. Despite the arguments from the applicant, it is still only Study 150998-006 which is considered to show a statistically significant and clinically relevant effect but only for the Q8 abicipar treatment. In Study 150998-005 the effect of abicipar is considered inferior to ranibizumab which is of concern. The methodological outstandings are not considered solved. Indeed, (optimally) statistically significant effect should be shown both for the PP and the ITT populations and in both studies. The observed effect in the PP population may be due to the differences in discontinuations and use of LOCF. The efficacy of the Q12 regimen is further compromised by the between-treatment worsening of vision which may indicate that the 12-weeks period between treatments is too long.

The efficacy MO is maintained: Only Study -006 is considered truly positive in both the PP and the ITT sets, but only in the 2Q8 abicipar pegol treatment arm. In Study -005 on the other hand, abicipar pegol is considered inferior to ranibizumab. Overall, non-inferiority has not been convincingly shown. Inconsistent outcomes between the studies further question the robustness of the effect of abicipar pegol, particularly for the 2Q12 regimen that is proposed for section 4.2 of the SmPC, but also for the 2Q8 regimen.

The applicant is requested to provide a thorough justification that abicipar administered Q8 as well as Q12 is an effective and sufficiently safe treatment providing a discussion on the overall efficacy considered the lack of consistent non-inferiority to ranibizumab across the PP and ITT populations in the pivotal studies. The discussion should include a thorough discussion of the high discontinuation rate and a justification for use of LOCF for discontinuations. **(MO)**

3.3.8. Clinical safety

The safety of abicipar has been evaluated in a total of 9 studies in patients with nAMD:

- Two global multicentre, double-masked, randomized, 104-week, parallel-group, active controlled Phase III studies (Studies 150998-005 and 150998-006)
- Two PK studies (Study 150998-012 in US and Study 1771 101-008 in Japan)
- One Phase 1 study (Study MP0112-CP01), three Phase 2 studies (Studies 150998-001, 150998-002 Japan and Study 150998-003 US), and one Phase 2 study (Study 1771 201 008).

Since the Phase I/II studies add limited information important from a safety view, unless indicated, the report focuses on safety data from the identically designed pooled Phase III studies.

Patient exposure

Overall, 1684 patients with nAMD from the pivotal Phase III and completed Phase I and II studies received at least 1 dose of abicipar, see below table.

Table 29: Summary of patient exposure

	Patients exposed	Patients exposed to the proposed dose range	Patients with long term safety data
Active controlled	1684	1300	1251/890
Phase III studies	1251	1251	1251/890*
Phase I and II studies	433	49	0

* Up to 24 months data/completed 24 months.

At Week 104, patients could have received to 14 active injections injections in the 2Q8 group, 10 in the 2Q12 group, and 25 active injections in the rQ4 group. The percentage of patients who received the maximum number of planned injections up to Week 104 was 58.6% in the 2Q8 group, 60.2% in the 2Q12 group, and 58.2% in the rQ4 group. The actual mean numbers of injections of active study treatment were 11.5, 8.2, and 22.5 for the 2Q8, 2Q12, and rQ4 groups, respectively.

Across the studies, approximately 71% (80 to 84%) of patients in the abicipar treatment arms completed Week 104 weeks (52 weeks in brackets), while 83% (93%) of subjects completed the 2nd (1st) treatment year in the ranibizumab treatment arms. The higher dropout rate in the abicipar treatment arms, were mainly due to a higher proportion of subjects discontinuing treatment due to ocular AEs in the abicipar treatment arms (11-13%) compared to ranibizumab (1.6%), see further **Figure 5** and **Figure 6**.

Overall, in the pooled Phase III dataset, the ITT population included 44% males and 55% females, and the mean age was 76 years, ranging from 50 to 99 years. Most patients were white (81%) or Asian (13%). Baseline demographics were well balanced within studies. Except for slightly higher proportions of Whites in Study -005 and Asians in Study -006, demographics were also similar between studies, see **Table 8**.

In the pooled Phase III dataset, the mean baseline BCVA was 57 letters and the mean baseline CRT was 380 µm. There were no important differences with regard to baseline disease characteristics, neither between treatment arms, nor between studies, see **Table 9**.

Adverse events

Week 52 and 104 safety database, pooled Phase III studies

All AEs were monitored and reported including seriousness, severity, action taken, and relationship to study treatment. All AEs with onset on or after the first dose date of study treatment were considered as treatment emergent adverse event (TEAEs).

The overall incidence of TEAEs, including ocular and non-ocular AEs, was similar between treatment groups in the pooled Phase III 52 week Safety Dataset with 76.0% of patients in the 2Q8 group, 79.6% in the 2Q12 group, and 73.6% in the rQ4 group reporting at least 1 TEAE. Within the eye disorder SOC 46.7%, 52.4% and 42.4% in the 2Q8, 2Q12 and rQ4 groups, respectively experienced a TEAE in the study eye. In the Phase 3 Safety Dataset at Week 104, TEAEs were reported for 87.7% of patients in the 2Q8 group, 88.2% in the 2Q12 group, and 85.6% in the rQ4 group. Ocular TEAEs in the study eye were reported for 58.1% of patients in the 2Q8 group, 62.8% of patients in the 2Q12 group, and 54.6% of patients in the rQ4 group.

The below summary table displays ocular and non-ocular TEAEs at Week 104.

Table 30: Treatment-emergent Adverse Events: Overall Summary (Pooled Phase III Safety Population Week 104)

System Organ Class Preferred Term	Abicipar 2Q8 (N = 625) n (%)	Abicipar 2Q12 (N = 626) n (%)	Ranibizumab rQ4 (N = 625) n (%)
TEAEs	548 (87.7)	552 (88.2)	535 (85.6)
Ocular	416 (66.6)	428 (68.4)	388 (62.1)
Non-ocular	418 (66.9)	435 (69.5)	465 (74.4)
Treatment-related TEAEs	237 (37.9)	257 (41.1)	196 (31.4)
Ocular	232 (37.1)	253 (40.4)	190 (30.4)
Study drug related	110 (17.6)	141 (22.5)	40 (6.4)
Study drug administration procedure related	171 (27.4)	184 (29.4)	177 (28.3)
Non-ocular	18 (2.9)	17 (2.7)	17 (2.7)
Serious TEAEs	186 (29.8)	184 (29.4)	173 (27.7)
Deaths	19 (3.0)	13 (2.1)	18 (2.9)
AEs leading to discontinuation	100 (16.0)	98 (15.7)	46 (7.4)

Treatment emergent adverse event (TEAE) is an event that began or worsened on or after the treatment start date. Patients are counted only once within each category.

Ocular adverse events

Pooled Phase III studies, Week 104 safety database

Ocular TEAEs in the study eye were reported for 58.1% (363/625) of patients in the 2Q8 group, 62.8% (393/626) of patients in the 2Q12 group, and 54.6% (341/625) of patients in the rQ4 group.

The commonly reported (at least 1% in any group) individual ocular TEAEs in the study eye that occurred with an incidence rate ≥ 1% higher in the abicipar groups (2Q8 or 2Q12) compared with the rQ4 group included vitreous floaters, intraocular pressure increased, visual acuity reduced, uveitis, cataract, vitreous detachment, vitritis, conjunctivitis, lacrimation increased, retinal hemorrhage,

iridocyclitis, iritis, ocular hypertension, retinal vasculitis, vitreous haemorrhage, photophobia, subretinal fluid, keratic precipitates, retinal artery occlusion, vitreous haze, vitreous opacities and autoimmune uveitis.

The commonly reported individual ocular TEAEs in the study eye that occurred with an incidence rate ≥ 1% higher in the rQ4 group compared with the abicipar groups (2Q8 or 2Q12) included conjunctival haemorrhage, cataract, dry eye hordeolum, cataract nuclear, swelling of eyelid, and metamorphopsia.

Most reported TEAEs were assessed by the investigator as mild to moderate in severity. Ocular TEAEs up to week 104 occurring in at least 1% of patients are summarised in the below table. Through week 104, approximately 8% in each of the two abicipar treatment groups vs. 3% in the ranibizumab group experienced severe ocular TEAEs.

Table 31: Ocular Treatment-emergent Adverse Events Occurring in At Least 1% of Patients in the Study Eye of Any Group: Number (Percent) of Patients in Descending Incidence (Pooled Phase III Safety Dataset, Week 104)

System Organ Class Preferred Term[a]	Abicipar 2Q8 (N = 625) n (%)		Abicipar 2Q12 (N = 626) n (%)		Ranibizumab rQ4 (N = 625) n (%)	
Overall	**363**	**(58.1)**	**393**	**(62.8)**	**341**	**(54.6)**
Eye pain	58	(9.3)	60	(9.6)	58	(9.3)
Vitreous floaters	47	(7.5)	48	(7.7)	32	(5.1)
Conjunctival haemorrhage	46	(7.4)	51	(8.1)	72	(11.5)
Intraocular pressure increased	41	(6.6)	55	(8.8)	31	(5.0)
Visual acuity reduced	38	(6.1)	47	(7.5)	18	(2.9)
Uveitis	35	(5.6)	34	(5.4)	0	
Cataract	33	(5.3)	19	(3.0)	25	(4.0)
Vitreous detachment	30	(4.8)	33	(5.3)	21	(3.4)
Vitritis	27	(4.3)	30	(4.8)	0	
Conjunctivitis	26	(4.2)	25	(4.0)	14	(2.2)
Lacrimation increased	24	(3.8)	8	(1.3)	10	(1.6)
Retinal haemorrhage	23	(3.7)	35	(5.6)	23	(3.7)
Iridocyclitis	23	(3.7)	35	(5.6)	4	(0.6)
Eye irritation	23	(3.7)	25	(4.0)	21	(3.4)
Conjunctival hyperaemia	22	(3.5)	27	(4.3)	25	(4.0)
Iritis	20	(3.2)	11	(1.8)	0	
Dry eye	18	(2.9)	20	(3.2)	26	(4.2)
Vision blurred	17	(2.7)	19	(3.0)	16	(2.6)
Ocular hypertension	17	(2.7)	19	(3.0)	10	(1.6)
Visual impairment	14	(2.2)	18	(2.9)	18	(2.9)
Posterior capsule opacification	14	(2.2)	10	(1.6)	13	(2.1)
Blepharitis	13	(2.1)	15	(2.4)	19	(3.0)
Retinal vasculitis	12	(1.9)	10	(1.6)	0	
Foreign body sensation in eyes	11	(1.8)	14	(2.2)	10	(1.6)
Macular fibrosis	11	(1.8)	6	(1.0)	10	(1.6)
Vitreous haemorrhage	11	(1.8)	5	(0.8)	4	(0.6)
Photophobia	11	(1.8)	1	(0.2)	4	(0.6)
Eye pruritus	10	(1.6)	11	(1.8)	13	(2.1)

System Organ Class Preferred Term[a]	Abicipar 2Q8 (N = 625) n (%)	Abicipar 2Q12 (N = 626) n (%)	Ranibizumab rQ4 (N = 625) n (%)
Subretinal fluid	9 (1.4)	18 (2.9)	7 (1.1)
Keratic precipitates	9 (1.4)	15 (2.4)	0
Retinal oedema	9 (1.4)	12 (1.9)	6 (1.0)
Punctate keratitis	8 (1.3)	10 (1.6)	13 (2.1)
Endophthalmitis	8 (1.3)	8 (1.3)	3 (0.5)
Ocular discomfort	8 (1.3)	7 (1.1)	6 (1.0)
Photopsia	7 (1.1)	8 (1.3)	5 (0.8)
Vitreal cells	7 (1.1)	3 (0.5)	1 (0.2)
Retinal detachment	7 (1.1)	0	4 (0.6)
Corneal abrasion	6 (1.0)	8 (1.3)	11 (1.8)
Cataract cortical	6 (1.0)	8 (1.3)	6 (1.0)
Retinal artery occlusion	6 (1.0)	6 (1.0)	0
Hordeolum	6 (1.0)	0	6 (1.0)
Cataract nuclear	5 (0.8)	13 (2.1)	11 (1.8)
Vitreous haze	5 (0.8)	8 (1.3)	2 (0.3)
Neovascular age-related macular degeneration	5 (0.8)	7 (1.1)	2 (0.3)
Keratitis	5 (0.8)	2 (0.3)	3 (0.5)
Meibomian gland dysfunction	5 (0.8)	1 (0.2)	2 (0.3)
Vitreous opacities	4 (0.6)	10 (1.6)	2 (0.3)
Corneal erosion	4 (0.6)	9 (1.4)	7 (1.1)
Conjunctivitis allergic	4 (0.6)	6 (1.0)	7 (1.1)
Detachment of retinal pigment epithelium	4 (0.6)	6 (1.0)	4 (0.6)
Cataract subcapsular	4 (0.6)	6 (1.0)	4 (0.6)
Corneal oedema	4 (0.6)	6 (1.0)	3 (0.5)
Eye discharge	4 (0.6)	4 (0.6)	5 (0.8)
Retinal tear	4 (0.6)	3 (0.5)	3 (0.5)
Erythema of eyelid	4 (0.6)	1 (0.2)	3 (0.5)
Retinal pigment epithelial tear	3 (0.5)	10 (1.6)	6 (1.0)
Glaucoma	3 (0.5)	9 (1.4)	4 (0.6)
Autoimmune uveitis	3 (0.5)	7 (1.1)	0

Ocular adverse events as marked by investigators. Ocular TEAEs are presented, regardless of relationship to treatment. Preferred terms are sorted by descending incidence in treatment groups from left to right. Within each preferred term, a patient is counted at most once. The incidence of intraocular inflammation was inclusive of all AEs reported following the study treatment, standard care of treatment, and protocol deviations.

[a] MedDRA version 20.1

[b] One patient who was randomized to the rQ4 group in Study 150998-006 received ranibizumab injection on Day 1. At Week 4, this patient received abicipar due to a kit error made by the site. This patient developed iridocyclitis after receiving abicipar; and was analyzed in the rQ4 group

Treatment related ocular adverse events were those that in the investigator's opinion may have been caused by the study treatment (drug or injection procedure) with reasonable possibility. Largely, the pattern of treatment-related TEAEs was similar as for the overall TEAEs, but lower frequencies were reported as summarised in the below table.

Table 32: Treatment-related Ocular Treatment-emergent Adverse Events in At Least 1% of Patients in Any Group: Number (Percent) of Patients in Descending Incidence (Pooled Phase 3 Safety Datasets, Week 52 and Week 104)

	Pooled Phase 3 Safety Dataset, Week 52			Pooled Phase 3 Safety Dataset, Week 104		
Preferred Term[a]	Abicipar 2Q8 (N = 625) n (%)	Abicipar 2Q12 (N = 626) n (%)	Ranibizu-mab rQ4 (N = 625) n (%)	Abicipar 2Q8 (N = 625) n (%)	Abicipar 2Q12 (N = 626) n (%)	Ranibizu-mab rQ4 (N = 625) n (%)
Any Term	203 (32.5)	233 (37.2)	152 (24.3)	230 (36.8)	252 (40.3)	190 (30.4)
Eye pain	38 (6.1)	32 (5.1)	43 (6.9)	44 (7.0)	43 (6.9)	50 (8.0)
Uveitis	32 (5.1)	31 (5.0)	0	33 (5.3)	32 (5.1)	0
Conjunctival haemorrhage	30 (4.8)	35 (5.6)	44 (7.0)	42 (6.7)	44 (7.0)	61 (9.8)
Vitreous floaters	30 (4.8)	33 (5.3)	21 (3.4)	30 (4.8)	35 (5.6)	23 (3.7)
Intraocular pressure increased	25 (4.0)	33 (5.3)	19 (3.0)	30 (4.8)	36 (5.8)	28 (4.5)
Vitritis	25 (4.0)	22 (3.5)	0	25 (4.0)	25 (4.0)	0
Iridocyclitis[b]	20 (3.2)	24 (3.8)	0	21 (3.4)	29 (4.6)	1 (0.2)
Eye irritation	17 (2.7)	18 (2.9)	16 (2.6)	18 (2.9)	21 (3.4)	18 (2.9)
Conjunctival hyperaemia	15 (2.4)	19 (3.0)	16 (2.6)	17 (2.7)	22 (3.5)	19 (3.0)
Iritis	13 (2.1)	5 (0.8)	0	16 (2.6)	7 (1.1)	0
Retinal vasculitis	12 (1.9)	10 (1.6)	0	12 (1.9)	10 (1.6)	0
Lacrimation increased	11 (1.8)	7 (1.1)	3 (0.5)	13 (2.1)	6 (1.0)	3 (0.5)
Visual acuity reduced	8 (1.3)	13 (2.1)	1 (0.2)	9 (1.4)	13 (2.1)	1 (0.2)
Foreign body sensation in eyes	8 (1.3)	11 (1.8)	3 (0.5)	9 (1.4)	14 (2.2)	5 (0.8)
Vision blurred	8 (1.3)	8 (1.3)	8 (1.3)	9 (1.4)	9 (1.4)	9 (1.4)
Ocular discomfort	8 (1.3)	3 (0.5)	4 (0.6)	8 (1.3)	5 (0.8)	4 (0.6)
Endophthalmitis	7 (1.1)	8 (1.3)	1 (0.2)	8 (1.3)[c]	8 (1.3)	3 (0.5)
Vitreous detachment	7 (1.1)	7 (1.1)	6 (1.0)	10 (1.6)	8 (1.3)	6 (1.0)
Keratic precipitates	6 (1.0)	11 (1.8)	0	7 (1.1)	14 (2.2)	0
Ocular hypertension	6 (1.0)	10 (1.6)	1 (0.2)	7 (1.1)	13 (2.1)	3 (0.5)
Eye pruritus	6 (1.0)	8 (1.3)	6 (1.0)	6 (1.0)	8 (1.3)	6 (1.0)
Retinal artery occlusion	6 (1.0)	3 (0.5)	0	6 (1.0)	3 (0.5)	0
Vitreous haze	5 (0.8)	8 (1.3)	0	5 (0.8)	8 (1.3)	0
Corneal abrasion	4 (0.6)	5 (0.8)	4 (0.6)	5 (0.8)	7 (1.1)	8 (1.3)
Corneal erosion	3 (0.5)	6 (1.0)	5 (0.8)	3 (0.5)	6 (1.0)	5 (0.8)
Autoimmune uveitis	3 (0.5)	5 (0.8)	0	3 (0.5)	7 (1.1)	0
Vitreous opacities	2 (0.3)	6 (1.0)	0	2 (0.3)	6 (1.0)	0
Visual impairment	2 (0.3)	5 (0.8)	7 (1.1)	4 (0.6)	7 (1.1)	9 (1.4)
Swelling of eyelid[d]	2 (0.3)	3 (0.5)	5 (0.8)	2 (0.3)	2 (0.3)	6 (1.0)

