21 March 2024
EMA/146883/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lytenava

International non-proprietary name: Bevacizumab gamma

Procedure No. EMEA/H/C/005723/0000

Note

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

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List of abbreviations

Aa	Amino acid
ADCC	Antibody dependent cellular cytotoxicity
AET	Analytical evaluation threshold
AEX	Anion exchange
AMD	Age-related macular degeneration
BET	Bacterial endotoxin test
BI	Bioindicator
ByPV	Bovine polyomavirus
C1q	Subcomponent of the first complement factor
CCIT	Container closure integrity test
CCS	Container closure system
CDC	Complement dependent cytotoxicity
CDR	Complementary determining region
CEX	Cation exchange
CFU	Colony-forming unit
CH	Heavy chain constant region
CHO	Chinese hamster ovary
CIP	Clean in place
CPP	Critical process parameter
CQA	Critical quality attribute
DNA	Desoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	Endotoxin unit
Fab	Fragment antigen binding
Fc	Fragment crystallisable
FcRn	Neonatal Fc receptor
FcγR	Fc gamma receptors
FDA	U.S. Food and Drug Administration
Flt-1	VEGF receptor 1

g/L	Grammes per litre
GMP	Good manufacturing practice
GOI	Gene of interest
HC	Heavy chain
HCP	Host cell protein
HMWs	High molecular weight species
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IPC	In-process control
IVT	Intravitreal
KDR	VEGF receptor 2
KPI	Key process indicator
LC	Light chain
LIVCA	Limit of *in vitro* cell age
LOD	Limit of detection
LOQ	Limit of quantitation
LRF	log10 reduction factor
MAA	Marketing authorisation application
mAb	Monoclonal antibody
MCB	master cell bank
MDI	Maximum daily intake
MET	Microbial enumeration test
MFI	Micro flow imaging
MIA	Manufacturing authorisation
mL	millilitres
MO	Major objection
MoA	Mode of action
NA	Not applicable
nAMD	Neovascular age-related macular degeneration
OC	Other concern

PAR	Proven acceptable range
PC	Process characterisation
PCR	Polymerase chain reaction
PD	Pharmacodynamics
Ph. Eur.	European pharmacopoeia
PHCCF	Preharvest cell culture fluid
PK	Pharmacokinetics
PP	Per protocol
PPQ	Process performance qualification
PRV	Pseudorabies virus
PS20	Polysorbate 20
QA	Quality attribute
QTPP	Quality target product profile
Reo3	Reovirus type 3
RT	Reverse transcriptase
rRT	Relative retention time
SD	Standard deviation
SDM	Scale-down model
SST	System suitability test
TEM	Transmission electron microscopy
TAMC	Total aerobic microbial count
$TCID_{50}$	Median tissue culture infective dose
TOR	Time out of refrigerator
TYMC	Total combined yeast/moulds count
UFDF	Ultrafiltration and diafiltration
USP	United States pharmacopoeia
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
USP	Upstream production
wAMD	Wet age-related macular degeneration

WCB	Working cell bank
WFI	Water for injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Outlook Therapeutics Limited submitted on 27 November 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Lytenava, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: Lytenava is indicated in adults for treatment of neovascular (wet) age-related macular degeneration (nAMD).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision CW/0001/2015 on the granting of a class waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Christian Gartner Co-Rapporteur: Beata Maria Jakline Ullrich

The application was received by the EMA on	27 November 2022
The procedure started on	28 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 March 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	30 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 April 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	06 September 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	17 October 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 October 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	09 November 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 January 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	07 February 2024
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant	22 February 2024
The applicant submitted the responses to the second CHMP second List of Outstanding Issues on	27 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP and PRAC members on	14 March 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lytenava on	21 March 2024

2. Scientific discussion

2.1. Problem statement

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in individuals >55 years of age in the developed world, accounting for 6–9% of legal blindness globally. Neovascular (wet) AMD (nAMD) is characterised by the growth of abnormal blood vessels (neovascularisation), which grow in the retina from the choroid or from retinal vessels. Although the neovascular form of the disease is only present in about 10% of all AMD cases, it accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-VEGF treatments.

2.1.1. Disease or condition

Neovascular age-related macular degeneration (nAMD) is characterised by newly formed vessels that have an increased likelihood to leak blood and serum, damaging the retina by stimulating inflammation and scar tissue formation. The natural history of nAMD is well-known and this damage to the retina results in progressive, severe, and irreversible vision loss.

2.1.2. Epidemiology

AMD is the leading cause of legal blindness in the elderly in the Western world. AMD is a progressive disease of the macula that leads to loss of central vision in its advanced stages. Neovascular (exudative) AMD (nAMD) accounts for approximately two thirds of prevalent late-stage AMD cases but is responsible for over 80% of legal blindness due to AMD (Wong et al. 2006). The global prevalence of AMD among those aged 45 to 85 years old is 8.7%, with a prevalence of 0.4% for advanced AMD. The global prevalence of any stage of AMD is predicted to increase from 196 million people in 2020 to 288 million by 2040. Prevalence for wAMD increases with age, varying from 0.5% in people 65 - 69 years old to 14.6% in the population of people 90 years or above (Rudnicka et al. 2015). Some evidence suggests higher risk of wAMD in women compared with men (Rudnicka et al. 2011).

2.1.3. Aetiology and pathogenesis

Neovascular (wet) AMD (nAMD), the advanced stage of AMD, is characterised by the growth of abnormal blood vessels (neovascularisation), which grow in the retina from the choroid or from retinal vessels (termed macular neovascularisation). Vascular endothelial growth factor is elevated in patients with nAMD and is thought to play a key role in the neovascularisation process. The natural history of nAMD is well-known and associated with a rapid decline in functional visual acuity that, if left untreated, culminates in a doubling of the visual angle (loss of 15 letters) in the year after initial presentation. It is a leading cause of visual impairment in older people.

2.1.4. Clinical presentation

nAMD is characterised by the growth of abnormal blood vessels (neovascularisation) under the retinal pigment epithelium or subretinal space from the subjacent choroid (termed choroidal neovascularisation). VEGF is elevated in patients with nAMD and is believed to play a role in the neovascularisation process.

Patients with nAMD usually present with a visual impairment and can have sudden changes in vision. The condition is diagnosed based on results of a slit lamp examination, fluorescein angiography and optical coherence tomography (OCT). The symptoms of nAMD include central vision loss characterised by metamorphopsia, scotomas, and blurriness, which negatively affect reading, driving, patient mobility, face recognition, and other daily activities, including self-care. The diagnosis of nAMD is made clinically by ophthalmoscopy and multimodal retinal imaging techniques, which include optical coherence tomography (OCT) and fundus fluorescein angiography (FFA). The clinical manifestation of nAMD includes the presence of subretinal fluid (SRF) and/or intraretinal fluid (IRF), retinal and subretinal haemorrhage, retinal thickening, and pigment epithelial detachment. Without treatment, progression of the disease results in the formation of a fibrous scar and consequently severely reduced vision.

2.1.5. Management

The major goal of treatment is to avoid or recover lost vision and subsequently maintain vision in nAMD patients over time. Previously, laser photocoagulation therapy and photodynamic therapy with verteporfin were the standard of care and were shown to stabilise, but not recover, vision.