At week 104, drug related ocular TEAEs were reported for a greater percentage of patients in both abicipar groups (17.6% in the 2Q8 group, 22.5% in the 2Q12 group) compared with 6.4% in the rQ4 group. Such drug-related TEAEs reported for ≥ 1% of patients in any treatment group included eye pain, uveitis, intraocular pressure increased, vitreous floaters, vitritis, iridocyclitis, iritis, retinal vasculitis, visual acuity reduced, keratic precipitates, ocular hypertension, autoimmune uveitis and vitreous opacities.

Administration procedure related TEAEs were reported for a similar percentage of patients across treatment groups: 27.0% in the 2Q8 group, 29.2% in the 2Q12 group, and 28.3% in the rQ4 group. Ocular TEAEs related to administration procedure reported for 1% or more patients in any treatment group included eye pain, conjunctival hemorrhage, uveitis, intraocular pressure increased, vitreous floaters, iridocyclitis, eye irritation, conjunctival hyperemia, lacrimation increased, vitreous detachment, foreign body sensation in eyes, blurred vision, endophthalmitis, ocular discomfort, ocular hypertension, eye pruritis, corneal abrasion, visual impairment, corneal erosion and swelling of eyelid.

Non-Ocular adverse events

Pooled Phase III studies, Week 104 safety database

Up to Week 104, non-ocular TEAEs were reported for a similar percentage of patients across treatment groups: 66.9% in the 2Q8 group, 69.5% in the 2Q12 group, and 74.4% in the rQ4 group.

The percentage of patients with non-ocular treatment related TEAEs was relatively low (2.9% in 2Q8, 2.7% in 2Q12, and 2.7% in rQ4 groups); most were reported by fewer than 2 patients overall, with no differences among treatment groups. The only non-ocular treatment-related TEAE at Week 104 occurring in at least 1% of patients for any group was headache (0.6% for 2Q8, 0.8% for 2Q12, and 1.1% for rQ4 respectively)..

Serious adverse events and deaths

Up to Week 104, SAEs, including fatal SAEs, were reported for 29.8% (125/625) of patients in the 2Q8 group, 29.4% (131/626) in the 2Q12 group, and 27.7% (101/625) in the rQ4 group.

Ocular serious adverse events

Pooled Phase III studies, Week 52 and 104 safety database

Up to Week 104, the percentage of patients who reported serious ocular AEs was similar across treatment groups except for eye disorders: 9.6% of patients in the 2Q8 group, 8.5% in the 2Q12 group, and 2.4% in the rQ4 group. Serious TEAEs reported for at least 1% of patients in any group are summarized in the below table.

Treatment related ocular SAEs were primarily events associated with intraocular inflammation.

Table 33: All Treatment-emergent Ocular Serious Adverse Events (Pooled Phase III Safety Dataset, Week 52 and 104)

	Up to Week 52			Up to Week 104		
Preferred Term	**Abicipar 2Q8**	**Abicipar 2Q12**	**Ranibizumab rQ4**	**Abicipar 2Q8**	**Abicipar 2Q12**	**Ranibizumab rQ4**
	(N = 625)	**(N = 626)**	**(N = 625)**			
Eye disorders	**52 (8.3)**	**46 (7.3)**	**9 (1.4)**	**60 (9.6)**	**53 (8.5)**	**15 (2.4)**
Uveitis	17 (2.7)	14 (2.2)	0	17 (2.7)	14 (2.2)	0
Retinal vasculitis	10 (1.6)	7 (1.1)	0	10 (1.6)	7 (1.1)	0
Vitritis	8 (1.3)	3 (0.5)	0	9 (1.4)	3 (0.5)	0
Retinal haemorrhage	5 (0.8)	1 (0.2)	3 (0.5)	6 (1.0)	1 (0.2)	6 (1.0)
Visual acuity reduced	4 (0.6)	5 (0.8)	0	5 (0.8)	6 (1.0)	0
Retinal detachment	4 (0.6)	0	1 (0.2)	6 (1.0)	0	2 (0.3)
Iridocyclitis	2 (0.3)	5 (0.8)	0	3 (0.5)	5 (0.8)	0
Retinal artery occlusion	2 (0.3)	4 (0.6)	1 (0.2)	2 (0.3)	4 (0.6)	1 (0.2)
Cataract	2 (0.3)	2 (0.3)	1 (0.2)	5 (0.8)	4 (0.6)	1 (0.2)
Autoimmune uveitis	1 (0.2)	2 (0.3)	0	2 (0.3)	2 (0.3)	0
Macular fibrosis	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Ocular hypertension	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Retinal vein occlusion	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Retinal pigment epithelial tear	1 (0.2)	0	2 (0.3)	1 (0.2)	0	2 (0.3)
Anterior chamber inflammation	1 (0.2)	0	0	1 (0.2)	0	0
Dacryostenosis acquired	1 (0.2))	0	0	1 (0.2)	0	0
Diplopia	1 (0.2)	0	0	1 (0.2)	0	0
Eye pain	1 (0.2)	0	0	1 (0.2)	1 (0.2)	0
Glaucoma	1 (0.2)	0	0	1 (0.2)	0	0

Keratitis	1 (0.2)	0	0	1 (0.2)	0	0
Lacrimation increased	1 (0.2)	0	0	1 (0.2)	0	0
Macular hole	1 (0.2)	0	0	1 (0.2)	0	0
Necrotising retinitis	1 (0.2)	0	0	1 (0.2)	0	0
Photopsia	1 (0.2)	0	0	1 (0.2)	0	0
Retinal oedema	1 (0.2)	0	0	1 (0.2)	0	0
Retinal tear	1 (0.2)	0	0	1 (0.2)	0	0
Subretinal fibrosis	1 (0.2)	0	0	1 (0.2)	0	0
Visual impairment	1 (0.2)	0	0	1 (0.2)	0	0
Age-related macular degeneration	0	2 (0.3)	0	0	2 (0.3)	0
Choroidal neovascularisation	0	1 (0.2)	0	0	1 (0.2)	0
Iritis	0	1 (0.2)	0	0	1 (0.2)	0
Macular scar	0	1 (0.2)	0	0	1 (0.2)	0
nAMD	0	1 (0.2)	0	0	1 (0.2)	0
Optic disc haemorrhage	0	1 (0.2)	0	0	1 (0.2)	0
Optic ischaemic neuropathy	0	1 (0.2)	0	0	1 (0.2)	0
Vitreous adhesions	0	1 (0.2)	0	0	1 (0.2)	0
Macular degeneration	0	0	1 (0.2)	0	0	1 (0.2)
Vitreous haemorrhage	0	0	1 (0.2)	0	2 (0.3)	2 (0.3)
Infections and infestations	**17 (2.7)**	**23 (3.7)**	**20 (3.2)**	**7 (1.2)**	**8 (1.3)**	**3 (0.5)**
Endophthalmitis	6 (1.0)	8 (1.3)	1 (0.2)	6 (1.0)	8 (1.3)	3 (0.5)
Retinitis				1 (0.2)	0	0
Investigations /Complications	**4 (0.6)**	**4 (0.6)**	**2 (0.3)**	**3 (0.5)**	**3 (0.5)**	**1 (0.2)**
Intraocular pressure increased	2 (0.3)	3 (0.5)	0	2 (0.3)	3 (0.5)	0
Ocular procedural				1 (0.2)	0	0
Cataract operation				0	0	1 (0.2)
Nervous system disorders - ocular				1 (0.2)	0	0
Optic neuritis				1 (0.2)	0	0

All serious treatment emergent adverse events are represented, regardless of relationship to treatment.

Of the serious ocular TEAEs, the below lead to discontinuation of the study.

Table 34: Treatment-emergent Ocular Serious Adverse Occurring in at least 1% of patients and leading to Study discontinuation (Pooled Phase III Safety Dataset, Week 104)

Preferred Term	**Abicipar 2Q8 (N = 625)**	**Abicipar 2Q12 (N = 626)**	**Ranibizumab rQ4 (N = 625)**
Any term	100 (16.0)	98 (15.7)	46 (7.4)
Eye disorders	7 (10.7)	72 (11.5)	10 (1.6)
Uveitis	17 (2.7)	18 (2.9)	0
Vitritis	15 (2.4)	12 (1.9)	0
Iridocyclitis	(1.3)	12 (1.9)	1 (0.2)
Retinal vasculitis	8 (1.3)	4 (0.6)	0
Retinal haemorrhage	6 (1.0)	5 (0.8)	2 (0.3)
Visual acuity reduced	5 (0.8)	6 (1.0)	1 (0.2)
Ocular hypertension	1 (0.2)	6 (1.0)	0
Infections and infestations	11 (1.8)	11 (1.8)	3 (0.5)
Endophthalmitis	5 (0.8)	4 (0.6)	1 (0.2)
Investigations	3 (0.5)	2 (0.3)	0
Intraocular pressure increased	2 (0.3)	2 (0.3)	0

Preferred Term	Abicipar 2Q8 (N = 625)	Abicipar 2Q12 (N = 626)	Ranibizumab rQ4 (N = 625)
Nervous system disorders	4 (0.6)	3 (0.5)	5 (0.8)
Optic neuritis	2 (0.3)	3 (0.5)	0

Serious treatment-emergent adverse events are represented, regardless of relationship to treatment. Ocular TEAEs include events reported from any eye (study eye or nonstudy eye). Preferred terms are sorted by descending frequencies of treatment groups from left to right. Within each preferred term, a patient is counted at most once. Source: ISS w104, Table 3-5.1

Phase I and II studies

One SAE of non-infectious endophthalmitis the day after receiving a single 2 mg abicipar was reported in Study MP0112 CP01 (Phase I), see further below.

In Study 150998 012 (Phase I), one SAE (abicipar 2 mg) of retinal detachment was reported.

During Stage 2 of Study 150998-001 (Phase II), SAEs overall were reported in 16.4% (11/67) of patients in the 4.2 mg abicipar group, 10.3% (6/58) in the 3 mg abicipar group, and 8.6% (5/58) in the ranibizumab group. The most common SAEs (reported in more than 1 patient) were uveitis and anterior chamber inflammation. No SAEs were reported in any of the treatment groups in Stage 3 of the study.

In Study 150998 002 (Phase II), the SAEs of angle closure glaucoma and cataract were reported for 1 patients in the ranibizumab group.

- Study 1771 201 008 - MAPLE

Study 1771-201-008 is a 28-week multicenter, single arm, open label study to evaluate the safety and treatment effects of abicipar. The study used a modified manufacturing process () where residual E. coli host cell protein (HCP) has been reduced as compared to the Phase 3 studies 150998-005 and 150998-006 (). The study aimed at investigate whether the reduction in HCP would reduce the incidence of IOI. In this study, 5 intravitreal injections of 2 mg abicipar were administered into the study eye at Day 1, and Weeks 4, 8, 16, and 24.

Below is a summary of the TEAEs.

Table 35: TEAEs by Category in Study 1771-201-008 (28 Week;)

TEAE Category	Abicipar 2 mg 2Q8 (N=123)
Any TEAE	73 (59.3)
Ocular, Study Eye	45 (36.6)
Nonocular	55 (44.7)
Treatment-related TEAEs	21 (17.1)
Ocular	20 (16.3)
Study drug related	12 (9.8)
Study administration procedure related	14 (11.4)
Nonocular	1 (0.8)
Serious	16 (13.0)

TEAEs	2 (1.6)
Leading to discontinuation	14 (11.4)

AE = adverse event; N/n = number of patients; TEAE = treatment-emergent adverse event
A TEAE was an event that began or worsened on or after the treatment start date. Patients are counted only once within each category. Within each type of relationship, a patient was counted at most once. All adverse events included all reported events, regardless of relationship to treatment. Treatment-related adverse events included events that could have been caused by the study treatment with reasonable possibility in the investigator's opinion.

The below table summarises the IOI at Week 28.

Table 36: Intraocular Inflammation (IOI) in Study 1771-201-008 (28 Weeks)

MedDRA Preferred Terma	**Study Eye, n (%)**
	Study 1771-201-008, n
	Abicipar 2 mg 2Q8 (N=123)
Any IOI Event (Any Severity)	11 (8.9)
Uveitis	3 (2.4)
Vitritis	2 (1.6)
Iridocyclitis	3 (2.4)
Iritis	3 (2.4)
Keratic precipitates	1 (0.8)
Vitreous haze	1 (0.8)
Any Severe IOI Event	2 (1.6)

The number of patients developing BABs at Week 28 was 25.5% (27/106). The number of patients developing NABs at Week 28 was 14.2% (15/106). The number of patients developing anti-PEGs at Week 28 was 0.9% (1/106). Among patients who reported any TEAE after abicipar treatment (59.3%), the majority were negative for BABs post baseline (63.0% [46/73]).

Ocular adverse events of special interest

For Study 1771 201 008 – MAPLE, see above

Pooled Phase III studies, Week 52 and 104 safety database

- **Intraocular Inflammation**

Events of intraocular inflammation (IOI) in the study eye were reported for a greater percentage of patients in the abicipar groups: Up to week 52 for 15.4% in the 2Q8 group, 15.3% in the 2Q12 group, and 0.3% in the rQ4 group and up to week 104 for 16.2% in the 2Q8 group, 17.6% in the 2Q12 group and 1.3% in the rQ4 group , see below table. Up to week 52, events of IOI in the non-study eye were reported in 0.3% of abicipar-treated patients (2 patients reported uveitis, 2 patients reported anterior chamber cell, and 1 patient reported iridocyclitis).

Of the subjects developing IOI at any time during the 52 weeks, most developed mild (44/192, 23.0%) to moderately (105/192, 54.7%) severe IOIs; however 22.4% (43/192) experienced a severe event of

IOI. Among all study subjects, the IOI was serious in 6.2% and 5.1% of subjects in the 2Q8 and 2Q12 treatment group, respectively, vs. none in the ranibizumab treatment group (see **Table 33**).