The introduction of anti-VEGF therapies has markedly improved vision outcomes and changed the management of nAMD. Today various ophthalmic anti-VEGF treatments for nAMD are approved for use throughout the European Union, including Lucentis (ranibizumab), Eylea (aflibercept), Beovu (brolucizumab), and Vabysmo (faricumab).

2.2. About the product

Mode of action: Bevacizumab gamma is a recombinant humanised IgG1 monoclonal antibody (mAb) specific for human vascular endothelial growth factor (VEGF). Bevacizumab gamma binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. Bevacizumab gamma is a human VEGF inhibitor that binds to all isoforms of VEGF-A, thereby preventing interaction with receptors VEGFR-1 and VEGFR-2. By inhibiting VEGF-A, bevacizumab gamma suppresses endothelial cells proliferation, neovascularisation, and vascular permeability. Inhibition of angiogenesis works to block the growth of abnormal blood vessels in the back of the eye.

Pharmacological classification: Monoclonal antibody

Claimed therapeutic indication: Treatment of neovascular (wet) age-related macular degeneration (wAMD or nAMD).

2.3. Quality aspects

2.3.1. Introduction

This marketing authorisation application (MAA) for Lytenava is being submitted as a full-mixed application for the treatment of neovascular (wet) age-related macular degeneration (AMD), in accordance with Article 8(3) of Directive 2001/83/EC. Bevacizumab gamma contained in Lytenava, also referred to as ONS-5010, is a known active substance. It is a humanised monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

The finished product is presented as a solution for intravitreal injection containing 25 mg/mL bevacizumab gamma. Each vial (2 mL Type I glass) contains 7.5 mg of bevacizumab gamma in 0.3 mL solution. This provides a usable amount to deliver a single dose of 0.05 mL containing 1.25 mg bevacizumab gamma.

Bevacizumab gamma is formulated with sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate, α,α-trehalose dihydrate, polysorbate 20 (E432) and water for injections.

2.3.2. Active Substance

2.3.2.1. General information

Bevacizumab gamma is a recombinant humanised IgG1 monoclonal antibody that targets the vascular endothelial growth factor (VEGF). It has a non-reduced mass (deglycosylated) of approximately 146.6 kDa, 12 intra-chain and 4 inter-chain disulfide bonds and is N-glycosylated at Asn_{303} with oligosaccharides to be primarily biantennary structures containing 0, 1 or 2 terminal galactose units (G0F, G1F, and G2F).

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

ONS-5010 active substance is produced at FUJIFILM Diosynth Biotechnologies Texas, LLC, 3939 Biomedical Way, College Station, Texas (TX) 77845, United States (USA). All sites involved in manufacture and controls operate in accordance with EU GMP.

The active substance is manufactured using a fermentation process in a bioreactor. The active substance is expressed in a CHO cell line. Manufacture of a batch starts from a single vial of the working cell bank (WCB). After serial sub-cultivations in shake flasks, cells are transferred to the production bioreactor, and cells are finally expanded and maintained under controlled conditions prior to harvesting the culture supernatant.

The purification process of the active substance comprises of a combination of chromatography steps, followed by ultrafiltration/diafiltration (UF/DF).

Two dedicated, orthogonal virus clearance steps, i.e. low-pH treatment and a second step, nanofiltration are integrated in the purification process. The filtered bulk active substance is then aseptically filled in bulk active substance bags constructed of ethylene vinyl acetate (EVA). After labelling the ONS-5010 active substance is stored at -20 ± 5°C. Reprocessing is not performed during the manufacture of ONS-5010 active substance.

The applicant provided a detailed description of the manufacturing process steps accompanied by flow charts including in-process control (IPC) tests and process parameters/quality attributes with their classification (critical quality attribute (CQA) / key process parameters (KPP) / critical process parameter (CPP)) and acceptable ranges/acceptance criteria as well as hold times. Composition of solutions and buffers are described. The classification of the process parameters and IPCs and their acceptable ranges/acceptance criteria are adequately justified.

Control of materials

Lists of raw materials, solvents and auxiliary materials are described in detail. Buffers and media used during the active substance manufacturing process are properly listed and described, including in-process testing controls and hold-times.

Information on the source of the cell substrate and analysis of the expression construct to develop the master cell bank (MCB) is satisfactorily described. In brief, the genes of interest coding for ONS-5010 light chains (LC) and heavy chains (HC) were assembled as single-stranded synthetic oligonucleotides and then turned into complete double stranded DNA sequences. The MCB is stored at a temperature of ≤ -120°C.

The procedures for the preparation of the MCB and WCB are described in the dossier. The WCB was tested regarding purity and post thaw viability. Nine vials were thawed to test out-of-freeze characteristics. A reduced characterisation approach was carried out, due to the full set of tests carried out for the MCB. This is regarded acceptable. No adventitious agents, neither microbial nor viral were detected in the WCB. Every three years the WCB will be retested, which is acceptable.

Provenance of all starting and raw-materials, generation of the research cell bank (RCB), the cell banking system, characterisation and testing are adequately described. WCB clonal stability was sufficiently addressed.

Control of critical steps and intermediates

The applicant classified CPPs and critical IPCs directly impacting product quality. This approach represents the control strategy for consistent manufacture of each lot of ONS-5010 active substance at the commercial production scale. Classification was done using existing process and product knowledge. Process steps are categorised as either CPP or KPP. Further process steps are classified as key process attributes (KPA). IPCs are performed during production to monitor and appropriately adjust the process if necessary. Targets and operating ranges, as well as acceptance criteria are presented. For the upstream process, the data from the three most recently manufactured lots are displayed that represented the commercial manufacturing process prior to the process performance qualification (PPQ) campaign. For the downstream process, data from the three most recently manufactured lots prior to the PPQ campaign were used. This approach is overall in line with current guidance documents ICH Q8 and Q11. A quality target product profile (QTPP) is presented.

As requested, the applicant has tightened the differential pressure limits at cell removal and filtration steps and has updated respective dossier sections. In addition, a justification for the dissolved oxygen range and the lower loading density of lot has been provided. A numerical acceptance criterion for integrity testing of the virus reduction nanofiltration step has also been provided by the applicant. Microbial testing strategy is summarised for all production units and criticality of testing is described. In case of non-compliance of critical tests, batches are rejected.

Allowable hold-times for six intermediate steps are defined. The proposed hold times are sufficiently supported by chemical and microbial hold time data.

In conclusion, the proposed process control strategy is considered appropriate to ensure consistent manufacture of ONS-5010 active substance with adequate quality.

Process validation

Process validation for ONS-5010 active substance was carried out at commercial scale, at the intended production site for ONS-5010 active substance. Process validation was performed on three consecutive active substance lots.

CPPs, KPPs and IPCs were challenged by means of normal operating ranges (NORs) and acceptable operating ranges (defined through historical manufacturing experience). The process parameters are comprehensibly listed in tables for each process step and are considered well-chosen.

There were no batch failures during validation throughout all investigated active substance PPQ lots. However, 20 individual deviations were encountered and all of them were adequately discussed. Each of the three ONS-5010 active substance PPQ lots met all release specifications and acceptance criteria.

Reprocessing is not foreseen at any steps and membranes are all single use. The study on re-filtration at the virus nanofiltration step after integrity testing was of characterisation purposes only and reprocessing is not registered for this step either.