Table 37: Special Interest Treatment emergent Adverse Events of Intraocular Inflammation in the Study Eye: Number (Percent) of Patients in Descending Incidence (Pooled Phase III Safety Dataset, Week 52 and Week 104)

	Pooled Phase 3 Safety Dataset, Week 52			Pooled Phase 3 Safety Dataset, Week 104		
MedDRA Preferred Term[a]	Abicipar 2Q8 (N = 625) n (%)	Abicipar 2Q12 (N = 626) n (%)	Ranibizu-mab rQ4 (N = 625) n (%)	Abicipar 2Q8 (N = 625) n (%)	Abicipar 2Q12 (N = 626) n (%)	Ranibizu-mab rQ4 (N = 625) n (%)
Overall[b]	96 (15.4)	96 (15.3)	2 (0.3)	101 (16.2)	110 (17.6)	8 (1.3)
Uveitis	34 (5.4)	33 (5.3)	0	35 (5.6)	34 (5.4)	0
Vitritis	27 (4.3)	27 (4.3)	0	27 (4.3)	30 (4.8)	0
Iridocyclitis[c]	22 (3.5)	29 (4.6)	1 (0.2)	23 (3.7)	35 (5.6)	4 (0.6)
Iritis	16 (2.6)	7 (1.1)	0	20 (3.2)	11 (1.8)	0
Retinal vasculitis	12 (1.9)	10 (1.6)	0	12 (1.9)	10 (1.6)	0
Keratic precipitates[c]	7 (1.1)	13 (2.1)	0	9 (1.4)	15 (2.4)	0
Vitreal cells	6 (1.0)	2 (0.3)	1 (0.2)	7 (1.1)	3 (0.5)	1 (0.2)
Vitreous haze	5 (0.8)	8 (1.3)	0	5 (0.8)	8 (1.3)	2 (0.3)
Autoimmune uveitis	3 (0.5)	5 (0.8)	0	3 (0.5)	7 (1.1)	0
Anterior chamber inflammation	3 (0.5)	2 (0.3)	0	3 (0.5)	3 (0.5)	1 (0.2)
Optic neuritis	3 (0.5)	2 (0.3)	0	3 (0.5)	2 (0.3)	0
Chorioretinitis	2 (0.3)	4 (0.6)	0	3 (0.5)	5 (0.8)	0
Anterior chamber cell	2 (0.3)	1 (0.2)	0	2 (0.3)	1 (0.2)	0
Anterior chamber flare	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Cyclitis	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Retinal perivascular sheathing	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Necrotising retinitis	1 (0.2)	0	0	1 (0.2)	0	0
Retinitis	1 (0.2)	0	0	1 (0.2)	0	0
Keratouveitis	0	1 (0.2)	0	0	1 (0.2)	0
Eye inflammation	0	0	0	1 (0.2)	0	0

All TEAEs of IOI are represented, regardless of relationship to treatment. Preferred terms are sorted by descending incidence for the study eye in treatment groups from left to right. Within each preferred term, a patient is counted at most once. The incidence of IOI was inclusive of all AEs reported following the study treatment, SOC, and protocol deviations.

[a] MedDRA version 20.1 and version 21.1 for Week 104

[b] One additional patient experienced an event of keratic precipitates prior to Week 52; although the event occurred on Day 232, it was not recorded in the Week 52 CSR but recorded in the Week 104 CSR resulting in underreporting of one record of intraocular inflammation in the 2Q8 group for the Week 52 analysis. The number of patients with intraocular inflammation in the 2Q8 group through Week 52 should be 97 (15.5%).

[c] One patient who was randomized to the rQ4 group in Study 150998-006 received ranibizumab injection on Day 1. At Week 4, this patient received abicipar due to a kit error made by the site. This patient developed iridocyclitis after receiving abicipar; and was analysed in the rQ4 group.

Events of severe IOI up to Week 52 and 104 are summarised in the below table.

Table 38: Severe Intraocular Inflammation in the Study Eye: Number (Percent) of Patients in Descending Incidence (Pooled Phase 3 Safety Datasets, Week 52 and Week 104)

	Pooled Phase 3 Safety Dataset, Week 52			Pooled Phase 3 Safety Dataset, Week 104		
MedDRA Preferred Term[a]	Abicipar 2Q8 (N = 625) n (%)	Abicipar 2Q8 (N = 625) n (%)	Abicipar 2Q8 (N = 625) n (%)	Abicipar 2Q8 (N = 625) n (%)	Abicipar 2Q12 (N = 626) n (%)	Ranibizu-mab rQ4 (N = 625) n (%)
Overall	23 (3.7)	20 (3.2)	0	25 (4.0)	20 (3.2)	1 (0.2)
Uveitis	9 (1.4)	8 (1.3)	0	9 (1.4)	8 (1.3)	0
Vitritis	6 (1.0)	3 (0.5)	0	7 (1.1)	3 (0.5)	0
Iridocyclitis[b]	3 (0.5)	3 (0.5)	0	4 (0.6)	3 (0.5)	0
Iritis	0	2 (0.3)	0	0	2 (0.3)	0
Retinal vasculitis	7 (1.1)	7 (1.1)	0	7 (1.1)	7 (1.1)	0
Autoimmune uveitis	0	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Anterior chamber inflammation	1 (0.2)	0	0	1 (0.2)	0	1 (0.2)
Optic neuritis	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Necrotising retinitis	1 (0.2)	0	0	1 (0.2)	0	0

All treatment emergent adverse events (TEAEs) of intraocular inflammation are represented, regardless of relationship to treatment. Preferred terms are sorted by descending incidence for the study eye in treatment groups from left to right. Within each preferred term, a patient is counted at most once. The incidence of intraocular inflammation was inclusive of all AEs reported following the study treatment, standard care of treatment, and protocol deviations.

a MedDRA version 20.1 for Week 52 and version 21.1 for Week 104

b One patient who was randomized to the rQ4 group in Study 150998-006 received ranibizumab injection on Day 1. At Week 4, this patient received abicipar due to a kit error made by the site. This patient developed iridocyclitis after receiving abicipar; and was analysed in the rQ4 group

Onset of IOI

The first onset of IOI occurred after the first IVT dose of abicipar for 32.3% and 37.5% of subjects in the 2Q8 and 2Q12 treatment arms, respectively. Within the first 3 treatments (including the first injection), the majority of patients have had their first onset of an IOI (64.6% and 72.9% for the 2Q8 and 2Q12 treatment arm, respectively). In the 2Q8 treatment arm, 35.5% of patients had their first onset of an IOI within the 4th and 8th injection. The corresponding figure for the 2Q12 regimen was 27.2%. Overall, there was a trend to a larger number of subjects developing IOI within the 1st and 4th injection in the 2Q12 treatment arm compare to the 2Q8 regimen while for patients on the 2Q8 regimen, a higher proportion vs. the 2Q12 group had their first onset of IOI within the 5th to the 8th injection. During the 2nd treatment year, 5, 14 and 6 additional subjects developed IOI in the 2Q8 2Q12 and rQ4 treatment arms, respectively.

Re-challenge

Up to week 52, of the 59.4% of subjects with IOI in each of the abicipar treatment arms that received subsequent abicipar injections, 49.1% and 63.2% in the 2Q8 and 2Q12 treatment arm, respectively experienced a re-challenge of the IOI. The total number of events of IOI events in each of the 96 subjects in the two abicipar treatment arms were 172 (2Q8) and 192 (2Q12) vs. 2 out of 2 in the ranibizumab group.

By Week 104, 57.8% (122/211) of the patients with intraocular inflammation received subsequent abicipar injections. Of the 122 patients who were re-challenged, 60.7% [37/61] of patients in the 2Q8 group and 65.6% [40/61] in the 2Q12 group) experienced a new event of intraocular inflammation

Duration of IOI

Up to week 104, the mean (min-max) duration of the events of IOI was 73.0 (41.5, 2-443) days and 58.7 (29.0, 2-488) days for the 2Q8 and 2Q12 groups, respectively. In the ranibizumab treatment group, the 8 subjects with an IOI mean duration was 42 days (min-max 8, 85).

In the 2Q8 and 2Q12 treatment groups 9.9% and 6.3%; 3.5% and 2.1%; and 2.9% and 1.0% the IOI had a duration of 4-6 months, 0.5-1 year and more than one year, respectively.

Overall, more than half (54.7%, 105/192) of the patients with IOI discontinued from the study by Week 52. For ongoing IOI events at Week 52, 35 ongoing events in 29 patients were reported; of these 29 patients, 11 patients reported their respective IOI events as resolved by Week104. In the remaining 18 patients with ongoing events at Week 104, 13 of those patients were lost to follow up after study discontinuation. Of the remaining 5 patients that were followed for the full duration of the second year of the study, 3 patients reported their respective intraocular events as recovering/resolving at Week 104.

Treatment of IOI – corticosteroid use (CS)

CS was the most common concomitant medication used in the study; at the 104-week cut-off approximately 90% of IOI patients were treated with CS. Among patients who had IOI starting prior to Week 52 who received CS treatment (followed up to Week 104), 57.5% were given topical CS for a mean treatment duration of approximately 3 to 5 months; 20.2% of the patients had intraocular CS injection(s) and 15.5% of the patients received systemic (oral or intravenous) CS treatment for a mean treatment duration of approximately 5 to 6 weeks.

Table 39: Corticosteroid Use for Treating Intraocular Inflammation Safety Population (Pooled Phase III Safety Dataset, Week 52)

CS Use/Route Duration (Days)[a]	**Abicipar 2Q8 (N=97)**	**Abicipar 2Q12 (N=96)**
CS Use Within 52 Weeks, n (%)[b]	86 (88.7)	88 (91.7)
Topical (Ophthalmic) Only, n (%)	57 (58.8)	54 (56.3)
Mean (SD)	79.8 (103.1)	144.6 (149.9)
Median (Min, Max)	43.0 (4, 629)	105.5 (5, 701)
Injectable (Conjunctival, Periocular, Intravitreal), n (%)[c]	19 (19.6)	20 (20.8)
Mean (SD)	36.9 (82.0)	30.0 (52.7)
Median (Min, Max)	1.0 (1, 309)	1.0 (1, 164)
Systemic (Oral or Intravenous), n (%)[c]	12 (12.4)	18 (18.8)
Mean (SD)	40.8 (37.3)	40.0 (38.8)
Median (Min, Max)	42.0 (1, 138)	30.0 (4, 137)

[a] Duration is calculated from the first start date after IOI to the stop date within each route. If the stop date was ongoing, the last visit date including postexit date was imputed.

[b] Analysis includes first IOI events that occurred prior to Week 52, but includes CS use up to Week 104 in order to maximize follow-up data.

[c] Patients may have received injectable and systemic medications, in which case, the patient contributed to both categories. CS = corticosteroid; n = number of patients (numerator); N = number of patients with an IOI event prior to Week 52;

Impact on visual acuity

See also **Table 19 and Table 20** that summarises BCVA outcomes by antibody and IOI status.

In patients with IOI, the number of patients with severe vision loss (≥30 letters) was markedly higher in both abicipar treatment groups compared with the rQ4 group and also a larger proportion of subjects treated with abicipar experienced a significant loss of visual acuity, i.e. ≥15 letters. The majority of IOI patients with ≥ 30 letters vision loss showed at least some visual recovery by Week 52 (36/54) and Week 104 (34/54). Twelve of these patients had no vision loss compared with baseline at both Week 52 and Week 104. The same applies to patients with ≥15 but < 30 letters vision loss, the majority of whom showed improved BCVA at both Week 52 (31/48) and Week 104 (32/48). Of these, 17 at Week 52 and 19 at Week 104 had no vision loss compared with baseline. For patients with ≥ 10 and < 15 letters of vision loss, improved BCVA was observed for 9/17 patients at Week 52 and 10/17 patients at Week 104. There were 9 patients with no vision loss compared with baseline at both Week 52 and Week 104.

Below is a summary of the number of subjects with IOI experiencing vision loss.

Table 40: Visual Acuity: Number (Percent) of Patients with Vision Loss and Intraocular Inflammation. Any Visit and Visit 52 and 104 Compared to Baseline (Pooled Phase III Safety Dataset, Week 52)

		Abicipar 2Q8 (N = 625) n (%)	**Abicipar 2Q12 (N = 626) n (%)**	**Ranibizumab rQ4 (N = 625) n (%)**
Patients with vision loss and IOI [1, 2]	**Week 52**			
Any visit up to week 52	**n [3]**	**623**	**624**	**620**
Any letter loss		84 (13.5)	79 (12.7)	2 (0.3)
≥30 letter loss		23 (3.7)	32 (5.1)	1 (0.2)
≥15 to < 30 letter loss		29 (4.7)	18 (2.9)	0
≥10 to < 15 letter loss		8 (1.3)	8 (1.3)	0
≥5 to <10 letter loss		12 (1.9)	13 (2.1)	1 (0.2)
> 0 to < 5 letter loss		12 (1.9)	8 (1.3)	0
Any visit up to week 104				
Any letter loss		90 (14.4)	93 (14.9)	5 (0.8)
≥30 letter loss		28 (4.5)	39 (6.3)	3 (0.5)
≥15 to < 30 letter loss		30 (4.8)	22 (3.5)	0
≥10 to < 15 letter loss		8 (1.3)	10 (1.6)	0
≥5 to <10 letter loss		13 (2.1)	13 (2.1)	2 (0.3)
> 0 to < 5 letter loss		11 (1.8)	9 (1.4)	0

[1] Source Table 4-14.a, iss-tables-app4, Table 11-7, iss-tables wk104
[2] Analysis is based on observed data. The worst score of each patient during the post-baseline visits, excluding post exit data and post standard of care data, was summarised.
[3] Subjects with analysis values at baseline and the specified visit.

Vision loss not related to IOI was similar between the abicipar and ranibizumab groups.

Other complications secondary to IOI

See also Endophthalmitis and Increased IOP below.

In patients with IOI, the rate of retinal vascular disorders was higher in abicipar-treated patients compared with ranibizumab-treated patients (7.3% and 8.3% in the abicipar 2Q8 and abicipar 2Q12 groups, respectively, vs zero in the ranibizumab rQ4 group). In patients without IOI, the corresponding figures were 0.2%, 0.6% and 0.1% in the respective treatment group. For patients treated with

abicipar, the relative risk of developing a retinal vascular event is 5.5 times higher in IOI patients than in non-IOI patients. Retinal vascular disorders at Week 52 in abicipar-treated patients with IOI are summarised below.

Table 41: TEAEs of Retinal Vascular Disorder In Patients With IOI (Studies 150998-005 and 150998-006 Pooled, 52 Week Cut-off)

Preferred Term	Number (%) of Patients With IOI	
	Abicipar 2Q8 (N=96)	Abicipar 2Q12 (N=96)
Any Term	7 (7.3)	8 (8.3)
Ocular ischaemic syndrome	1 (1.0)	0
Optic disc vascular disorder	0	1 (1.0)
Optic ischaemic neuropathy	0	1 (1.0)
Retinal artery embolism	1 (1.0)	1 (1.0
Retinal artery occlusion	5 (5.2)	5 (5.2)
Retinal ischaemia	1 (1.0)	0
Retinal vein occlusion	0	3 (3.1)

Phase I, II and III studies

The dataset pooling events of IOI from all studies reflected the pattern of IOI observed in the pivotal studies.

- **Endophthalmitis**

In the term endophthalmitis, infectious as well as non-infectious events are included.

Pooled Phase III studies, Week 52 safety database

By Week 52, endophthalmitis was reported for 1.3% (16/1251) of abicipar-treated patients in the two groups and 0.2% (1/625) in the rQ4 group. Culture-proven endophthalmitis was observed in 0.3% (4/1251) of abicipar-treated subjects and in the single ranibizumab-treated subject. All events of endophthalmitis occurred in the study eye and were moderate to severe. During the second year of treatment, there were two new cases of endophthalmitis reported in the ranibizumab group and none in the abicipar groups.

Of the 19 patients with endophthalmitis, 14 had aqueous humour collected for microbial culture; 4 patients in the abicipar groups and 3 in the rQ4 group tested positive for microbial growth.

Table 42: Treatment Emergent Adverse Events of Endophthalmitis by Maximum Severity Number (Percent) of Patient by Preferred Term with Severity Safety Population up to Week 104: Studies 005 and 006 Pooled

Preferred term Severity	**Abicipar 2Q8** **(N = 625)** **n (%)**	**Abicipar 2Q12** **(N = 626)** **n (%)**	**Ranibizumab rQ4** **(N = 625)** **n (%)**
Overall	8 (1.3)	8 (1.3)	3 (0.5)
Moderate	3 (0.5)	0	0
Severe	5 (0.8)	8 (1.3)	6 (0.5)
Endophthalmitis	7 (1.1)	8 (1.3)	3 (0.5)
Moderate	2 (0.3)	0	0
Severe	5 (0.8)	8 (1.3)	3 (0.5)
Non-infectious endophthalmitis	1 (0.2)	0	0
Moderate	1 (0.2)	0	0
Severe	0	0	0

All TEAEs of endophthalmitis are represented by maximum severity.

The clinical course for the non-culture-proven events of endophthalmitis were similar as for the other events of IOI. There are also a number of re-challenges (new event of endophthalmitis or other IOI) when treatment with abicipar was re-initiated. Accounting these events to IOI, the overall incidence of IOI would be close to 18% (17.8%, 223/1251) in the combined abicipar treatment groups and 10 additional events, i.e. 4.4% (55/1251) of IOI would be regarded severe events of IOI.

According to the narratives, at the time of the Week 52 database lock 5/17 events of endophthalmitis had resolved without sequelae, 7/17 were ongoing of had resolved with more or less sequelae and for the remaining subjects the outcome is not clear. At Week 104, 10/12 non-culture-proven events of endophthalmitis had resolved without sequelae or the outcome is not clear from the narratives.

Phase I and II studies

One subjects developed endophthalmitis in Study MP0112 CP01 that was terminated early due to this event. In Stage 2 of Study 150998-001, 1 subjects experienced endophthalmitis. Both events resolved without sequelae.

- **Increased intraocular pressure (IOP)**

Pooled Phase III studies, Week 52 and Week 104 safety database

As expected, by Week 52, a large proportion (>50%) of patients experienced post-injection increases in IOP. Otherwise, increases in IOP were generally infrequent, but more frequent in the abicipar treatment groups (≥10 mmHg increase at any visit: 6.3% and 8.5% in the 2Q8 and 2Q12 group, respectively) than the rQ4 groups (1.8%). In patients with an IOI, the majority of abicipar-treated subjects reported an increased IOP of ≥10 mmHg (74% and 77% in the 2Q8 and 2Q12 group, respectively) vs. none in the ranibizumab groups. In 1.4%, 4.5% and 0% of the 2Q8, 2Q12 and ranibizumab treatment groups, an IOP of ≥35 mmHg was reported at any time.

Up to Week 104, the total rate of increased IOP (including also different terms containing glaucoma) was higher in abicipar-treated patients with IOI (25.8% and 37.5% in the 2Q8 and 2Q12 groups, respectively) compared with abicipar-treated patients without IOI (4.5% and 6.2% in the 2Q8 and 2Q12 groups, respectively). The rate of increased IOP in ranibizumab-treated patients without IOI (5.3%) was similar to abicipar-treated patients without IOI; there were no TEAEs of increased IOP in ranibizumab-treated patients with IOI.

The majority of patients in all groups (i.e. all treatment groups, patients with and without IOI) received IOP-lowering medication treatment. The proportion of patients with IOP using IOP-lowering medication within 52 weeks was 92.0% and 92.7% in the 2Q8 and 2Q12 groups, respectively compared with abicipar-treated patients without IOI (70.8% and 57.6% in the 2Q8 and 2Q12 groups, respectively). Following IOP-lowering medication, the majority increases in IOP were recovered or resolved at the 104-week cut-off, irrespective of whether patients had IOI. The proportions of patients not recovered or recovering were similar between the 2 groups (16.0% and 8.3% in the 2Q8 and 2Q12 groups with IOI, respectively vs 12.5% and 15.2% in the 2Q8 and 2Q12 groups without IOI, respectively); the proportion of patients with a TEAE outcome of not recovered or recovering was also similar in the ranibizumab group (18.2%).

For patients who reported a TEAE of increased IOP, the overall rate of vision loss was higher in those who also had IOI compared with those who did not have IOI (64.0% and 55.6% vs 29.2% and 24.2% in the 2Q8 and 2Q12 abicipar treatment groups). This difference was driven by the incidence a ≥ 30 letters decrease from baseline (28.0% and 13.9% vs 4.2% and 3.0% in the 2Q8 and 2Q12 abicipar treatment groups) and ≥ 5 and < 10 letters decrease from baseline (12.0% and 13.9% vs 0% and 3.0% in the 2Q8 and 2Q12 abicipar treatment groups), both of which were higher in patients who had IOI compared with those who did not have IOI.

Phase I and II studies

Overall, no safety signals related to IOP were noted during the Phase 2 studies. In Study 150998 001, one patient had IOP scores of ≥ 25 mm Hg, or ≥ 10 mm Hg increases from baseline at any given visit.

- **Ocular adverse Events Potentially Related to Systemic VEGF Inhibition**

Ocular adverse events potentially related to VEGF inhibition (or to IOI) included ocular vascular events, such as retinal artery and vein occlusion, which occurred in close to 1% of the abicipar-treated population (please refer to section of ocular adverse event above).

Non-ocular serious adverse events

Pooled Phase III studies, Week 52 and Week 104 safety database

In the pooled Phase III Safety Dataset, Week 52, SAEs, including fatal SAEs, were reported for 20.0% (125/625) of patients in the 2Q8 group, 20.9% (131/626) in the 2Q12 group, and 16.2% (101/625) in the rQ4 group and were primarily within the SOC of eye disorders (8.3%, 7.3% and 1.4% in the respective treatment groups).

Except for Eye disorders, the majority of serious non-ocular TEAEs (including deaths) in the pooled Phase III studies were reported for organ classes Cardiac disorders (2-3% year 1, 4-6% year 2), Gastrointestinal disorders (1%), Infections and infestations (3% year 1, 6% year 2), Injury, poisoning and procedural complications (1-2% year 1, 4-6% year 2), Musculoskeletal and connective tissue disorders (1%), Neoplasms benign, malignant (2-3% year 1, 4-6% year 2), Nervous system disorders (1-2% year 1, 2-4% year 2), Respiratory, thoracic and mediastinal disorders (1-2% year 1, 2-4% year 2) and Vascular disorders (1%). There were no obvious difference between treatment arms and most were considered unrelated to treatment, see Non-Ocular adverse events.

Phase I and II studies

In Study 150998 012 (Phase I), one SAE of atrioventricular block (abicipar 2 mg) second degree was reported. In Study 150998-001, treatment emergent SAEs of pneumonia and renal failure acute were reported for 1 patient treated with abicipar during Stage 1. In Study 150998 002, there were 3 SAEs reported for 1 patient in the ranibizumab group. These included chronic respiratory failure, pneumonia,

and embolic stroke. In Study 150998 003, there were 3 SAEs reported for 2 patients (1 patient in the abicipar 2 mg group and 1 patient in the abicipar 1 mg group). These included SAEs of pneumonia and Escherichia bacteremia in 1 patient and basal cell carcinoma in the other.

Non-ocular adverse events of special interest

- **Adverse Events Potentially Related to Systemic VEGF Inhibition**

Pooled Phase III studies, Week 52 and Week 104 safety database

Up to Week 52, ATEs based on the Antiplatelet Trialist's Collaboration (APTC) definition were reported for 1.3% (8/625) of patients in the 2Q8 group, 1.8% (11/626) in the 2Q12 group, and 1.6% (10/625) in the rQ4 group. These and other events potentially related to systemic VEGF inhibition that were considered TEAEs of special interest were reported in a similar percentage of patients in each treatment group, including 8.5% (53/625) of patients in the 2Q8 group, 8.1% (51/626) in the 2Q12 group, and 9.8% (61/625) in the rQ4 group. There were no patterns or imbalances noted among treatment groups based on either summary. The most common TEAE potentially related to systemic VEGF inhibition in all treatment groups was hypertension reported for 5.8% (36/625) of patients in the 2Q8 group, 5.8% (36/626) in the 2Q12 group, and 5.4% (34/625) in the rQ4 group.

Anti-VEGF was administered in the non-study eye to 14-18% of patients in the three treatment groups. Within this subset of patients, TEAEs potentially related to systemic VEGF inhibition medication were reported for 8.1% (9/111) of patients in the 2Q8 group, 10.1% (9/89) in the 2Q12 group, and 13.5% (14/104) of patients in the rQ4 group.

Approximately 66% of patients who reported ATEs or other events potentially related to systemic VEGF inhibition had a medical history of hypertension.

By Week 104, the number of patients with ATEs remained low; ATEs were reported for 1.8%, of patients in the 2Q8 group, 2.4% of patients in the 2Q12 group, and 3.0% of patients in the rQ4 group.

These and other events potentially related to systemic VEGF inhibition were reported in a similar percentage of patients in each treatment group: 12.8%, 13.4% and 16.6% in the 2Q8, 2Q12 and rQ4 group, respectively. The most common TEAE potentially related to systemic VEGF inhibition was hypertension.

At Week 104, VEGF inhibition medication was administered in the non-study eye to 19.7%, 18.7% and 20.2% in the respective treatment groups. Within the subset of bilaterally treated patients TEAEs potentially related to systemic VEGF inhibition medication were reported for 12.2%, 17.9% and 19.8% in the respective groups.

Phase I and II studies

Few TEAEs potentially related to systemic VEGF inhibition were reported, most commonly, hypertension.

Deaths

Pooled Phase III studies, Week 104 safety database

In the Pooled Phase III Safety Dataset, Week 104, deaths were reported for 50 patients: 3.0% (19/625) of patients in the 2Q8 group, 2.1% (13/626) in the 2Q12 group, and 2.9% (18/625) in the rQ4 group. No deaths were deemed by the investigator to be related to treatment and were not different from what could be expected in the study population. SAEs from the Neoplasm benign, malignant and unspecified SOC caused the most deaths (13 patients) followed by the SOCs of Cardiac

disorder (11 patients), Infections and infestations (9 patients), and Respiratory, thoracic and mediastinal disorder (11 patients). There were no patterns or imbalances noted among treatment groups.

Phase I and II studies

There were no deaths in Studies MP0112-CP01 or in Studies 150998 001, 150998 002, and 150998 003. There were 2 deaths in Study 1771-201-008.

Laboratory findings

For Studies 150998 005 and 150998 006, there were minimal changes in all laboratory test results between baseline and post baseline laboratory values. The number of patients with abnormal lab test results deemed Potentially Clinically Significant (PCS), included erythrocytes, haematocrit, haemoglobin, blood urea nitrogen, creatinine, and urate. Shift from Baseline by Visit indicate that baseline values defined as LOW or HIGH tend either to normalize or remain abnormal in the same direction as at baseline. NORMAL baseline values predominantly tend to remain normal with only small frequencies of change to either LOW or HIGH with not clear trend. Most abnormal values post-baseline are associated with abnormal values in the same direction at baseline. Overall, the number of patients with potentially clinically significant laboratory values occurred in few patients and were also similar among the 3 treatment groups; no clinically meaningful trends or patterns were observed.

Also in Phase I and II, changes between screening and post dose for all laboratory test results were minimal and no clinically meaningful trends or patterns were observed.

Except for systolic blood pressure increases of ≥20 mmHg and/or blood pressures ≥160 mmHg in 12-18% of subjects across treatment arms, overall, there were no clinically meaningful mean changes from baseline for systolic or diastolic blood pressure or pulse rate in any treatment group in any of the studies. It is noted however that in Phase III, blood pressure minimum and maximum ranges suggest that some patients were experiencing clinical significant changes with min/max ranges of ±50 mmHg and ±30 mmHg for systolic and diastolic blood pressure, respectively.

Safety in special populations

nAMD is a disease in an elderly to very elderly population and the disease does not occur in the paediatric population. Also the vast majority of female patients are post-menopausal and non-clinical studies did not produce embryofoetal structural abnormalities. Nevertheless, the potential risk of use of abicipar in pregnancy is unknown and due to the anti-VEGF mechanism of action, abicipar must be regarded as potentially teratogenic and embryo/foetotoxic.

The overall incidence of all TEAEs was similar across the following sub-groups: age group (= 65 years, > 65 to = 75 years, > 75 years), sex (male or female), race (Caucasian or non-Caucasian), and disease severity (predominantly classic, minimally classic or occult). With respect to IOI, female patients reported higher intraocular inflammation incidence (20.1% in the 2Q8 group and 20.3% in the 2Q12 group). Subgroups of renal or hepatic impairment have not been investigated.

The standard table on systemic events in all age groups is not relevant for abicipar where the systemic exposure is very low and non-ocular AEs rarely expected to be treatment-related.

Immunological events

The majority of patients with IOI had positive BAB responses post baseline. See further, Section 3.3.2 Pharmacodynamics and Ocular adverse events of special interest above.

Safety related to drug-drug interactions and other interactions

No dedicated drug-drug interaction studies have been conducted with abicipar, see also 3.3.1 Pharmacokinetics, Interactions above. Overall, the interaction potential of abicipar pegol is considered low.

Discontinuation due to AES

In the Pooled Phase 3 Safety Dataset, Week 52, the percentage of patients who discontinued due to AEs before Week 52 was higher in the abicipar groups (10.8% [65/625] of patients in the 2Q8 group, 11.3% [71/626] in the 2Q12 group) than in the rQ4 group (3.5% [22/625]). Most of the AEs leading to discontinuation were ocular in nature, and involved IOI.

By week 104, 15.9% (2Q8) to 15.7%% (2Q12) of the patients in the abicipar groups had discontinued due to AEs vs. 7.3% of the patients in the ranibizumab groups. See **Figure 5** and **Figure 6** above.

Post marketing experience

Not applicable.

3.3.9. Discussion on clinical safety

The safety of abicipar has been evaluated in a total of 9 studies in patients with nAMD that altogether included 1684 subjects treated with at least 1 dose of abicipar. Around 1000 subjects have been treated for at least 12 months in the Phase III studies. Of these, 890 patients were treated for 104 weeks.

The pivotal Phase III studies that include 1251 treated subjects form the main basis for assessment of the safety profile of abicipar. With the exception of Study 1771-201-008 (MAPLE) that provides some additional safety data, the Phase I and II studies adds very limited safety information of importance. Unless indicated, the below discussion refers to the safety data from the pooled Phase III studies.

The percentage of patients who received the maximum number of active injections up to Week 104 was 58.6% in the 2Q8 group, 60.2% in the 2Q12 group, and 58.2% in the rQ4 group.

The overall incidence of AEs was similar between treatment with 76.0% and 87.7% (Week 52 resp Week 104) of patients in the 2Q8 group, 79.6% and 88.2% (Week 52 resp Week 104) in the 2Q12 group, and 73.6% and 85.6% (Week 52 resp Week 104) in the rQ4 group reporting at least 1 AE. For ocular AEs up to Week 52, 46.7%, 52.4% and 42.4% in the 2Q8, 2Q12 and rQ4 groups, respectively, experienced an AE in the study eye. The rates for ocular AEs up to Week 104 were 58.1% of patients in the 2Q8 group, 62.8% of patients in the 2Q12 group, and 54.6% of patients in the rQ4 group.

In the respective 2Q8, 2Q12 and rQ4 treatment arms, 16.5%, 17.7% and 6.7% of patients discontinued the studies before Week 52, the majority due to ocular AEs. Approximately 12% of subjects in the two abicipar-treatment arms vs. 4% in the ranibizumab treatment arms discontinued the studies due to a serious AE, for abicipar, the majority being IOI. Across the studies, approximately 71% of patients in the abicipar treatment arms completed Week 104 weeks, while 83% of subjects completed the first 2nd treatment year in the ranibizumab treatment arms.

Ocular AEs

The most obvious difference in AE profile between abicipar and ranibizumab is the higher incidence of intraocular inflammation (IOI, e.g. uveitis, vitritis, iridocyclitis, iritis, vision blurred, retinal vasculitis,

keratic precipitates, endophthalmitis, vitreal cells and vitreous haze) or indications of IOI (e.g. vitreous floaters) in the abicipar treatment arms (15%) compared to ranibizumab (0.3%).

The IOIs are to a large extent drug-related, might be serious and are potentially sight-threatening events and remains of major concern as discussed further below. (**Part of MO)**

Although there was no major difference between the 2Q8 and 2Q12 treatment arms of abicipar, there was a trend towards a more frequently reported AEs related to IOI in the 2Q12 treatment group (vitreous haze, vitreous opacities and autoimmune uveitis) and 5 subjects in the 2Q8 treatment arm vs. 14 subjects in the 2Q12 treatment arm developed IOI during the 2nd treatment year. Further, mean duration of use of corticosteroid use was 80 and 145 days in the 2Q8 and 2Q12 treatment groups, respectively. The extent of IOP-lowering medication was also higher in the 2Q12 treatment group (27% vs. 15% for 2Q8). It appears thus that the IOI was more frequent and more difficult to manage in the 2Q12 treatment group. This is however not consistent with the reporting of severe IOI. In addition, by Week 52, for discontinued patients, a ≥ 30 letter vision loss was reported for 5.8% and 18.9% patients in the abicipar 2Q8 and 2Q12 groups, respectively. By Week 104 a ≥ 30 letter loss was reported for 9.5% vs. 16.5% of discontinued patients in the abicipar 2Q8 and 2Q12 groups, respectively. These trends of a potentially inferior safety profile of the 2Q12 regimen needs to be further elaborated on **(OC)**. Together with the not fully non-convincing efficacy of the 2Q12 regimen, this adds negatively to the B/R balance.