Intermediate Hold time studies:

Samples were stored in sample bags constructed of polyethylene, a representative product-contact material that is utilised for the bulk intermediate totes utilised at-scale during manufacturing. In-process hold times (6 process hold points) were validated using in-process samples from commercial scale batches. Based on the physicochemical testing of the samples and the microbial tests the proposed hold times are acceptable. In addition, hold times for buffers and cell culture media are adequately validated.

Resin lifetime studies:

Lifetime studies of the chromatography resins were performed in small-scale models with the same models utilised to execute process characterisation studies. Further, qualification of small-scale models is adequately described and performed. Based on the studies, the target maximum resin lifetimes have been set.

Carry-over studies were performed to evaluate cleaning of the columns. The study is performed in small-scale columns. Available data demonstrate sufficient cleaning of the columns.

Impurity clearance:

Impurity clearance studies were performed with small-scale columns. Evaluated impurities included host Cell DNA, host cell protein (HCP) and residual Protein A. Sufficient clearance of process-related impurities was demonstrated.

Extractables/leachables:

Levels of extractables and leachables have been investigated for material in contact with the active substance during the manufacturing process. Worst case studies detected levels of caprolactam and silicone, but clearly below levels of toxicological concern. The presented study is regarded sufficient.

Shipping validation:

The applicant presented an acceptable bracketing approach, where both the minimum and maximum load of ONS-5010 active substance were used to challenge the maximum distance in which ONS-5020 will be

transported. The shipment of approximately two days of transport duration could maintain the active substance container within -20 ± 5°C.

Overall, the active substance manufacturing process is considered adequately validated.

Manufacturing process development

Throughout development, three different process versions were used:

- A1.0 for non-clinical studies and early-phase clinical trials;

- A1.1 for phase 3 clinical trials;

- B1 (commercial process).

In the course of a tech transfer and scale up between the different process versions and sites, a risk assessment of each unit operation was conducted and is endorsed.

Overall, the upstream and downstream process characterisation studies (PCS), OFAT (one-factor-at-a-time) and DoE (multi-variate design-of-experiments) provided insight in the process ranges and impacts on product quality attributes. Results of the studies were and are planned to be combined with manufacturing experience from PPQ manufacturing and will allow for continuous re-assessment of failure modes and effects analysis (FMEA) parameters and scoring.

Subtle changes between process A1.0 and A1.1 were introduced. The main changes of the production process came with introduction of process B1.0.

An overview of the changes related to specifications and analytical methods between the different process versions has been submitted.

Comparability:

Analytical comparability of the active substance obtained from process version A1.0, A1.1 and B1.0 has been investigated in two comparability studies. Testing was generally performed in a side-by-side manner and/or using historical batch data. The set of analytical procedures applied to investigate analytical comparability is deemed adequate to detect changes in relevant quality attributes of bevacizumab gamma.

Comparability of process versions A1.0 and A1.1:

In sum, the presented data demonstrate comparability of bevacizumab gamma active substance originating from processes A1.0 and A1.1. The observed minor differences are not further discussed by the applicant. However, it is not expected that they affect the clinical performance of bevacizumab gamma.

Comparability of process versions A1.1 and B1.0:

For most quality attributes, similar physicochemical and functional results were obtained by side-by-side testing and thermal stress stability testing comparing active substance from process A1.1 with active substance from process B1.0 Observed minor differences are unlikely to impact clinical performance of the product. The binding and other biological activities are highly comparable for A1.1 and B1.0 active substance.

Overall, the presented data indicate comparability of active substance across the different development stages. Upon request, the applicant has presented a satisfying rationale for the rather low number of used pre-change batches for the comparability study between process variants.

Characterisation

Elucidation of structure and other characteristics:

The applicant characterised physicochemical and biological properties of ONS-5010 using orthogonal, state-of-the art qualified analytical methods in accordance with the guideline ICH Q6B. Seven ONS-5010 active substance batches manufactured according to the intended commercial process (i.e. B1.0) have been characterised. The characterisation of the structures (primary, secondary, and higher order), purity/impurities, charge variants, potency, and binding activity demonstrate a high level of conformance and quality observed among ONS-5010 lots.

A comprehensive control strategy is in place to ensure process consistency through the in-process control and monitoring of process and product related impurities, release, and stability testing programs.

Overall, characterisation of the active substance is considered satisfactory.

Specification

Specifications

The proposed specification for ONS-5010 active substance includes a comprehensive set of tests that have been developed and validated to characterise protein content, identity, purity, potency, and other general compendial tests. The test were chosen based on physicochemical, and biological characterisation, validation of the manufacturing process, pharmaceutical development and stability studies conducted on the active substance.

The stability specification acceptance criteria are nearly set as tight as for release specifications and comprise the same methods with the exception of testing for identity, process-related impurities and osmolality. As no change in these parameters is expected, this is deemed acceptable. Polysorbate 20 content is also not foreseen to be tested during stability studies, which is acceptable as it is foreseen to be tested during finished product stability studies.

The overall set of test methods for specification and acceptance criteria are chosen in compliance with ICH topic Q6B, Ph. Eur. And EMA/CHMP/BWP/532517/2008 and are considered acceptable. Method identifiers (respective SOP numbers) have been included for all methods. This applies to the methods of the active substance and of the finished product specifications.

Justification of specification:

The acceptance criteria have been established based on product specific knowledge and release/stability data of batches manufactured according to Process A1.0, A1.1 and B1.0 that have been used as engineering, primary batches, clinical batches, one toxicology batch and supportive batches.

Additional justification has been provided and the proposed release and shelf life acceptance limit is considered acceptable**.**

The release and shelf life specifications for the active substance are considered acceptable.

Analytical procedures

The analytical procedures used during release and stability testing of the ONS-5010 active substance are described and key instruments, reagents and materials are presented in tables and figures. ONS-5010 active substance quality attributes are tested with at least one suitable analytical method; additional orthogonal

methods are also described for testing of certain quality attributes. ONS-5010 active substance is tested against reference standards, whenever possible. The analytical methods have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. Validation summaries as well as detailed validation reports have been provided for those methods which are not conducted according to the Ph. Eur. Compendial methods are performed according to the respective Ph. Eur.

Validation of analytical procedures

Overall, the presented validation and verifications of the analytical methods for protein content, identity, purity, potency, and other general compendial tests as well as process related impurities used for analysis of IPC, active substance and finished product samples (where applicable) are adequate and in accordance with ICH Q2(R1) and demonstrate the suitability of the analytical procedures for their intended use. As requested, the applicant clarified in a comprehensible way that ONS-1045 is the same material as ONS-5010 and that the name ONS-1045 was used in early development. It is used synonymously to ONS-5010. The characterisation of the commercial anti-CHO HCP assay revealed a limited coverage of the proteins derived from the ONS-5010 cell line.

Summaries of method transfer studies to the respective testing sites have been provided and are found acceptable.

Batch analyses

Batch analyses data are presented for batches manufactured according to Process B1.0. These batches have been used for batch consistency, stability, clinical trial, working reference standard, and process performance qualification. All results comply with the specifications valid at time of testing.

Further, batch data for clinical scale batches manufactured according to process A1.0 and clinical scale batches manufactured according to process A1.1 are presented. These batches were used for batch consistency, stability, non-clinical toxicology, finished product for phase 1 IV trial, system suitability standard, active substance for finished product phase 3 clinical trials, interim reference standard and PCS. All results comply with the specifications valid at time of testing.

In summary, the presented data resulted from representative batches and demonstrate that the manufacturing process reliably delivers ONS-5010 active substance batches of consistent quality.

Reference standard

The origin of five reference standards used throughout development of ONS-5010 is satisfactorily described. The reference standards were either commercially available US- and EU-bevacizumab lots or were manufactured from ONS-5010 active substance batches representing the respective development stage.

Reference standard lot 626307 was a commercially available US bevacizumab gamma lot and was chosen as the starting point and qualified REF-2016-003, an EU commercial bevacizumab lot.

The qualification history of the reference standards is adequately described and the fact that a comparability study between processes A1.1 and B1.0 has been performed, is endorsed. However, the applicant did not compare the in-house reference standards with the first WHO international standard of bevacizumab gamma. The applicant presented a justification on keeping the in-house reference standard.

The set of release tests for the reference standard material appears meaningful and certain acceptance criteria were tightened upon request.

The stability protocol and the set of stability tests for the ONS-5010 primary reference standard material is well chosen and the extended characterisation methods for release and stability are endorsed. The specifications for primary reference standard stability testing for certain quality attributes were harmonised between sections upon request.

The selection of future reference standards is sufficiently described.

Container closure system

The active substance is stored in single use EVA bags with 1 inlet, 1 outlet and a sampling tubing port. Bags are pre-sterilised by gamma irradiation and protected by a semi rigid cassette from high density polyethylene (HDPE). The ONS-5010 active substance container closure system is adequately described. Concerning the primary packaging container materials of construction, contact materials meet USP Class IV Biological Test for Plastics and USP <87>, <88> and <661> requirements and the container closure system (CCS) meets the requirements set in the specifications. The CCS showed to be suitable for use, according to photostability, biocompatibility and leachable studies.

In summary, the active substance container closure system is considered suitable.

Stability

The ongoing stability studies are conducted at different storage conditions. All primary stability lots, manufactured using commercial active substance ONS-5010 manufacturing process were placed at the recommended storage temperature of -20 ± 5°C, and at accelerated temperature of 5 ± 3°C and stressed temperature of 30 ± 2°C/65% RH ± 5%. Supportive ONS-5010 stability lots manufactured using process A1.0, and lots manufactured using process A1.1, as well as a lot manufactured using Process B1.0 were also placed on stability at the recommended storage temperature of -20 ± 5°C and at the accelerated temperature of 5 ± 3°C and the stressed temperature of 30 ± 2°C/65% RH ± 5%.

The stability studies are designed in accordance with ICH Q5C and ICH Q1A (R2).

Tested quality attributes are identical to those tested at active substance release, with exceptions for identity, process related impurities, osmolality and polysorbate 20 content, which were not tested, which is acceptable.

Regarding primary batches full stability datasets at -20 ± 5°C of 36 month (plus accelerated and stressed up to 12 months) are available. For a second primary batch, 18 month data (plus accelerated and stressed data up to 12 months) have been submitted. For a third primary batch, data at -20 ± 5°C for 12 months (plus accelerated/stressed up to 12 months) are available.

Regarding supportive stability lots, sufficient 36 months real-time and accelerated/stressed data are available. The supportive batches were partly manufactured by a manufacturing process differing from the commercial process, but comparability between manufacturing processes could be shown. As such, data from these additional batches, can be used to support the to date limited dataset of primary stability batches.

The applicant has provided a full 36 month data-set (real time -20 ± 5°C) for two active substance lots, namely (engineering batch) and (primary batch), produced according to the commercial manufacturing process. Further, 12 months data from accelerated (5 ± 3°C) studies for six active substance lots manufactured by the commercial manufacturing process were presented. In addition, 18 months long term storage data have been provided for a primary active substance batch. The data provided, support long term storage of the active substance at -20°C ± 5°C for this storage period. As such and in compliance with ICH

Q5C, long term stability data over 18 months from active substance batches (engineering and primary batches and manufactured according to the commercial process) have been presented.

Upon request for shelf life correction, the applicant revised its shelf life claim to 18 months,
The post approval stability protocol and commitment are provided and is acceptable.

Overall, the acceptable shelf life for the active substance is 18 months when stored at -20 ± 5°C in the described CCS.

Finished Medicinal Product

2.3.2.2. Description of the product and pharmaceutical development

Description of the product

ONS-5010 finished product is a sterile solution for intravitreal injection containing bevacizumab gamma as active substance and is supplied in one strength (25 mg/mL). The formulation of active substance and finished product are identical. The container closure system consists of a single-use Type I 2 mL borosilicate glass vial with a chlorobutyl rubber stopper with a Flurotec coating. The minimum fill volume (0.3 mL) is sufficient to withdraw the nominal volume (0.05 mL) and dose of 1.25 mg of bevacizumab gamma.

Bevacizumab gamma is formulated with sodium phosphate monobasic monohydrate (sodium dihydrogen phosphate monohydrate), sodium phosphate dibasic, anhydrous (disodium hydrogen phosphate), trehalose dihydrate, polysorbate 20 and water for injections. All excipients are commonly used and of compendial quality. Sodium phosphate monobasic monohydrate cannot be located in the Ph. Eur. But in the USP only. Nitrogen, used for overlay, is listed as a component, but not considered as an excipient, this approach is acceptable.

The components of the finished product - active substance and excipients – are adequately described and references to the respective sections are included. No excipients of animal or human origin are used.

Pharmaceutical development

The formulation of ONS-5010 active substance and ONS-5010 finished product are identical. No formulation step takes place during finished product manufacturing. The development of the formulation of the finished product is based on the initial development of the substance as a biosimilar to the commercially available bevacizumab. Since ONS-5010 is designed for intravitreal administration, the search of excipients permitted for formulation and stabilisation of intravitreal ophthalmic products guided the formulation studies. The protein concentration (25 mg/mL) was defined from the beginning and not subject to further development studies. The pH range, the buffer system and the use of trehalose dihydrate as a stabiliser were evaluated in studies, which confirmed the chosen formulation.

The dose volume is 0.05 mL and an overfill of 0.25 mL per vial is applied. ONS-5010 is manufactured without overage.

The finished product manufacturing process involves active substance thawing and homogenisation, sterile filtration, filling into glass vials and stoppering, visual inspection, and packaging and labelling. The active substance is fully formulated and there is no additional formulation activity involved during finished product manufacturing.

A CQA assessment was conducted for active substance and finished product together. As part of development, process parameters affecting product CQAs at each step of the manufacturing process were identified. All process parameters underwent a quality risk assessment to identify CPPs impacting finished product CQAs. NORs based on process knowledge from previously manufactured finished product batches were established. The ranges were challenged concurrently with PPQ. Critical IPCs were identified as preventive controls to mitigate processing risks that lead to potential impact on CQAs. The description of identification of CPPs is found to be acceptable.

Thawing conditions including considerations of time, batch size and mixing speed were evaluated. The bulk finished product is sterile filtered through sterile filters into a sterile single use, bag. The chemical compatibility of the filter membrane with the finished product and potential binding of the finished product to the membrane were evaluated by respective studies under worst case conditions. In addition, a study to evaluate extractables and potential leachables from the filter was performed. These filter studies conformed adequacy of the selected filter.