Up to Week 52, serious ocular AEs were reported for 8.3% of patients in the 2Q8 group, 7.3% in the 2Q12 group, and 1.4% in the rQ4 group. At Week 104, the rates in the corresponding dose groups were 9.6%, 8.5% and 2.4%. Of the events of IOI, 3.4% (3.6% at Week 104) abicipar-treated patients (vs. 0 for ranibizumab) were regarded severe by the applicant. This is also the figure presented in the SmPC, section 4.8. The applicant has clarified the distinction between severe and serious events of IOI where serious AEs for example consider those being deemed important based on medical judgment. However, among the serious AEs reported up to Week 52, there were a total of 5.7% (71/1251) of abicipar-treated patients that experienced a serious IOI. However, it would be reasonable to present the serious AEs i.e. including those deemed important based on medical judgement and could lead to e.g. significant disability. The use of both severe and serious AEs in section 4.8 is further considered confusing. It would finally be consistent with the SmPCs for Lucentis, Eylea and Beovu (brolicuzumab) where serious AEs are reported in section 4.8. Thus, the applicant is requested to report serious instead of severe AEs in section 4.8. (**SmPC**).

The outcomes of patients that discontinued treatment/study due to ocular AEs and serious AEs (including IOI) in the abicipar treatment arms is not fully clear. Unfortunately, the follow up of patients discontinuing treatment is very limited. At the week 52 cut-off, there were 12, 22, and 1 ongoing events of IOI in the 2Q8, 2Q12 and rQ4 treatment groups, respectively. Of these, only 3 and 6 in the 2Q8 and 2Q12 treatment groups had resolved without sequelae, while the remaining subjects recovered with sequelae, were still ongoing or were lost to follow-up (discontinued) at week 104. At week 104, 18 subjects (8, 9, 1 in the 2Q8, 2Q12 and rQ4 treatment arms, respectively) still had an ongoing event of IOI. However, 13/18 of these subjects were not followed and their outcome is unknown. This adds uncertainty of the safety profile of abicipar.

Further, although not entirely clear, it appears that overall, 54 subjects had a ≥30 letter IOI-related vision loss compared to baseline prior to week 52. At week 52, 18 of these subjects still had a loss of ≥30 letters in BCVA while at week 104, 20 such subjects presented with this severe vision loss. Of the 48 subjects with a significant (≥15 to <30 letter) vision loss before week 52, 17 and 16 subjects still had a ≥15 letter loss at week 52 and 104, respectively. Taken together, there is some uncertainty on the figures, but it appears that around 1/3 of patients with a severe or significant vision loss did not improve over 104 weeks. The applicant is asked to explain how persistent loss of BCVA is defined and

how many subjects with IOI that had persistent loss of ≥10, ≥15 and ≥30 letters at week 52 and week 104. **(OC)** The applicant is also requested to present the number and proportions of patients with no, ≥5-10, ≥10-15, ≥15-30 and ≥30 letter loss together with discontinuation rates among these (**OC**).

IOIs occurred after the first dose of abicipar for approximately one third of patients, within the first 3 treatment cycles for more than half of patients, a significant number of patients developed IOIs during the latter part of the studies. During the 2nd treatment year, 5, 14 and 6 additional subjects developed IOI in the 2Q8 2Q12 and rQ4 treatment arms, respectively. Consequently, it appears not possible to predict whether an initially and successfully treated patient will develop an IOI at a later stage. Monitoring of patients between injections to allow prompt management of an IOI is not considered an option that is realistic in clinical practice especially since it appears that an IOI can appear at any time during treatment. It is also not realistic to conduct repeated testing to identify whether a patient develops ADAs, and thereby having an increased risk for an IOI (see further below), during treatment. The applicant was therefore requested to elaborate on other measures to allow early identification and prompt management of patients that develop an IOI.

The proposed risk mitigations measures including a warning (SmPC 4.4) for re-challenge with abicipar after prior IOI, prompt treatment of retinal vasculitis with ocular or oral corticosteroids, monitoring of IOP and educational materials are all supported in principle; except continued treatment with other anti-VEGF of progressing CNV is not considered a viable measure because of contraindication in severe active IOI. However, the patient's risk mitigation proposal for development of IOI needs to be expanded to increase the chance to detect any signs of IOI (**OC**) With risk mitigation, the applicant estimates that only 0.8%-1.5% of patients would experience IOI-related ≥30 letter vision loss compared to 0.2% for ranibizumab. However, while 0.8% is based on rather speculative assumptions, despite the proposed risk mitigation measures, this still leaves us with what must be considered a "best-case" scenario of 1.5% incremental risk of severe persistent visual loss after one single abicipar-injection:

This figure is likely underestimated; however, there is large uncertainty to what extent and of concern that it might be largely underestimated. First, rather than 15% of subjects experiencing an IOI, a more accurate figure is likely close to 18% (4.4% severe) in view of the majority of events reported as endophthalmitis appears clinically more consistent with severe IOI **(SmPC)**. Obviously, the IOI as such needs to be managed as the IOI as such increases the risk of severe retinal vascular complications and increased IOP. However, it is difficult to believe that patients will be as closely monitored and promptly managed in clinical practice as in a setting of a clinical trial. The effect of the proposed risk mitigation measures is thus difficult to estimate. This is of even more concern with regard to the IOI that were reported after longer-term treatment with abicipar where diligence is expected to be reduced. Recovery of the severe vision loss (as well as the IOI) is in addition unclear due to the very limited follow-up. Together, this translates into a major concern that these are not sufficient to reduce the risk of severe vision loss to an acceptable extent. The risk of persistent (to be defined) and clinically significant loss of ≥15 letters or even ≥10 letters of BCVA that might be of high importance for the individual patient that might have expectations of a gain in BCVA after anti-VEGF treatment has further not been addressed **(OC)**.

In addition, of the close to 18% of patients that reported IOI during the 1st treatment year, 90%, i.e. around 15% of all abicipar-treated patients, were treated with CS. Even without any re-challenge in subjects experiencing an IOI after their first injection (35% of all patients with IOI), at least 5% of all abicipar-treated subjects are at risk for developing an IOI that requires treatment with CS after their first injection. This translates into a need for close monitoring, a risk of CS-induced AEs (e.g. increased IOP, cataract, systemic AEs) and a need for additional treatment that in turn increases the risk of additional AEs. Besides that this counteracts the benefit of a reduced treatment and monitoring interval compared to other intravitreal anti-VEGFs that has comparable efficacy, in subjects with

severe and active IOI, treatment with the approved anti-VEGFs is contraindicated. This means that in addition to the IOI-induced risk of persistent vision loss and thus a loss of chance, the underlying and irreversible progressive CNV can not be treated. This is consequently another reason for the insufficiency of the proposed risk mitigation measures and another reason for a loss of chance.

The applicant has evaluated 17 baseline characteristics in an attempt to identify a patient population not at risk of developing IOI. The analyses demonstrate that the risk for any IOI was higher in women (OR 2.55), in non-Asian subjects (OR 1.94) and in patients without intraretinal fluid (OR 1.55). The outcome that some influential variables are found is not surprising due to the multiple analyses conducted and overall, it is agreed that this does not provide any useful information.

However, the risk of a severe IOI as well as a severe vision loss (≥30 letters) was markedly higher in women (OR 8.08; 95% CI: 2.86, 22.87). A similar gender difference was also reflected in the ORs for inflammation resulting in ≥ 15 to < 30 letter decrease in BCVA (OR = 3.02; 95% CI: 1.49, 6.1) and ≥ 30 letter loss in BCVA during the first treatment year (OR = 4.18; 95% CI: 1.42, 12.30), see also OC 162). The applicant speculates that the risk of severe IOI might be due to a higher risk of urinary tract infection in women with a higher prevalence of antibodies to E coli remnants in the drug product and with that, a risk of an early fulminant inflammatory response to abicipar. The applicant recognises that the hypothesis is not supported by data and the applicant concludes that it is not possible to identify a patient population that is not at risk of developing IOI. Indeed, this remains speculative.

Still, the increased risk for severe IOI and ≥15 and ≥30 letter vision loss appears remarkable considering the consistently high ORs (8.1, 3.0 and 4.2, respectively) and consequently less likely to be a chance finding. Females also had a higher risk of developing BABs, see MO121. Even if striking and not understood, this raises an additional concern that needs to be addressed and elaborated on in the attempts to minimise the risks of IOI and severe vision loss. **(OC)**

The applicant presents the final data from the 28-week open-label Study 1771-201-008 (MAPLE) where a refined drug process reducing host cell protein (HCP) was evaluated. Also in MAPLE a high proportion of subjects (8.9%, 11/123) developed IOI and the study was not controlled which makes the high figure of concern (note 0.2% IOI for ranibizumab in Phase 3). Further, the study was limited to 5 treatments and even if the majority of IOI appeared after the first 5 injections in the pivotal studies, the rate of IOI in MAPLE might be underestimated. Taken together, the study 008 does not change the safety profile markedly, although it is agreed that the study 008 does not aggravate the safety profile either. However, even if the applicant ascertains that different manufacturing processes will be used in the future, it remains to be justified that these will markedly change the clinical safety profile of abicipar. However, since the applicant aims for an initial MAA with the drug substance used in Phase III, this is irrelevant.

Subgroup analyses by IOI demonstrated that the overall visual acuity outcomes are inferior in ADA positive subjects with IOI and the applicant was requested to further explore the relationship between ADAs and IOI as well as other potential underlying reasons for the development of IOI. While a causal relationship with ADAs that were detected in 80-90% of abicipar-treated subjects could not be established, it can also not be excluded. It is evident that subjects being BAB positive has an approximately 10-fold higher risk of developing an IOI; however, it is agreed that there are likely additional underlying factors contributing to the IOI since some ADA negative subjects developed IOI and there is no clear temporal relationship between ADA status and IOI onset. Besides residual HCP, the applicant hypothesises that multiple immune pathways might be involved in the inflammatory reactions, and that a CD4 TH1-mediated reaction might be a reason behind the events of retinal vasculitis. An ex vivo T-cell proliferation assay showed that abicipar pegol is low to moderately immunogenic whereas ranibizumab is not very immunogenic. As T helper cells are MHC restricted differences of the patients under study in the MHCII variants could present another risk factor (allelic

frequencies of MHCII proteins differ among subpopulations) contributing to the individual propensity to amount an immune response and finally to the overall IOI rate. The applicant is therefore asked to elaborate on these limitations of ex vivo T cell proliferation assays and – ideally – provide computational analysis data and verify if any risk minimization measured can be deduced from these results. (**OC**)

It remains that to be demonstrated that the safety profile of abicipar is acceptable and clinically manageable. Convincing clinical data that this has been achieved and additional measures to manage this incremental risk needs to be provided. (**MO**). In addition, a number of changes to the SmPC, e.g. that abicipar should be contraindicated in patients with active as well as previous IOI following treatment with abicipar, are requested (**SmPC**).

Non-ocular AEs

For non-ocular TEAEs, there were no major differences between treatment groups and the safety profile is in line with that expected in an elderly to very elderly patient population with associated co-morbidities. Through Week 52, SAEs, including fatal SAEs, were reported for 20.0% (125/625) of patients in the 2Q8 group, 20.9% (131/626) in the 2Q12 group, and 16.2% (101/625) in the rQ4 group and were primarily within the SOC of eye disorders (8.3%, 7.3% and 1.4% in the respective treatment groups). No new concerns are identified. Approximately 5% of abicipar-treated patients received anti-VEGF treatment in the non-study eye. The data indicate no increased risk for systemic AEs; however, since data are limited and there is no experience with bilateral treatment with abicipar, further rephrasing is needed in section 4.4 of the SmPC. **(SmPC)**

The results of the integrated analyses of AEs in all studies by duration of exposure are largely consistent with the Pooled Phase III Safety Dataset, Week 52.

Deaths: Up to week 104, in the Phase III studies, deaths were reported for 50 patients: 3.0% (19/625) in the 2Q8, 2.1% (13/626) in the 2Q12, and 2.9% (18/625) in the rQ4 groups. More subjects treated with ranibizumab died due to cardiac disorders. However, the narratives confirm the applicant's conclusion that the deaths appears consistent with the expected common underlying diseases in the study patient population since all subjects had relevant co-morbidities. There were no deaths in the Phase I and in the dose-response Phase II studies. It is noted that there were 2 deaths (in Study 1771-2001-008 (MAPLE).

Additional expert consultation

Not applicable

Assessment of paediatric data on clinical safety

Not applicable

Additional safety data needed in the context of a <conditional> MA <under exceptional circumstances

Not applicable

3.3.10. Conclusions on clinical safety

The applicant has not convincingly demonstrated that the safety profile of abicipar is acceptable and clinically manageable. The applicant proposes a marketing of the abicipar drug substance used in the Phase III trials. A safety profile of a drug that induces inflammation in at least 15% of subjects and

serious such in close to 6% of the overall abicipar-treated population remains of major concern. In subsets of the patients, the inflammation was serious, resulted in severe loss of vision and was persistent. The major concerns are raised for both regimens; however, a number of the findings disfavour the 2Q12 regimen also from a safety view.

The proposed risk mitigations measures i.e. a warning (SmPC 4.4) for re-challenge with abicipar after prior IOI, continued treatment with other anti-VEGF of progressing CNV, prompt treatment of retinal vasculitis with ocular or oral corticosteroids, monitoring of IOP and educational materials are in principle supported. However, even with these, a "best-case" but likely underestimated scenario would put 1.5% of patients at risk of severe persistent visual loss after one single injection of abicipar and thus a loss of chance. In addition, the IOI as such increases the risk for retinal vascular events and handling of the IOI needs close monitoring, use of corticosteroids (frequently long-term) with a risk of additional steroid-induced AEs that in turn needs to be monitored and treated. Both from the perspective of the patient and the health care system, this counteracts the benefit of a reduced treatment and monitoring interval compared to other intravitreal anti-VEGFs that has comparable efficacy. Finally, in subjects with severe and active IOI, treatment with the approved anti-VEGFs is contraindicated. This means that the underlying and irreversible progressive CNV cannot be treated and as a risk mitigation measure, the impact is questioned. Further, this leads another reason for a loss of chance.

The final data from Study 1771-201-008 (MAPLE) evaluating a refined drug process does not change the safety profile of abicipar markedly. However, even if the applicant ascertains that different manufacturing processes will be used in the future, it remains to be justified that these will markedly change the clinical safety profile of abicipar. However, since the applicant aims for an initial MAA with the drug substance used in Phase III, this is irrelevant.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 43

Summary of safety concerns	
Important identified risks	Endophthalmitis Severe intraocular inflammation Increased intraocular pressure Retinal detachment and retinal tear
Important potential risks	Arterial thromboembolic events Immunogenicity
Missing information	Long term safety beyond 2 years

3.4.2. Discussion on safety specification

The applicant has sufficiently addressed Part II Module SI to Module SV, this is endorsed.

The applicant has included "arterial thromboembolic events" as a potential risk, however as the potential risk for systemic effects of free VEGF is considered minimal the applicant is requested to delete "arterial thromboembolic events" as an important potential risk in the RMP.

3.4.3. Conclusions on the safety specification

Having considered the responses on day 120 the applicant is requested to delete "arterial thromboembolic events" as an important potential risk in the RMP, as the potential risk for systemic effects of free VEGF is considered minimal.

3.4.4. Pharmacovigilance plan

Summary of planned additional PhV activities from RMP

No additional pharmacovigilance activities are proposed by the applicant. The applicant proposes routine pharmacovigilance for all safety concerns. Furthermore, targeted follow-up questionnaires were developed for the important risks of endophthalmitis and intraocular inflammation, see below.

Additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures

Not applicable.

Overall conclusion on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

The targeted questionnaires developed for the important risks of endophthalmitis and intraocular inflammation are considerd acceptable provided that:

- they are supplemented with lot number and patient risk factors (i.e. reflux of lacrimal drainage, dry eye, immunocompromised patient) to further characterise IOI and endophthalmitis and in line with other VEGH inhibitors.
- the "general instructions" at the top of the questionnaire stating the form is to be used to incorporate specific questions by the PV call center when engaging the reporter on the phone or in a follow-up request letter that will be sent to a health care professional and part of the questions can be cut and pasted that apply to the event of interest, are removed.

Depending on the outcome of the CHMP discussion, the pharmacovigilance plan should be updated to reflect the amendments requested to the safety specification, as well as all other relevant parts of the RMP.

3.4.5. Plans for post-authorisation efficacy studies

None proposed by applicant, which is agreed.