The product contacting materials used in the finished product manufacturing process were evaluated for the risk of potential leachables considering a respective evaluation already done for the active substance manufacturing process. For the materials identified as high risk an extractable assessment was performed. The data provided on extractables assessment on product contacting manufacturing materials is considered to be sufficient.

Standard materials for the primary packaging of medicinal products, which are in line with Ph. Eur. Requirements, have been selected for primary packaging of ONS-5010 finished product and have been the same for clinical trials, supportive stability, registration stability, and intended commercial production. The primary container closure system for ONS-5010- finished product consists of a 2 mL Type 1 borosilicate glass vial, a chlorobutyl rubber stopper with Flurotec® coating and an aluminium seal with a plastic flip-off cap. Suitability of the primary packaging container closure system in terms of container closure integrity and compatibility with the finished product has been demonstrated. Integrity of the CCS is evaluated by helium leak testing during stability testing which confirmed container integrity.

The microbiological attributes of ONS-5010 finished product are sufficiently described. The process design and microbial controls ensure adequate microbiological quality.

The solution from the vial is intended to be transferred with a commercially available filter needle to the commercially available injection syringe (not co-packed with the medicinal product) prior to use for intravitreal injection.

Administration of ONS-5010 by medical professionals is directed by the SmPC. A summary of a dosing consistency and product recovery study has been provided to demonstrate dosing consistency and product recovery of ONS-5010 with the administration components used during clinical trials.

In general, the information provided under section Pharmaceutical Development is not very detailed; but considering the type and low complexity of manufacturing operations (thawing of active substance and filling into primary containers), this is considered sufficient.

Manufacture of the product and process controls

Description of the manufacturing process

The finished product is manufactured, tested and released at facilities which operate in accordance with EU GMP.

Batch formula has been provided. As requested, the amount per dose (per vial) has been included in the table for batch formula.

The manufacturing process is based on standard pharmaceutical processing steps (i.e., preparation of components, thawing and homogenisation of bulk active substance, sterile filtration, aseptic filling and stoppering, capping, sealing, 100% visual inspection and labelling and packaging).

All product contact components used in the manufacturing process are single-use and are either purchased pre-sterilised or are steam sterilised or depyrogenated prior to use at the finished product manufacturing site. Flow charts for the manufacturing process, including IPCs have been provided and a narrative description of each step is given. In addition, information on hold times and processing times during the manufacturing process has been presented. The finished product manufacturing process is described in sufficient details and in line with the requirements of the guideline on the manufacture of the finished dosage form (EMA/362427/2017). As requested, the batch numbering system for commercial finished product has been described. No reprocessing is foreseen for finished product manufacturing.

The critical process steps and the critical and non-critical process parameters are described. The identified CPPs include thaw duration, hold temperature, mixing duration, mixing and homogenisation process duration, filtration flow rate, filtration pressure and filtration duration, fill volume, fill weight, line speed, crimper setting, recipe/format number, nitrogen overlay set point, bulk processing yield. Process and hold time limits for the manufacture of the finished product are presented and are supported by data. The proposed IPC tests and the acceptance criteria are mainly in line with expectations for this type of process. No explicit classification of IPC is given, but indirectly explained over differentiating between action limits or acceptance criteria.

Process validation

A summary of the PPQ batch data has been provided. The performed process validation followed a traditional approach on three consecutive, commercial scale batches, produced from one single active substance batch only. In addition, data from further finished product batches that were manufactured prior to the PPQ batches from further active substance batches and according to the commercial finished product process have been provided to support process consistency. In order to account for the variability of the active substance as the starting point for the finished product process, the batches designated to be part of the PPQ should be manufactured from independent active substance batches. Thus, the applicant has provided release data on further batches that were considered for complementing the PPQ and were manufactured under the PPQ protocol. These additional batches have been included into the respective dossier section summarising the PPQ and containing the actual PPQ results.

During the PPQ campaign selected process parameters (CPP, non-CPP) were challenged to ensure reproducibility across the three consecutive finished product lots. The other process parameters were set on target. Data are provided in order to demonstrate homogeneity during filling have been provided. For the crimping operation a separate validation study was performed.

The total time out of refrigeration time and maximum processing time were challenged during the manufacture of one PPQ lot. Provided data on media fills (1 batch) support the storage temperature and time of the sterile filtered bulk, with regards to microbial control. According to the applicant, data collected from the PPQ lots met the pre-established (PPQ protocol, not submitted) process parameter control criteria. A list of deviations encountered during the PPQ is provided and found acceptable.

The stoppers are sterilised in an autoclave. Information on the sterilisation site and cycle is provided and is in accordance with Ph. Eur. The vials are sterilised and depyrogenated in a despatch depyrogenation oven. The qualification of the depyrogenation oven demonstrates that, in line with Ph. Eur. 5.1.1, a 3 log reduction in heat-resistant endotoxins is achieved. Production conditions for depyrogenation of vials are provided.

Aseptic manufacturing is regularly confirmed by media fills. The conditions applied for these media fill runs cover the conditions during ONS-5010 finished product manufacture. The media fills were performed with a different fill volume (1 mL) compared to the commercial fill volume for ONS-5010 finished product (0.3 mL), which is acceptable considering the larger volume as a worst case.

A summary on sterile filter validation has been provided including summaries on bacterial retention, filter compatibility and filter extractable studies. The main aspects for sterile filter validation have been considered by the applicant. Detailed information on bacterial retention and filter compatibility study have been provided.

Information on transport verification for finished product shipment has been provided. Upon request, further data with regards to shipment at summer conditions and justification on the representativeness of the shipping lane selected for qualification studies have been provided.

Overall, the finished product manufacturing process is considered adequately validated.

Product specification

Specifications

The proposed finished product release and shelf life specifications have been provided and comply with the requirements of general monographs Ph. Eur. 2031 (Monoclonal Antibodies for human use) and 0520 (Parenteral Preparations) as well as with ICH guideline Q6B. The proposed specifications include a comprehensive set of tests developed and validated to characterise protein content, identity, purity, potency, and other general compendial tests. In addition, polysorbate 20 concentration is included in the specifications.

The applicant has provided sufficient additional explanation with regards to the justifications of specifications.

The applicant has provided actual batch data currently available for polysorbate 20 content. The tested batches include the three initial and two additional PPQ batches. No formal stability data are available for polysorbate 20 content.

The release and shelf life specifications for the finished product are considered acceptable.

Analytical procedures

Analytical methods for finished product release and stability testing are described. Sufficiently detailed descriptions on the analytical methods have been provided for the non-compendial methods. Method identifiers have been included for all methods (in order to maintain a clear link between specifications, methods and methods validations), upon request. For compendial methods, the respective Ph. Eur.

Monograph is referenced. The analytical methods appear adequate for their intended purpose. The capability of the stability indicating methods to detect product degradation/modification has been adequately demonstrated by forced degradation studies and during method validation.

For methods performed at the active substance level as well, respective validation has been described under the active substance section. The presented validation and verifications of the analytical methods specific for finished product are adequate and in accordance with ICH Q2(R1) and demonstrate the suitability of the analytical procedures for their intended use.