3.4.6. Risk minimisation measures

Routine Risk Minimisation Measures

Summary of additional risk minimisation measures

Table 44: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Endophthalmitis	Routine risk minimisation measures: *SmPC section 4.2, 4.3, 4.4, 4.8 and 6.6* *PL section 2, 3, 4 and 6* Other routine RMMs beyond the Product Information: *Pack size:* Ancilliary kit (vial + injection kit) and Vial-only pack for single use only *Legal status:* Prescription only medicine; RAYOQTA must be administered by a qualified ophthalmologist experienced in intravitreal injections Additional risk minimisation measures: *Healthcare Professional Guide* *Patient Guide*	Routine PV activities beyond ICSR reporting and signal detection: *Targeted follow-up questionnaires* Additional pharmacovigilance activities: *None*
Severe intraocular inflammation	Routine risk minimisation measures: *SmPC section 4.3, 4.4, and 4.8* *PL section 2, and 4* Other routine RMMs beyond the Product Information: *Pack size:* Ancilliary kit (vial + injection kit) and Vial-only pack for single use only *Legal status:* Prescription only medicine; RAYOQTA must be administered by a	Routine PV activities beyond ICSR reporting and signal detection: *Targeted follow-up questionnaires* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	qualified ophthalmologist experienced in intravitreal injections Additional risk minimisation measures: *Healthcare Professional Guide* *Patient Guide*	
Increased intraocular pressure	Routine risk minimisation measures: *SmPC section 4.2, 4.4, 4.8 and 4.9* *PL section 2, 4 and 6* Other routine RMMs beyond the Product Information: *Pack size:* Ancilliary kit (vial + injection kit) and Vial-only pack for single use only *Legal status:* Prescription only medicine; RAYOQTA must be administered by a qualified ophthalmologist experienced in intravitreal injections Additional risk minimisation measures: *Healthcare Professional Guide* *Patient Guide*	Routine PV activities only
Retinal detachment and retinal tear	Routine risk minimisation measures: *SmPC section 4.2, 4.4, and 4.8* *PL section 2, 4 and 6* Other routine RMMs beyond the Product Information: *Pack size:* Ancilliary kit (vial + injection kit) and Vial-only pack for single use only *Legal status:* Prescription only medicine; RAYOQTA must be administered by a qualified ophthalmologist experienced in intravitreal injections	Routine PV activities only

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: *Healthcare Professional Guide* *Patient Guide*	
Arterial thromboembolic events	Routine risk minimisation measures: *SmPC section 4.4, and 4.8* *PL section 2 and 4* Other routine RMMs beyond the Product Information: *Pack size:* Ancilliary kit (vial + injection kit) and Vial-only pack for single use only *Legal status:* Prescription only medicine; RAYOQTA must be administered by a qualified ophthalmologist experienced in intravitreal injections Additional risk minimisation measures: *None*	Routine PV activities only
Immunogenicity	Routine risk minimisation measures: *SmPC section 4.4, and 4.8* *PL section 2 and 4* Other routine RMMs beyond the Product Information: *Pack size:* Ancilliary kit (vial + injection kit) and Vial-only pack for single use only *Legal status:* Prescription only medicine; RAYOQTA must be administered by a qualified ophthalmologist experienced in intravitreal injections Additional risk minimisation measures: *None*	Routine PV activities beyond ICSR reporting and signal detection: *Detachable label*
Long term safety	Routine risk minimisation measures:	Routine PV activities only

Safety concern	Risk minimisation measures	Pharmacovigilance activities
beyond 2 years	*SmPC section 4.8* Other routine RMMs beyond the Product Information: *Pack size:* Ancilliary kit (vial + injection kit) and Vial-only pack for single use only *Legal status:* Prescription only medicine; RAYOQTA must be administered by a qualified ophthalmologist experienced in intravitreal injections Additional risk minimisation measures: *None*	

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures to minimise the risks of the product in the proposed indication(s) require amendments:

HCP material

Considering the experience with other anti VEGF therapies with intravitreal injections, which are being used for more than 10 years, the instructions for the prescribers to be included in the HCP educational material (e.g. aseptic technique) are considered standard practise for qualified ophthalmologists. Intravitreal administration is considered part of standard practice for ophthalmologists and is part of standard ophthalmology training.

Considering the proposed SmPC and experience with intravitreal injection in routine ophthalmology practice, and the proposed key elements for the HCP additional risk minimisation measures, the PRAC Rapporteur is of the opinion that HCP material may not further contribute to minimisation of the risk of IOI, endophthalmitis, increased inocular pressure and retinal detachment and retinal tear as compared to the recommendations provided in the SmPC. Therefore additional risk minimisation for the HCPs is not considered justified. The RMP should be updated accordingly.

Patient material

The proposed key elements for the patient guide are generally agreed. However in line with other anti VEGF drugs, the applicant should supplement the key elements with the "Patient information leaflet".

The list of signs and symptoms of IOI should be extended with those for mild and moderate IOI. The educational material for the patient should describe the signs and symptoms of any IOI (mild, moderate and severe) and not only for severe IOI. In addition, the patients should have a prompt

evaluation by an ophthalmologist if any of the signs of IOI develop. The key elements for the patient guide should be updated accordingly.

With regard to the audio material the applicant's proposal to agree upon the type of audio format at national level can be accepted. However, Annex 6 of the RMP and annex IID should mention that the patient information pack should be available in both the form of patient information booklets and an audio format.

Also, the applicant states the audio format will be made available upon request. This is agreed and Annex 6 of the RMP and annex IID should mention *"Information on how to obtain the special formats will be provided in the patient card".*

Depending on the outcome of the CHMP discussion, all relevant parts in the RMP including addressing RMM should be updated to reflect the amendments requested to the safety specification.

3.4.7. Summary of the risk management plan

The public summary of the RMP may require revision based on the comments made throughout the report.

PRAC Outcome

During its plenary meeting held from 11-14th May, the PRAC fully supported the assessment of the pharmacovigilance plan and risk minimisation measures as detailed in the assessment report and agreed that the RMP for Rayoqta could be acceptable provided that an update to RMP version 2.0 and satisfactory responses to the questions detailed in the D180 LoOI are submitted.

3.4.8. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 2.0 is not yet acceptable. Details are provided in the Rapporteur assessment report and in the list of questions in section 5 of this overview AR.

3.5. Pharmacovigilance system

The Rapporteur considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the {EBD} or {IBD} to determine the forthcoming Data Lock Points. 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.

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

The claimed indication is: Rayoqta is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD).

Neovascular AMD (nAMD) is characterised by the growth of abnormal growth of leaky choroidal blood vessels. This results in retinal oedema and choroidal neovascularisation (CNV). The neovascular lesions turn into scars resulting in a rapid destruction of the macula with severe and irreversible loss of central vision. Without treatment, nAMD results in severe visual impairment with an average loss of around 4 lines (20 letters) of visual acuity within 2 years of disease onset.

The process of angiogenesis is multi-factorial, but vascular endothelial growth factor (VEGF) is critical both in physiological and in pathological angiogenesis. Abicipar pegol binds to human VEGF-A thereby inhibiting its activity. The aim of therapy is to halt or reduce the progression of nAMD. In addition, by reducing the macula oedema, on average, patients improve their visual acuity. Linking abicipar to mPEG-Mal aims to prolong the intravitreal half-life of abicipar thus allowing less frequent injections. The longer durability of effect compared to ranibizumab was supported in animal models.

4.1.2. Available therapies and unmet medical need

Today, the mainstay of treatment is intravitreal (IVT) injections of anti-VEGFs that are administered through the IVT route. Three such therapies are approved, Lucentis (ranibizumab), Eylea (aflibercept) and Beovu (brolucizumab). In addition, Avastin (bevacizumab) is used off-label for the treatment of nAMD.

Still, there is no curative treatment for nAMD. Even if to a marked extent, the available therapies only slow down the disease progress and some subjects eventually lose vision. The IVT injections are further not free of risks, for example of sight-threatening complications such as infectious endophthalmitis. Finally, since there is an overall need for frequent injections, this results in a significant burden to the patient as well as to the health care system. Thus, there is still an unmet medical need.

4.1.3. Main clinical studies

Two identically designed Phase III studies, (Studies 150998 005 and 150998 006) form the basis to support registration of abicipar pegol for the treatment of patients with nAMD.

The studies are global, multicentre, double-masked, randomized, 104-week, parallel-group, active controlled, non-inferiority studies to evaluate the safety and efficacy of abicipar compared with monthly ranibizumab in treatment-naive patients with nAMD. Patients were to be randomised by region to 2 mg abicipar every 8th week (2Q8) after three initial monthly injections, 2 mg abicipar every 12th week (2Q12) after two initial monthly injections, or to monthly ranibizumab with a 1:1:1 allocation ratio.

4.2. Favourable effects

Unless indicated, the below summary focuses on the 52-week data from the pivotal studies.

Please note that missing treatment was the most common reason for excluding patients from the PP set. Missing treatments were to an important extent due to ocular AEs, mainly abicipar-induced intraocular inflammation (IOI) that in turn had an adverse impact on BCVA. Thus, the PP set excludes a proportion of the abicipar-treated subjects that developed IOI with a subsequent loss of efficacy.

In Study 150998-005, the proportions of patients in the PP population losing less than 15 letters in BCVA at week 52 vs. baseline (primary endpoint) were 91.7%, 91.2% and 95.5, in the abicipar 2Q8, 2Q12 and ranibizumab treatment arms, respectively. The differences (95.1% CIs) vs. ranibizumab were -3.8% (-8.2, 0.3) and -4.2% (-8.7, 0.0) for the 2Q8 and 2Q12 dose groups of abicipar, respectively. In the ITT population, the differences vs. ranibizumab were -5.4% (-9.6, -1.3) and -7.3% (-11.8, -3.1) for the respective regimen.

For the primary endpoint in Study 150998-006, 94.8%, 91.3% and 96.0%, in the abicipar 2Q8, 2Q12 and ranibizumab treatment arms, respectively lost less than 15 letters in BCVA. The differences (95.1% CIs) vs. ranibizumab were -1.2% (-5.0, 2.4) and -4.6% (-9.0, -0.5) for the 2Q8 and 2Q12 dose groups of abicipar, respectively. In the ITT population, 92.4%, 88.9% and 95.3% of subjects in the respective treatment group lost <15 letters in BCVA and the differences vs. ranibizumab were -2.9% (-6.8, 0.9) and -6.4% (-10.8, -2.2).

In the pooled phase III studies, the differences vs. ranibizumab in the proportions of patients losing <15 letters (95.1% CIs) were -2.5% (-5.3, 0.2) and -4.5% (-7.5, -1.6) in the PP set for the 2Q8 and 2Q12 regimens of abicipar. In the ITT sets, the corresponding figures were -4.1% (-7.0, -1.4) and -6.9% (-9.9, -3.9).

At week 104, 93.0%, 91.0% and 93.8% in the abicipar 2Q8, 2Q12 and ranibizumab treatment arms, respectively lost <15 letters in BCVA (completer population, observed data and LOCF) in Study 150998-005. The corresponding percentages in Study 150998-006 were 92.9%, 88.7% and 94.9%.

Excluding subjects with IOI, 95.3% (95.1% CI for difference: -3.1, 2.1), 92.4% (95.1% CI for difference:-6.4, -0.5) vs. 95.8% in the abicipar 2Q8, 2Q12 and ranibizumab treatment arms, respectively lost <15 letters in BCVA (pooled studies, PP set).

For the key secondary endpoint, the mean change in BCVA between baseline and Week 52, the outcome in the PP population in Study 150998-005 was a 6.7, 5.6 and 8.5 letter gain in the abicipar 2Q8, 2Q12 and ranibizumab treatment arms, respectively. The differences vs. ranibizumab (95.1% CIs) were -2.4 (-4.7, -0.1) and -3.7 (-6.0, -1.3) letters in the 2Q8 and 2Q12 treatment arms. In the ITT set, the differences (95.1% CIs) vs. ranibizumab were -3.5 (-5.9, -1.1) and -5.0 (-7.5, -2.6) letters in the two abicipar treatment arms.

In Study 150998-006, the corresponding mean changes in BCVA were 8.3, 7.3 and 8.3 letters (PP population) in the three treatment groups. Differences vs. ranibizumab were -0.2 (-2.4, 2.0) and -1.6 (-3.8, 0.6) letters. In the ITT set, the mean gain in BCVA was 8.2, 7.0 and 8.3 letters in the respective groups and the differences vs. ranibizumab were -1.5 (-3.7, 0.8) and -3.0 (-5.3, -0.7) letters.

In the pooled phase III studies, the differences vs. ranibizumab in the mean change in BCVA vs. baseline (95.1% CIs) were -1.3 letters (-2.9, 0.3) and -2.6 letters (-4.2, -1.0) in the PP set for the 2Q8 and 2Q12 regimens of abicipar. In the ITT sets, the corresponding figures were -2.5 letters (-4.2, -0.8) and -4.0 letters (-5.7, -2.4).

At week 104, in Study 150998-005 the mean gain in BCVA vs. baseline was 6.4, 5.0 vs. 8.8 letters in the abicipar 2Q8, 2Q12 and ranibizumab treatment arms, respectively (completer population). The corresponding mean letter gain in Study 150998-006 were 7.9, 6.0 and 7.5.

Excluding subjects with IOI, at Week 52, there was a mean BCVA gain from baseline of 8.4 (95.1% CI for difference: -1.7, 1.4), 6.9 (95.1% CI for difference:--3.5, -0.4) vs. 8.4 letters in the abicipar 2Q8, 2Q12 and ranibizumab treatment arms, respectively (pooled studies, PP set).

In Study 150998-005 (ITT set), the proportions (differences vs. ranibizumab; 95.1% CIs) of subjects that gained ≥15 letters in BCVA (secondary endpoint) in the 2Q8 and 2Q12 treatment groups were 22.6% (-4.7%; -11.5, -5.6) and 19.2% (-8.2%; -14.7, -1.5) whereas 27.2% gained ≥ 15 letters in the ranibizumab treatment group.

In Study 150998-006, the corresponding proportions (differences vs. ranibizumab; 95.1% CIs) that gained ≥15 letters in BCVA in the respective abicipar group were 28.2% (1.4%; -5.5, 8.4) and 24.4% (-2.3%; -9.1, 4.5) whereas 26.7% gained ≥ 15 letters in the ranibizumab treatment group.

The reductions in central retinal thickness (CRT) at week 52 were 140-150 µm without any differences between treatment groups and studies. Other imaging analyses indicated that both regimens of abicipar in both studies cleared subretinal fluid, reduced intraretinal thickening and dried the retina faster than ranibizumab.

The outcomes of the visual function questionnaire 25 were largely similar between studies with trends of a favour for ranibizumab.

Subgroup analyses (pooled studies) based on baseline demographics and disease characteristics generally followed the overall outcomes with a numerical favour for ranibizumab in the majority of subgroups.

4.3. Uncertainties and limitations about favourable effects

In both studies, larger proportions discontinued the studies in the abicipar treatment arms, mainly due to ocular AEs of which IOI was the most common, compared to ranibizumab.

The primary endpoint, the proportion of subjects that lose <15 letters in BCVA is considered outdated and not sufficiently informative since today, there is an expectation of an average increase in BCVA with intravitreal anti-VEGF therapy. Further, a loss of close to 15 letters in BCVA is regarded of clinical relevance.

The 10% non-inferiority margin for the primary endpoint is considered somewhat wide (note the CHMP-approval of Macugen in 2006 where the difference between active and sham was 14%). It was nevertheless accepted (CHMP advice) for the individual studies, while a 7% margin to demonstrated non-inferiority was recommended for the pooled studies. Further, with response rates of 89-96% and a 10% margin, the sensitivity to detect potential differences between treatment arms is questioned.

Similarly, the 5 letter non-inferiority margin for the key secondary – and preferred – endpoint, the mean change from baseline in BCVA at Week 52 was considered wide as this cannot be excluded to be of relevance. While a margin of 3-4 letters was recommended in the advice, a 4 letter margin was tentatively accepted for the pooled studies.

The applicant has chosen the PP set as the primary analysis population. However, subjects withholding or discontinuing treatment due to AEs, notably due to a large extent of abicipar-related IOIs that had an adverse impact on BCVA, were excluded from the PP set. The PP analyses are consequently more likely to allow the conclusion of non-inferiority than the ITT analyses and thus anti-conservative.

When analysed per protocol with the non-inferiority margin of 10% in the PP population, both studies met its primary objective for both the 2Q8 and 2Q12 regimens. However, in the ITT populations (both studies), the upper bound 95.1% CIs for all but the 2Q8 regimen in study -006 was below zero and abicipar was consequently inferior to ranibizumab. Also in the pooled studies, the lower bound of the

95.1% CI was -7.5% (PP) and -9.9% (ITT) for the 2Q12 regimen and borderline (-7%) in the ITT set for the 2Q8 regimen and abicipar is judged to be inferior to ranibizumab (upper bound CI < 0) in all analyses except for the 2Q8 regimen in the PP set.