Batch analyses

Finished product release testing results from ONS-5010 finished product batches used for toxicology, stability, and clinical supplies are summarised. Release testing results from the consecutive PPQ batches intended for process confirmation and commercial distribution are also provided.

All batch analysis results meet the specifications that were in effect at the time of testing and release for each batch. All available release data from the finished product batches produced during the PPQ campaign meet the commercial release specification acceptance criteria.

Reference standard

The same reference standards are used for active substance and finished product (see above).

Characterisation of impurities

Since the ONS-5010 active substance and finished product are the same formulation and concentration, the expected impurities are the same.

The applicant provided a risk evaluation regarding the potential presence of nitrosamines in the finished product. The risk is considered low and no mitigation measure is considered necessary. This is acceptable.

Characterisation testing of ONS-5010 finished product was executed to evaluate the actual levels of elemental impurities as defined in ICH Q3D (R1). Levels of detected impurities are well below permitted daily exposures. This is acceptable.

Impurities are adequately addressed and controlled.

Container closure system

A detailed description of each of the CCS components is provided in the dossier.

Stability of the product

Stability studies were performed in accordance with ICH Q5C. Upon request the applicant has sufficiently justified the selected conditions for accelerated stability studies. Conditions tested for long-term storage, duration of the testing and sampling times are overall considered acceptable.

Forced degradation studies performed on the active substance, indicate, that the finished product is sensitive to photo stress and as such the finished product should be protected from light over the course of its shelf life.

Upon request the stability protocol has been modified in order to include determination of polysorbate 20 content and alignment with the specifications. Upon request, data considering a potential degradation of polysorbate 20 over the shelf life of the product have been provided.

Long-term stability data have been provided for the primary/clinical batches and PPQ batches. Data from accelerated stability studies indicate a similar trending of critical quality attributes across all batches, when stored at accelerated storage conditions.

Based on the provided stability data and the supportive data on polysorbate 20 content over time, the proposed shelf life of 24 months at 5°C is acceptable.

The statement in package leaflet and SmPC, with regards to storage of the unopened vial at room temperature (below 25°C) has been set to a maximum storage period of 12 hours.

The SmPC states that administration has to take place immediately after preparation of the dose. No in-use stability data have been provided. However, compatibility data with commonly used filter needle (5 micron sterile filter needle, 18-gauge × 1½ inch (micro acrylic copolymer filter; polycarbonate/stainless steel needle or equivalent)) and administration syringe (1 mL sterile silicone-free syringe with marking to measure 0.05 mL (polypropylene/polyethylene or equivalent)) have been provided upon request.

Post-approval stability protocol and stability commitment are provided.

2.3.2.3. Biosimilarity

Not applicable.

Adventitious agents

Multiple complementing measures are implemented to ensure product safety with regard to non-viral and viral adventitious agents. The measures include selection and testing of materials, testing of cell banks and process intermediates, testing of microbial attributes as IPCs and at release, implementation and validation of dedicated virus clearance steps and steps contributing to virus reduction. In addition, microbial quality is ensured by process design (microbial reduction filtrations, sterile filtration, aseptic processing) and adequate sanitisation procedures. With regards to sanitisation of chromatography columns additional information has been provided upon request.

The applicant has included additional information in the dossier or referred to other parts of the dossier on the origins: origin of materials used in the manufacture of MCB, WCB, active substance and finished product and respective TSE certifications/statements, testing of cell banks and control of non-viral and viral adventitious agents throughout the manufacturing process. References to the respective Ph. Eur. Monographs (actual number of the monograph) used for testing for absence of bacterial/fungal contamination and mycoplasma have been included.

Information on the inclusion of hold and non-spike controls in the viral clearance studies has been provided. Furthermore, sufficient additional justification has been provided with regards to the adequacy of chromatography column sanitisation also in connection with detected viral carry-over.

The ONS-5010 active substance manufacturing process includes five orthogonal steps with the capacity to inactivate or remove potential adventitious virus. Four model viruses were chosen for viral validation studies. The outcome is satisfactory in terms of viral safety.

Based on the information provided by the applicant, adventitious agents safety is considered demonstrated.

2.3.3. Discussion on chemical, pharmaceutical and biological aspects

Active substance

ONS-5010 active substance (bevacizumab gamma) is a recombinant humanised monoclonal antibody produced by DNA technology in Chinese Hamster Ovary cells, belonging to the class of compounds known as ophthalmic vascular endothelial growth factor (VEGF) inhibitors.

Bevacizumab gamma is manufactured using a standard manufacturing process for monoclonal antibodies. ONS-5010 active substance is expressed in fed-batch mode in a CHO cell line and subsequently purified by a series of column chromatography steps, followed by ultra/diafiltrations. Two dedicated virus clearance steps are implemented in the active substance manufacturing process. The manufacturing process including process parameters and IPCs have been described in sufficient detail. Valid manufacturing authorisations and/or GMP certificates for the manufacturing sites are available.

Raw and starting materials used in the manufacture of active substance are listed, identifying where each material is used in the process. Sufficient information on the quality and control of these materials has been provided. The expression system and cell banks intended for commercial manufacture are sufficiently characterised and qualified, respectively.

CQAs of ONS-5010 active substance have been determined, and as requested, justifications for the designation of the presented CQAs with respect to the QTPP have been presented and re-evaluated using a tiered approach assigning the quality attributes respective to their impact on product quality. The applicant extensively characterised the bevacizumab gamma molecule and its variants using orthogonal state-of-the art analytical methods. The degradation pathways of bevacizumab gamma have been evaluated in forced degradation studies.

An adequate process control system is in place, which ensures a consistent routine manufacture of ONS-5010 active substance. The provided batch analyses data show sufficient consistency of active substance batches. The submitted process characterisation and validation data support the conclusion that the commercial active substance manufacturing process (B1.0) reliably generates active substance (and subsequently finished product) meeting its predetermined specifications and quality attributes. Column lifetimes are supported by small-scale validation data; protocols for concurrent validation at large scale are available. Reprocessing is not foreseen at any steps and membranes are all single use.

Hold times are sufficiently justified. Removal of product-related impurities, process-related impurities, residual raw materials and leachables to acceptable low levels has been demonstrated or sufficiently justified. A validated shipping process has been established.

Process development and changes implemented with the different process versions of the active substance manufacturing process are sufficiently described and justified. ONS-5010 active substance originating from the different process versions (A1.0, A1.1 and B1.0) used across development and commercial manufacture was shown to be comparable; the limited use of batches during the comparison studies has been justified.

Characterisation of physicochemical and biological properties of ONS-5010 using orthogonal, state-of-the-art analytical methods, was done.

The proposed active substance specifications are tightly linked to the finished product specifications and are mostly considered acceptable. Some acceptance criteria were tightened upon request. Descriptions of the analytical methods including method identifiers were provided. The presented validation and verifications of the analytical methods used for analysis of IPC, active substance and finished product samples (where

applicable) are adequate and in accordance with ICH Q2(R1) and demonstrate the suitability of the analytical procedures for their intended use.

A WHO reference standard is available for the bevacizumab molecule.

Active substance is stored in single use bags. The CCS is sufficiently described. From a current perspective, there is no risk related to extractables and leachables.