Also for the key secondary analysis of the mean change in BCVA from baseline, when analysed per protocol with the non-inferiority margin of 5 letters, Study -006 met its objectives, while Study -005 failed to do so for the 2Q12 regimen. Further, in Study -005, abicipar was inferior to ranibizumab in for both regimens since the upper bound 95.1% CIs were below zero. In the ITT set, only for the 2Q8 regimen in Study -006 non-inferiority vs. ranibizumab was demonstrated. Also in the pooled studies, non-inferiority (< 4 letter margin) was demonstrated only for the 2Q8 regimen in the PP set while the lower bound 95% CI was smaller and the upper was below zero in the other analyses again indicating superiority of ranibizumab over abicipar. The overall outcome is not convincing and the lack of consistency between the pivotal studies questions the robustness of data, particularly for the 2Q12 regimen of abicipar that is the regimen recommended in the SmPC, section 4.2. Linking of abicipar to mPEG-Mal has consequently not been convincingly demonstrated to lead to a longer duration of efficacy in the clinical setting.

In the analyses excluding the 62 subjects with IOI markedly improved the outcome of abicipar treatment rendering an impression that the 2Q8 regimen of abicipar being non-inferior to ranibizumab. The 2Q12 regimen remains non-impressing as these analyses deliver evidence for a treatment difference, albeit small, vs. ranibizumab. However, the interpretation of this analysis is difficult given that a group of patients were excluded based on a post-randomization variable, and therefore randomization is broken. In other words, the comparison of abicipar with the ranibizumab arm is not straightforward because the patients are different. It is not possible to forsee to the size of the bias in this analysis.

A large proportion, around one third of patients randomised to either 2Q8 or 2Q12 abicipar, developed NABs and/or BABs against abicipar. The majority of subjects that developed IOIs (around 80-90%) were positive for ADAs. In the analyses of BCVA outcomes by IOI (yes/no), the mean visual acuity was even reduced in ADA positive subjects with IOI (-6.9 and -0.8 letters in the 2Q8 and 2Q12 treatment arms, respectively). In the responder analysis of the corresponding subgroup, 62.5% and 78.8% in the 2Q8 and 2Q12 treatment arms had lost <15 letters in BCVA. This consequently means that 37.5% and 21.2% of these patients lost ≥15 letters in BCVA. However, from the data presented it cannot be concluded whether efficacy might be directly affected in NAB(+) subjects or whether this is a consequence of the IOI.

The reduction in CRT that provides an objective measure of a treatment effect was similar between treatment groups. Of potential concern however are the fluctuations observed between injections in the abicipar treatment groups. Although the increases in CRT between injections were below the 50µm generally regarded to be of clinical relevance, this implies that there is some disease activity between injections. The visual acuity outcomes also suggest that patients with higher CRT fluctuation have a less favourable visual acuity outcome. However, rather than fluctuations in CRT, the recurrences of intraretinal fluids (IRF) that occurred between abicipar injections might lead to an adverse impact on long-term BCVA outcomes. Indeed, at week 104, there was no mean gain in BCVA in abicipar-treated patients with a higher number of occasions with IRF while the corresponding ranibizumab-treated subjects gained a mean of 4 letters. In the subgroups with lower number of visits with IRF, the corresponding gains in BCVA were 6, 6 and 10 letters in the abicipar 2Q8, 2Q12 and ranibizumab treatment arms, respectively. This adds uncertainty, especially of the 2Q12 regimen, and it seems likely that a proportion of patients are in need of more frequent dosing. An even more frequent injection interval than Q8 might further be optimal for certain patients. However, neither a potential added benefit of more frequent injections, nor the safety profile abicipar administered more frequently has been explored.

4.4. Unfavourable effects

Unless indicated, the below summary focuses on the 52-week data from the pivotal studies.

Across the studies, approximately 71% of patients in the abicipar treatment arms completed Week 104 weeks, while 83% of subjects completed the first 2nd treatment year in the ranibizumab treatment arms. The percentage of patients who discontinued due to AEs before Week 52 was higher in the abicipar groups (12.3% of patients in the 2Q8 group, 12.0% in the 2Q12 group) than in the ranibizumab group (4.0%). Most of the AEs leading to discontinuation were ocular in nature and involved intraocular inflammation (IOI).

Ocular AEs

The most obvious difference in AE profile between abicipar and ranibizumab is the higher incidence of IOI (e.g. uveitis, vitritis, iridocyclitis, iritis, vision blurred, retinal vasculitis, keratic precipitates, endophthalmitis, vitreal cells and vitreous haze) in the abicipar treatment arms (week 52: 15.4% in the 2Q8 group, 15.3% in the 2Q12 group, week 104: 16.2%, 17.6%) compared to ranibizumab (week 52: 0.3%, week 104: 1.3%). There was no major difference between the 2Q8 and 2Q12 treatment arms of abicipar although it appears that the IOI was somewhat more severe in the 2Q12 treatment arms. Apart from this and a higher incidence of endophthalmitis, the ocular safety profile of abicipar is essentially consistent with that observed with other anti-VEGF therapies and to a large extent related to injection-related complications.

The commonly reported (at least 1% in any group) individual ocular AE that occurred with an incidence rate ≥ 1% higher in the abicipar groups compared with the ranibizumab group included vitreous floaters, intraocular pressure (IOP) increased, uveitis, vitritis, iridocyclitis, visual acuity reduced, iritis, retinal vasculitis, keratic precipitates, and retinal artery occlusion. The commonly reported individual ocular AE that occurred with an incidence rate ≥ 1% higher in the ranibizumab group compared with the abicipar groups included conjunctival haemorrhage and dry eye.

Drug related ocular AEs were reported for a greater percentage of patients in both abicipar groups (16.8% in the 2Q8 group, 20.4% in the 2Q12 group) compared with 4.5% in the ranibizumab group.

Up to week 52, serious ocular AEs were reported for 8.3% of patients in the abicipar 2Q8 group, 7.3% in the abicipar 2Q12 group, and 1.4% in the ranibizumab group.

Intraocular inflammation (IOI)

Of the subjects developing IOI at any time during the 52 weeks, most developed mild (44/192, 23.0%) to moderately (105/192, 54.7%) severe IOIs while 22.4% (43/192) experienced a severe event of IOI. Thus, in the overall Phase III study population, the IOI was serious in 6.2% and 5.1% of subjects in the 2Q8 and 2Q12 abicipar treatment group, respectively, vs. none in the ranibizumab treatment group. In addition, IOI appeared in the non-study eye in 5/1876 patients, all in the abicipar treatment groups.

The first onset of IOI occurred after the first IVT dose of abicipar for 32.3% and 37.5% of subjects in the 2Q8 and 2Q12 treatment arms, respectively. Within the first 3 treatments (including the first injection), the majority of patients had their first onset of an IOI (64.6% and 72.9% for the 2Q8 and 2Q12 treatment arm, respectively). In the 2Q8 treatment arm, 35.5% of patients had their first onset of an IOI within the 4th and 8th injection. The corresponding figure for the 2Q12 regimen was 27.2%. 59.4% of subjects with IOI in each of the abicipar treatment arms received subsequent abicipar injections. Of these, 49.1% and 63.2% in the 2Q8 and 2Q12 treatment arm, respectively experienced a re-challenge of the IOI. During the 2nd treatment year, 5, 14 and 6 additional subjects reported IOI in the 2Q8, 2Q12 and ranibizumab treatment arms, respectively. Up to week 104, the rate of IOI over

2 years was at least 17% (see endophthalmitis below) in the abicipar-treated groups (vs. 1.3% for ranibizumab).

At the 52-week cut-off, the median duration of IOI was 42 and 23 days for the 2Q8 and 2Q12 abicipar regimens, respectively. However, for 17/192 patients (8.9%) with an IOI, the IOIs were persistent and lasted for more than 6 months. At week 104, 18 subjects (8, 9, 1 in the 2Q8, 2Q12 and ranibizumab treatment arms, respectively) still had an ongoing event of IOI.

At the 104-week cut-off approximately 90% of IOI patients were treated with CS of which 57.5% were topical and used for an average duration of 80 and 145 (days in the 2Q8 and 2Q12 treatment groups, respectively. Conjunctival, periocular or intravitreal CS were used in 20.2% of IOI patients with an average duration of 37 and 30 days in the two abicipar groups. Systemic (oral or iv) CS were administered to 12.4% and 18.8% of IOI patients with a mean duration of 41 and 40 days in the 2Q8 and 2Q12 treatment groups, respectively. Some subjects were treated with CS for close to 2 years.

At any time up to week 52, severe loss of vision (≥ 30 letters) was observed in 6.7% and 9.0% in the abicipar 2Q8 and 2Q12 treatment groups vs. 2.7% for ranibizumab. It was persistent (still evident at week 52) in 2.4% of patients in both abicipar treatment arms vs. 1.1% for ranibizumab.

In subjects with an IOI, a ≥30 letter vision loss was observed in 3.7%, 5.1% and 0.2% of subjects in the respective treatment arms while around 8% of subjects with an IOI in the two abicipar-treatment arms (vs. 0.2% for ranibizumab) lost ≥15 letters in BCVA at any visit. At Week 104, 4.5%. 6.3% and 0.5% of subjects with IOI had a ≥30 letter vision loss at any time in the in the 2Q8, abicipar 2Q12 and ranibizumab treatment groups, respectively. At week 104, 20 such subjects presented with this severe vision loss. Of the 48 subjects with a significant (≥15 to <30 letter) vision loss before week 52, 17 and 16 subjects still had a ≥15 letter loss at week 52 and 104, respectively.

IOI was also associated increases in intraocular pressure (IOP). The overall rates of increased IOP in abicipar-treated patients with IOI were 25.8% and 37.5% in the 2Q8 and 2Q12 groups, respectively and in patients without IOI: 4.5%, 6.2% and 5.3% in the 2Q8, 2Q12 and rQ4 groups, respectively. The majority of patients with an IOI and an increased IOP received IOP-lowering agents (92% and 93% in the 2Q8 and 2Q12 groups, respectively).

The majority of subjects that developed IOIs (around 80-90%) were positive for ADAs. At week 52, 82% vs. 91% of patients with IOI in the 2Q8 and 2Q12 treatment arms, respectively were BAB+ and 12% vs. 20% in the respective treatment arm were PEG+. Subjects being BAB positive had an approximately 10-fold higher risk of developing an IOI. Among the subgroup of ADA+ subjects with an IOI, at week 52, 37.5% and 21.2% in the 2Q8 and 2Q12 treatment arm had lost ≥15 letters in BCVA compared to baseline.

In the 28-week Study 1771-2001-008 (MAPLE) evaluating 2Q8 abicipar where residual host cell protein was reduced, IOI was reported in 11/123 (8.9%) of patients of which 2 were severe.

Endophthalmitis

By Week 52, endophthalmitis was reported for 8/625 (1.3%) of patients in the abicipar 2Q8 group, 8/626 (1.3%) in the abicipar 2Q12 group, and 1/625 (0.2%) in the ranibizumab group. Of the 17 patients with endophthalmitis, 14 had aqueous humour collected for microbial culture; 4 patients in the abicipar groups and 1 in the rQ4 group tested positive for microbial growth. Treatment included local (eye drops, intraocular) and systemic antibiotics and CS. At the time of the Week 52 database lock 5/17 events of endophthalmitis had resolved without sequelae, 7/17 were ongoing or had resolved with more or less sequelae and for the remaining subjects the outcome is not clear. There were also a number of re-challenges (new event of endophthalmitis or other IOI) when treatment with abicipar was re-initiated and the clinical course of the non-culture-proven events of endophthalmitis was

consistent with that of severe IOI. No abicipar-treated patients reported endophthalmitis during the second year while 2 ranibizumab-treated subjects reported culture-proven endophthalmitis.

In the Phase I and II studies, 2 additional events of endophthalmitis was reported in abicipar-treated subjects. Both events resolved without sequelae.

Non-Ocular AEs

No new concerns not previously identified for the available ocular VEGF-inhibitors have been identified and the safety profile of abicipar is in line with that expected in an elderly to very elderly patient population with associated co-morbidities.

Up to Week 52, events potentially related to systemic VEGF inhibition were reported in a similar percentage of patients in each treatment group, including 8.5% of patients in the 2Q8 group, 8.1% in the 2Q12 group, and 9.8% in the ranibizumab group. There were no patterns or remarkable imbalances noted among treatment groups based on either summary and no new concerns were raised during the 2nd treatment year. By Week 52, the most common AE potentially related to systemic VEGF inhibition in all treatment groups was hypertension reported for 5.8% of patients in the 2Q8 group, 5.8% in the 2Q12 group, and 5.4% in the ranibizumab group. In the 14-18% of patients who received anti-VEGF also in the non-study eye, AEs potentially related to systemic VEGF inhibition were reported for 8.1% of patients in the 2Q8 group, 10.1% in the 2Q12 group, and 13.5% of patients in the ranibizumab group.

Up to week 104, deaths were reported for a total of 50 patients without any patterns or imbalances noted among treatment groups. No deaths were reported in Phase I and the dose-finding Phase II studies.

4.5. Uncertainties and limitations about unfavourable effects

The reasons behind the IOIs are not fully clear. IOIs were reported in a large proportion of abicipar-treated patients compared to those treated with ranibizumab. While the presence of ADAs increased the relative risk experiencing an IOI 10-fold, a proportion of ADA negative subjects also developed an IOI and there was no clear temporal relationship between ADA status and IOI onset. While a causal relationship cannot be established, such can also not be included. It is possible that multiple immune pathways and that a CD4 TH1-mediated reaction might contribute to the IOI, for example impurities such as residual host cell protein or even a direct pro-inflammatory action of abicipar pegol through a T-cell driven mode of action. In the 28-week Study 1771-2001-008 (MAPLE), residual host cell (E. coli) protein was reduced in the abicipar drug substance. Unfortunately, the study was not controlled, and IOI was reported in 11/123 (8.9%) of patients of which 2 were severe. Taken together, the study 008 does not change the safety profile markedly, although it is agreed that the study 008 does not aggravate the safety profile either. However, since the applicant aims for an initial MAA with the drug substance used in Phase III, this is irrelevant and this MAA need to be based on clinical data in which material has been used. The applicant is requested to reconsider if any further investigations can be done to identify and potentially eliminate the cause of the increased IOI risk (**MO**)

It seems difficult to predict whether a patient will experience an IOI and be at risk of clinically significant (≥15) or severe (≥30) letter vision loss. IOIs occurred after the first dose of abicipar for approximately one third of patients and within the first 3 treatment cycles for more than half of patients and it has not been possible to identify a patient at no, or at lower risk for a severe IOI. Further, a significant number of patients developed IOIs during the latter part of the first treatment year and during the 2nd treatment year, 19 additional abicipar-treated subjects experienced an IOI. Consequently, it appears not possible to predict whether an initially and successfully treated patient will develop an IOI at a later stage. Monitoring of patients between injections to allow prompt

management of an IOI is not considered an option that is realistic in clinical practice especially since it appears that an IOI can appear at any time during treatment. It is also not realistic to conduct repeated testing to identify whether a patient develops ADAs, and thereby having an increased risk for an IOI, while on treatment with abicipar. The applicant proposes risk mitigations measures including a warning (SmPC 4.4) for re-challenge with abicipar after prior IOI, continued treatment with other anti-VEGF of progressing CNV, prompt treatment of retinal vasculitis with ocular or oral corticosteroids, monitoring of IOP and educational materials. Around 35% of patients experienced an IOI after the first abicipar injection, and the applicant estimates that if discontinuing treatment after the first event of IOI only 0.8%-1.5% of patients would experience IOI with a severe (≥30 letter) vision loss compared to 0.2% for ranibizumab. However, this is a "best case" scenario of 1.5% incremental risk of severe persistent visual loss after one single abicipar-injection and the figure is likely underestimated. Further, the extent of vision loss is still not fully clear and there is large uncertainty to what extent this will aid to reduce the risk of a sight-threatening IOI to a sufficient extent, see further below.

There is a risk of secondary complications due to the IOI and/or due to management of the IOI. With an IOI, there is an increased risk for complications – due to the IOI as such, and/or due to AEs related to concomitant treatment needed to handle the event. Besides the risk of a severe and persistent adverse impact on BCVA, IOI as such increases the risk for severe, secondary retinal vascular complications (e.g. retinal vasculitis, retinal artery/vein occlusion and ischaemic optic neuropathy). Even if the risk mitigation measures include prompt treatment of any IOI, it is difficult to believe that patients will be as closely monitored and promptly managed in clinical practice as in a setting of a clinical trial, especially after longer-term treatment when diligence is expected to be reduced. In addition, of the close to 18% of patients (see below) that reported IOI, 90%, i.e. around 15% of all abicipar-treated patients, were treated with CS. Even without any re-challenge in subjects experiencing an IOI after their first injection (35% of all patients with IOI), at least 5% of all abicipar-treated subjects are at risk for developing an IOI that requires treatment with CS after a single abicipar injection. This translates into a need for close monitoring, a risk of CS-induced AEs (e.g. increased IOP, cataract, systemic AEs) and a need for additional treatment that in turn increases the risk of additional AEs. Further, in subjects with severe and active IOI, treatment with the approved anti-VEGFs is contraindicated and in addition to the IOI-induced risk of persistent vision loss, the underlying and irreversible progressive CNV will not be treated. There is thus high uncertainty on the impact of the proposed risk mitigation measures.

Of the 17 baseline characteristics evaluated, some influential variables were identified. In view of the multiple testing conducted, this is not surprising; however, the risk of a severe IOI as well as a severe vision loss (≥30 letters) was markedly higher in women (OR 8.1 and 4.2, respectively). This appears striking considering the high ORs and consequently less likely to be a chance finding. Women also had a higher risk of developing ADAs.

Although there was no major safety difference between the 2Q8 and 2Q12 treatment arms of abicipar, there was a trend towards a more frequently reported AEs related to IOI in the 2Q12 treatment group (14 vs. 5 events) during the 2nd treatment year. Further, the mean duration of use of corticosteroid use was 145 and 80 days in the 2Q12 and 2Q8 treatment groups, respectively. The extent of IOP-lowering medication was also higher in the 2Q12 treatment group (27% vs. 15% for 2Q8). It appears thus that the IOI was more frequent and more difficult to manage in the 2Q12 treatment group. This is not consistent with the reporting of severe IOI. In addition, by Week 52, for discontinued patients, a ≥ 30 letter vision loss was reported for 5.8% and 18.9% patients in the abicipar 2Q8 and 2Q12 groups, respectively. By Week 104 a ≥ 30 letter loss was reported for 9.5% vs. 16.5% of discontinued patients in the abicipar 2Q8 and 2Q12 groups, respectively. Finally, more subjects with IOI were BAB+ (91% vs. 82%) and anti-PEG+(20% vs. 12%) in the 2Q12 treatment arm.

Classification of endophthalmitis. The increased frequency of infectious or non-infectious events of endophthalmitis is not was to expect when the injection interval is reduced. The clinical course of (the majority of) the non-culture proven events of endophthalmitis appears however consistent with IOI rather than with infectious endophthalmitis. For example, there were a number of re-challenges. This translates into an uncertainty on the rate of IOI that is likely underestimated and a more accurate figure at week 52 is likely close to 18% (4.4% severe).

Finally, due to the very limited follow-up of patients discontinuing the study, there is uncertainty on the extent of reversibility of IOI and vision loss.

4.6. Effects Table

Table 45: Effects Table for Abicipar Pegol in the treatment of adults for the treatment of neovascular (wet) age-related macular degeneration (AMD)

Effect	Short Description	Unit	A2Q8	A2Q12	rQ4	Uncertainties/ Strength of evidence	Refe-rences
Favourable Effects							
BCVA	Proportion losing <15 letters w. 52	% PP ITT	 91.7 (-8.2, 0.3) 90.1 (-9.6, -1.3)	 91.2 (-8.7, 0) 88.2 (-11.8, -3.1)	 95.5 95.5	Not sensitive endpoint to detect differences between treatments. Somewhat wide NI-margin (10%), PP population (primary) excludes subjects with abicipar-related IOI that negatively impacts BCVA and thus anti-conservative. Effect not convincing and inferior to rQ4 in a number of analyses, notably for 2Q12. Inconsistent outcomes between studies, study (2) better.	(1)
		% PP ITT	 94.8 (-6.8, 0.9) 92.4 (-6.8, 0.9)	 91.3 (-9.0, -0.5) 88.9 (-10.8, -2.2)	 96.0 95.3		(2)
BCVA Proportion losing <15 letters excluding IOI w. 52		% PP ITT	 94.7 (-4.9, 2.9) 94.0 (-5.5, 2.2)	 93.4 (-6.4, 1.9) 92.5 (-7.3, 0.9)	 95.5 95.5	Markedly improved outcomes for the 2Q8 regimen with lower bound 95.1% CI well within the ideal -7%, less so for 2Q12. Extent of bias in view of exclusion being a post-randomisation variable?	(1)
		% PP ITT	 96.0 (-3.7, 3.4) 95.1 (-4.2, 3.1)	 91.5 (-9.0, -0.4) 92.1 (7.6, 0.6)	 96.0 95.6	As above	(2)
BCVA Mean change from baseline to week 52 Mean change from baseline to week 52		Letters PP ITT	 6.7 (-4.7,-0.1) 5.9 (-5.9, -1.1)	 5.6 (-6.0, -3.1) 5.5 (-7.5, -2.6)	 8.5 8.5	Somewhat wide NI-margin (5 letters), PP population excludes subjects with abicipar-related IOI that negatively impacts BCVA and thus anti-conservative. Effect not convincing and inferior to rQ4 in a number of analyses, notably for 2Q12. Inconsistent outcomes between studies, study (2) better.	(1)

Effect	Short Description	Unit	A2Q8	A2Q12	rQ4	Uncertainties/ Strength of evidence	Refe-rences
		Letters PP ITT	8.3 (-2.4, 2.0) 8.2 (-3.7, 0.8)	7.3 (-3.8, 0.6) 7.0 (-5.3, -0.7)	8.3 8.3	As above	(2)
BCVA	Mean change from baseline to week 52 excluding IOI	Letters PP ITT Letters	7.7 (-3.1, 1.4) 7.4 (-3.2, 1.3)	5.8 (-4.9, -0.4) 5.6 (-5.0, -0.5)	8.5 8.4	Markedly improved outcomes for the 2Q8 regimen with lower bound 95.1%CI within the "ideal"-3 to -4 letters, less so for 2Q12.	(1)
		 PP ITT	 9.0 (-1.7, 2.8) 8.7 (-1.8, 2.7)	 7.2 (-3.4, 1.0) 7.0 (-3.4, 1.0)	 8.4 8.2	Extent of bias as exclusion being a post-randomisation? Markedly improved outcomes for the 2Q8 regimen with lower bound 95.1%CI within -3 to -4 letters for both regimens in both analyses.	(2)
CRT	Mean change from baseline to week 52	µm observed data	-142 (-3.8, 20.9)	-150 (-10.1, 14.7)	-141	Fluctuations observed between injections in the abicipar treatment groups might indicate some disease activity between injections	(1)
			-147 (-7.1, 14.0)	-142 (-4.7, 16.5)	-147		(2)
Unfavourable Effects							
IOI	Incidence all IOI up to w. 52	%	15.4	15.3	0.3	Figure in pooled abicipar groups likely close to 18% since a number of IOI events were reported as endophthalmitis. Reasons for IOIs not fully clear, likely multifactorial, but a 10-fold increase in RR in ADA+ subjects. Seems not possible to predict, mix of early and late onsets. Long-standing events ongoing. Limited follow-up of discontinuations precludes conclusion on final recovery. Approximately 90% of all subjects with IOI required treatment with CS (topical 58%), ocular injections (19%), systemic (oral, IV 15%).	(3)
IOI	Incidence serious IOI	%	6.2	5.1	0	Persistent loss of BCVA. Limited follow-up of discontinuations precludes conclusion on final reversibility.	(4)
Endophthalmitis	Incidence Endophthalmitis	%	1.0	1.3	0.2	High incidence in abicipar treatment arms. Majority of events of non-culture-proven endophthalmitis more consistent with severe IOI.	(5)
Severe vision loss	Proportions losing ≥30 letters in BCVA at any time up to week 52	%	6.7	9.0	2.7	Persistent loss of BCVA. Limited follow-up of discontinuations precludes conclusion on final reversibility.	(6)

Effect	Short Description	Unit	A2Q8	A2Q12	rQ4	Uncertainties/ Strength of evidence	Refe-rences
Persistent severe vision loss	Proportions with a ≥30 letter loss at week 52	%	2.4	2.4	1.1	Extent of missing data larger in abicipar treatment arms and outcome not clear. Limited follow-up of discontinuations precludes conclusion on final reversibility.	(6)

Abbreviations: A2Q8=abicipar 2 mg every 8th week, A2Q12=Abicipar 2 mg every 12th week, rQ4=ranibizumab 0.5 mg every 4th week, BCVA = best corrected visual acuity, CRT=central retinal thickness, IOI=intraocular inflammation, ADA+= positive for anti-drug antibodies, RR=relative risk
Notes: (1) Study 150998-005 (2) Study 150998-006 (3) All AEs of IOI including for example the terms of Uveitis, Retinal vasculitis, Vitritis, Iridocyclitis, Iritis up to week 52in pooled studies 150998-005 and 150998-006. (4) All serious AEs of IOI up to week 52in pooled studies 150998-005 and 150998-006. (5) Other serious ocular AEs of special interest up to week 52 in pooled studies 150998-005 and 150998-006. (6) Available data up to week 52. Pooled studies 150998-005 and 150998-006

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Although ranibizumab was consistently favoured with regard to the point estimates, more than (PP set) or close to (ITT set) 90% of subjects in the abicipar treatment groups lost <15 letters in BCVA. Essentially maintaining BCVA in around 90% of subjects is per se considered of clear relevance compared to no treatment since without treatment, only 60-65% of subjects with nAMD would be expected to lose <15letters in BCVA over one year (see the MARINA study in the SmPC for Lucentis). However, when scrutinising the methodology and put the outcomes in context with that of the comparator ranibizumab, there are remaining concerns.

When analysed per protocol with the non-inferiority margin of 10% in the PP population, both studies met its primary objective for both the 2Q8 and 2Q12 regimens. However, besides that the non-inferiority margin is considered somewhat wide and that the responder analysis is outdated (today, a mean gain in BCVA is expected) and not expected to be sensitive to detect differences between treatment, the PP population excluded subjects withholding/discontinuing treatment due to ocular AEs, mainly IOI that reduced BCVA, in the abicipar treatment arms. The applicant justifies the strategy to exclude subjects with IOI from the analysis population as it would confound the evaluation of a treatment effect. However, this would mean that the effect in the PP set is overestimated and the analyses in the ITT set has to be carefully considered. In the ITT analyses, only Study -006 is considered truly positive (PP and ITT set, lower bound NI-margin at or above -7%), and this only for the 2Q8 abicipar treatment regimen.

There are the same concerns for the key secondary endpoint (the preferred primary endpoint), the mean BCVA change from baseline to week 52.

The applicant's claim that the efficacy of abicipar to improve visual acuity is confounded by IOI, reported by approximately 15 % of the patients, is not agreed. The AE are caused by abicipar treatment, and it is a requirement in this disease to be able to receive treatment to delay the progression of the disease.

The applicant presented several analyses were patients who suffered IOI AE were excluded. The AE are post-baseline events and therefore the exclusion of such patients will give biased results. The analyses presented excluding those patients are not considered interpretable since a fair comparison would have been among those patients who would have never developed IOI AE regardless of the treatment arm

they were assigned. If the applicant aims for such a comparison another methodological framework should be used (see for example Principal stratum estimand in E9 addendum). The major concern remains.

A safety profile of a drug that induces IOI in close to 18% of subjects over one year and serious such in around 6% of the overall abicipar-treated population, this with an, in some instances severe and persistent, adverse effect on visual acuity, remains of major concern. This is also the most obvious difference in AE profile between abicipar and ranibizumab (IOI 0.3%). The IOIs are to a large extent drug-related, might be serious and are potentially sight-threatening. In subjects with an IOI, 4-5 % of subjects in the two abicipar-treatment arms (vs. 0.2% for rQ4) lost ≥30 letters in BCVA at any visit. This is again of major concern.

In addition, there is a trend towards an inferior safety profile of abicipar in the 2Q12 treatment arm that overall translates into an impression IOI in these treatment groups was more severe and more difficult to manage. Considering the non-convincing efficacy profile of the 2Q12 regimen, together, this is of major concern. Even if it is recognised that IOIs was a very common AE when Lucentis was initially approved in 2007, the concurrent comparison clearly demonstrates an inferior safety profile of abicipar in this regard. It is not reasonable to put patients at risk for severe reduction or a loss of vision when there are alternative effective treatments that do not induce this extent of serious IOIs. There is further concern that the proposed risk mitigation measures will not reduce the extent of IOI with subsequent risk of clinically significant (≥15 letter) or severe (≥30 letter) and persistent vision loss to a sufficient extent. The extent of recovery of the severe vision loss (as well as the IOI) is further unclear due to the very limited follow-up, which adds to the uncertainty. The IOIs may develop after one injection. This means that even if treatment is permanently discontinued in all patients that experience an IOI, at least 5% of all treated patients are at risk of developing IOI after the first abicipar treatment. Subjects are also at risk of developing IOI after several injections and there were 19 new onsets in abicipar-treated subjects during the 2nd treatment year. This translates into a need for close monitoring of patients. It is difficult to believe that patients will be as closely monitored and promptly managed in clinical practice as in a setting of a clinical trial. This is of even more concern with regard to the IOI that were reported after long-term treatment where diligence is expected to be reduced. The effect of the proposed risk mitigation measures is thus difficult to estimate.

Obviously, the IOI as such needs to be managed as the IOI as such increases the risk of severe retinal vascular complications and increased IOP. This in turn translates into a risk of corticosteroid-induced AEs (e.g. increased IOP, cataract, systemic AEs) and a need for additional treatment that in turn increases the risk of additional AEs. Further, in subjects with severe and active IOI, treatment with the approved anti-VEGFs is contraindicated. Consequently, in addition to the IOI-induced risk of persistent vision loss and thus a loss of chance, the underlying and irreversible progressive CNV cannot be treated in the important subset of patients with severe IOI. This is thus another reason for a loss of chance and not what to expect with intravitreal anti-VEGFs to treat nAMD.

Based on the experience gained with the approved anti-VEGFs for intravitreal use, in general, the majority of AEs associated with intravitreal injections are injection-related. Even though most are benign (e.g. conjunctival haemorrhage), some (albeit rare) are sight threatening. The frequent injections also puts a significant burden on the patient and the health care system. Therefore, maintaining visual acuity while reducing the number of injections would pose a significant benefit to patients and the health care system. In case a clearly superior safety profile would have be demonstrated with a markedly reduced number of injections for abicipar, a somewhat lower effect might have been acceptable. This has however not been demonstrated since abicipar is judged to have an inferior ocular safety profile compared to ranibizumab, a safety profile that is expected to lead to a need for close monitoring and additional management of patients. This counteracts the benefit of a

reduced treatment and monitoring interval compared to other intravitreal anti-VEGFs that has comparable efficacy.

4.7.2. Balance of benefits and risks

Taken together, the applicant's claim that the efficacy of abicipar to improve visual acuity is confounded by IOI, reported by approximately 15 % of the patients, is not agreed. The AE are caused by abicipar treatment, and it is a requirement in this disease to be able to receive treatment to delay the progression of the disease.

The ocular safety profile of abicipar is clearly worse than for ranibizumab since a large extent of IOIs in the abicipar treatment arms resulted in clinically significant and persistent loss of visual acuity in a subset of patients and it has not been possible to identify a patient population at no, or at lower risk for a severe IOI. There is further a trend of the 2Q12 regimen being inferior to the 2Q8 regimen also from a safety point of view.

The proposed risk mitigations measures leave a "best-case" where 1.5% of patients would be at risk of severe persistent visual loss after one single injection of abicipar and thus a loss of chance. This figure is likely underestimated, but it is not clear to what extent. In addition, the IOI as such increases the risk for secondary adverse events that needs close monitoring and further treatment. Both from the perspective of the patient and the health care system, this counteracts the benefit of a reduced treatment and monitoring interval compared to other intravitreal anti-VEGFs that has comparable efficacy. Finally, in subjects with severe and active IOI, treatment with the approved anti-VEGFs is contraindicated. This means that the underlying and irreversible progressive CNV cannot be treated in a proportion of patients. This consequently means another loss of chance.

Except for the surprising and striking finding that women are at higher risk for IOI and ≥30 letter vision loss, it has not been possible to identify a subgroup of patients at higher risk for an IOI. The finding that women are at higher risk might be a chance finding; however, in view of the high odds ratios (OR 8.1 and 4.2, respectively) it adds to the concern.

The final data from Study 1771-201-008 (MAPLE) evaluating a refined drug process does not change the safety profile of abicipar markedly. Even if the applicant ascertains that different manufacturing processes will be used in the future, it remains to be justified that these will markedly change the clinical safety profile of abicipar. However, since the applicant aims for an initial MAA with the drug substance used in Phase III, this is irrelevant.

Taken together, the applicant has not convincingly demonstrated that the safety profile of abicipar is acceptable and clinically manageable.

Consequently, the benefit/risk balance of abicipar is currently negative. Robust support that abicipar is a sufficiently safe treatment is needed. Furthermore, convincing clinical data demonstrating that the treatment of patients with abicipar pegol does not induce intraocular inflammation that might have an adverse impact on visual acuity is needed.

4.7.3. Additional considerations on the benefit-risk balance

Not applicable.

4.8. Conclusions

The overall B/R of Rayoqta is negative.