Except for the engineering batch, which was manufactured according to the commercial process, supportive stability data have been derived from batches produced with manufacturing processes A1.0 and A1.1; these lots were placed on stability in containers differing in material composition compared to the primary stability lots produced with commercial manufacturing process B1.0. Upon request, the applicant presented satisfying information on the usage of differing container materials.

The applicant proposes a shelf-life claim of 18 months according to available real-time data sets from batches, which is acceptable.

Finished product

ONS-5010 finished product is a sterile solution for intravitreal injection containing bevacizumab gamma as active substance and is supplied in one strength. The container closure system consists of a single-use Type I glass vial with a chlorobutyl rubber stopper with a Flurotec® coating. The minimum fill volume (0.3 mL) is sufficient to withdraw the nominal volume (0.05 mL) and dose of 1.25 mg of bevacizumab gamma. ONS-5010 solution for injection contains 25 mg/mL bevacizumab gamma as active substance, sodium phosphate monobasic monohydrate and 1 sodium phosphate dibasic, anhydrous as buffering agents, trehalose dehydrate and polysorbate 20 as stabilisers, and water for injections.

The manufacturing process of ONS-5010 finished product comprises preparation of components, active substance thawing and homogenisation sterile filtration and aseptic filling and is adequately described. The definition of CQAs and overall control of the process appears reasonable. Process characterisation process validation and batch data indicate that the manufacturing process reliably generates finished product meeting its predetermined specifications and quality attributes. Valid manufacturing authorisations and/or GMP certificates are available for the finished product manufacturers. Information on process validation is not very detailed but summaries have been provided that contain the most important elements in order to demonstrate validity of the manufacturing process. The performed process validation followed a traditional approach on consecutive, commercial scale batches, however, produced from one single active substance batch only. Additional batches from independent active substance batches have been manufactured according to the PPQ protocol.

The excipients comply with the requirement of respective Ph. Eur. monograph and no novel excipient is used in the finished product. No excipients of human or animal origin are used in the manufacture of the finished product.

The proposed finished product specifications are tightly linked to the active substance specifications, are generally in line with requirements of general monographs Ph. Eur. 2031 and 0520 and ICH Q6B and are acceptable. Descriptions of the analytical methods are mostly sufficiently detailed; the methods are appropriately validated.

An overview on a nitrosamine risk assessment is included in the dossier and is considered to be sufficient.

Reference standards are described under the active substance section.

The chosen CCS is adequate and is adequately described.

A shelf life of 24 months is proposed for ONS-5010 finished product when stored at 5 ± 3°C in the commercial container closure system, stored in the marketing pack to protect it from light. Based on the provided additional stability data and the supportive data on polysorbate 20 content over time, the proposed shelf life 24 months at 5°C can be endorsed.

Upon request the applicant provided data from a photostability study according to ICH Q1B in order to demonstrate adequacy of the commercial packaging of ONS-5010 finished product with regards to protection against light exposure, which is acceptable.

Adventitious agents

The risk for transmission of adventitious agents is adequately controlled and minimised by complementary measures implemented at various stages of the manufacturing process.

Comparative assessment of ONS-5010 and Avastin

The applicant submitted in accordance with Article 8(3) of Directive 2001/83/EC a full-mixed MAA for the treatment of AMD. Hence, this application relied partially on the applicant's own studies, but also on literature references. At the time of submission, together with two pivotal Phase 3 studies with Lytenava, the applicant provided data on clinical comparability (IV bioequivalence study vs Avastin (bevacizumab) in healthy subjects). However, bridging at the quality level was not sufficiently established. In order to extrapolate bibliographic data of Avastin used in the (off-label) treatment of AMD as supportive evidence for Lytenava, a quality comparability bridging data exercise between ONS-5010 and Avastin was provided by the applicant.

2.3.4. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Lytenava is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

Recommendations for future quality development have been agreed by the applicant.

In conclusion, based on the review of the data provided, the MAA for Lytenava is considered approvable from the quality point of view.

Recommendation(s) for future quality development

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

2.4. Non-clinical aspects

2.4.1. Introduction

The applicant submitted a full-mixed application for its medicinal product ONS-5010 (Lytenava), containing bevacizumab gamma, a recombinant humanised monoclonal immunoglobulin (IgG) gamma antibody against human VEGF, indicated for the treatment of neovascular age-related macular degeneration (nAMD).

Bevacizumab selectively binds with high affinity to all isoforms of human VEGF. The binding of VEGF-A to VEGFR-1 and VEGFR-2 results in the activation of survival pathways leading to endothelial cell proliferation and angiogenesis. Bevacizumab neutralises the biological activity of VEGFs through a steric inhibition of the binding of VEGF to its receptors Flt-1 (VEGFR-1) and KDR (VEGFR-2) on the surface of endothelial cells (Gerber and Ferrara 2005; Presta et al. 1997).

2.4.2. Pharmacology

To assess the pharmacodynamic properties of the active substance, bevacizumab gamma, in the intravitreal formulation ONS-5010, several functional *in vitro* assays were conducted with the intravenous dosage form ONS-1045.As another intravenous bevacizumab formulation (Avastin) is currently used off-label in the treatment of nAMD, all these assays were conducted with ONS-1045 in comparison to EU-Avastin as well as US-Avastin batches.

Functional *in vitro* assays with ONS-5010 are also included in Module 3 of this marketing authorisation application. Therefore, please refer to the quality section for a detailed review of these studies.

2.4.2.1. Primary pharmacodynamic studies

For the investigation of bevacizumab's mode of action, dose-dependent inhibition of VEGF-mediated HUVEC (human umbilical vein endothelial cell) cell proliferation was assessed by measuring a luminescence signal produced by viable cells and IC_{50} values were calculated. Furthermore, binding of bevacizumab to $VEGF_{165}$ was determined by an enzyme-linked immunosorbent assay (ELISA).

The results of the HUVEC cell proliferation and $VEGF_{165}$ binding assay revealed a similar concentration-dependent inhibition of VEGF by ONS-1045 and its comparator Avastin.

As bevacizumab is a well-known active substance, and it has been in use as anti-cancer therapy as well as off-label (Avastin) in the treatment of nAMD for several years, the applicant submitted literature references of primary and secondary pharmacodynamics *in vitro* and *in vivo* studies related to retinal indications.

Overall, in vitro studies in human microvascular endothelial cells have shown, that bevacizumab is noncytotoxic, increases apoptosis, decreases cellular proliferation, migration, vascular assembly and VEGF secretion and also decreases VEGFR expression and activity. The Fc domain and sugar residues present on bevacizumab mean that the antibody can interfere with the physiological metabolism or functioning of retinal cells and result in complement-mediated cell death. (Meyer and Holz 2011)

Overall, *in vivo* studies in rabbit and monkey models of corneal and choroidal neovascularisation have consistently demonstrated that the intravitreal administration of bevacizumab reduces the formation of neovascularisation lesions and attenuates vascular leakage from lesions, with mixed results in rat and murine models of choroidal neovascularisation. In monkeys, a dose of bevacizumab as low as 0.5 mg/eye was effective when administered intravitreally.

2.4.2.2. Secondary pharmacodynamic studies

No specific studies on secondary pharmacodynamics were conducted with ONS-1045. However, the assessment of Fab- and Fc-associated functions were included in the in vitro comparability exercise.

Results revealed approximately comparable relative FcRn, FcγRI and FcγRIIa binding (%) of Avastin (EU- and US-licenced) to ONS-1045, whereas the affinity of ONS-1045 to one FcR was apparently higher than for commercial bevacizumab (EU- and US-licensed). Relative C1q binding (%) values were comparable as well, but nevertheless slightly higher for ONS-1045 than for commercial bevacizumab. No ADCC activity was observed, neither for US- and EU- licenced bevacizumab, nor for ONS-1045.

The applicant also conducted a literature search regarding off-target activities of bevacizumab.

As bevacizumab does not undergo degradation in the eye (Semeraro et al. 2015) and systemic metabolism and elimination of bevacizumab is similar to that of endogenous IgG (Heroman and Kaplan 2010), off-target toxicity for monoclonal antibodies such as bevacizumab is rare, and any effects observed are likely to be directly related to the pharmacology of the molecule, i.e., the inhibition of physiological angiogenesis (Martin and Bugelski 2012). As reported by Kim et al. 2009, topical administration of bevacizumab delayed epithelial healing in rabbit cornea at 1.0, 1.5, 2.5, or 5 mg/mL. In contrast, as investigated by Cornacoff et al. 2008, wound strength was reduced in macaques undergoing skin incisions, when bevacizumab was administered intravenously at 20mg/kg. Ryan et al. (1999) investigated tissue cross-reactivity or nontarget tissue binding of recombinant humanised antivascular endothelial growth factor (rhuMAbVEGF) in normal adult human, cynomolgus monkey and rabbit tissues by immunohistochemistry, with no observations made at any dose and in any species.

2.4.2.3. Safety pharmacology programme

No dedicated safety pharmacology studies were conducted with bevacizumab gamma.

Cardiovascular safety was assessed within the course of the good laboratory practice (GLP)-compliant comparative toxicity and toxicokinetic study conducted with ONS-1045 and Avastin, where cynomolgus monkeys received intravenous (slow bolus) biweekly administrations of bevacizumab (ONS-1045 or Avastin, 50 mg/kg/dose) or control for 4 weeks.

No treatment related effects were observed for any cardiovascular safety parameters [e.g. heart rate (HR) from RR interval, PR, QRS and QT durations and QTcT (QT corrected for HR using individual animal corrections)] determined in this *in vivo* study.

2.4.2.4. Pharmacodynamic drug interactions

Since the systemic exposure of ONS-5010 in humans is assumed to be low following intravitreal administration, the applicant did not conduct any pharmacodynamics drug interaction studies. As parenteral administered bevacizumab is currently in use as anti-cancer therapy, literature regarding pharmacodynamics drug interactions is available for bevacizumab in combination with other anti-cancer-drug therapies (Avastin SmPC 2021; Avastin USPI 2020).

2.4.3. Pharmacokinetics

The applicant did not conduct specific studies on the pharmacokinetics of ONS-5010 but provided published studies on the general PK properties of bevacizumab after intravitreal or intravenous administration to rabbits or monkeys. The GLP-compliant repeat-dose toxicology study (Study HUD0445) of ONS-1045 in monkeys included a toxicokinetics component. Slight differences were observed regarding toxicokinetics between ONS-1045 and Avastin over time in monkeys intravenously administered over 4 weeks. However, the kinetics of

bevacizumab are already sufficiently known from clinical studies and the systemic exposure after intravitreal administration is negligible as demonstrated in clinical studies.

With regard to absorption of bevacizumab after ocular or non-ocular administration the applicant provided a literature-base discussion.

Synoptically, the intravitreal half-life for bevacizumab in rabbits was 4.2 days and C_{max} of bevacizumab was reached at Day 1 in both vitreous and aqueous humour, with very low concentrations of bevacizumab in the fellow noninjected eye and low systemic exposure. Intravitreal injection of bevacizumab in monkeys was shown to penetrate the retina and also be transported into the retinal pigment epithelium, the choroid and, in particular, into photoreceptor outer segments. Ocular VEGF concentrations were decreased for at least 4 weeks post-injection, with minimal effects on the untreated fellow eyes and low systemic exposure. Intravitreal PK studies of bevacizumab in rats and rabbits have demonstrated 2-phase vitreous clearance in some studies or mono-exponential elimination PK profiles in others. Intravenous PK studies with approximately 10 mg/kg bevacizumab demonstrated serum clearance of 15.7, 4.83, and 5.59 mL/day/kg in mice, rats and monkeys, respectively, and a terminal half-life that ranged from 6 to 12 days across these species. Bevacizumab administered IV was distributed primarily to the vascular space with limited distribution to the tissues in rabbits.

The systemic metabolism and elimination of bevacizumab is similar to that of endogenous IgG, occurring primarily via proteolytic catabolism throughout the body, and not relying on elimination through the kidneys and liver.

No data on the metabolism and excretion of bevacizumab have been provided which is acceptable considering the nature of the product, i.e. an IgG1 monoclonal antibody. In line with that no studies on pharmacokinetic drug interactions were conducted which is acceptable as no such interactions are expected.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

No single-dose toxicity studies were conducted with ONS-5010.

2.4.4.2. Repeat dose toxicity

A comparative 4-week **repeat-dose toxicity study** (RDT) was conducted in cynomolgus monkeys that received 50 mg/kg Avastin or ONS-1045 intravenously twice weekly. The monkey was chosen as it is the only relevant species expressing the therapeutic target.

Parameters investigated included body weight, clinical signs, food consumption, ophthalmology, electrocardiography, blood pressure/pulse rate, haematology, blood chemistry, urinalysis, macro- and histopathology. Overall, both products were well tolerated. Treatment-related physeal dysplasia was observed in the femoral growth plates of comparable expression in all males treated with Avastin or ONS-1045. The applicant related this finding to the immaturity of the male monkeys in relation to the female animals. One male animal treated with Avastin presented with generalised vasculitis, which was most probably not treatment related.

Published data on toxicity after intravitreal injection

A summary of published results of single and repeat intravitreal administration of bevacizumab was provided by the applicant. No retinal toxicity was observed at doses of up to 0.25 mg/eye or 0.625 mg/eye in rodents or rabbits, respectively. Nevertheless, a clear increase in apoptosis in rabbit photoreceptor cells was noted. Intravitreal injections of 5 mg to rabbits elicited the immigration of inflammatory cells into the vitreous. No ocular pathologic changes were reported in monkeys that received intravitreal doses of 12.5 mg/eye. In line with that, also i.v. administration of doses of up to 50 mg/kg did not result in any ophthalmic or systemic toxicity. Physeal dysplasia and depletion of corpora lutea were histopathologically observed at systemic doses ≥ 10 mg/kg for 4 weeks or ≥ 2 mg/kg for 3 months and ≥ 10 mg/kg, respectively.

2.4.4.3. Genotoxicity

No genotoxicity studies were conducted with ONS-5010 which is acceptable considering the nature of the product.

2.4.4.4. Carcinogenicity

In order to justify the absence of carcinogenicity studies the applicant referred to ICH guidelines S1A – Guideline on the need for carcinogenicity studies of pharmaceuticals (CPMP/ICH/140/95) and S6 (R1) – Preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998) according to which biotechnology-derived pharmaceuticals can be exempted from the conduct of carcinogenicity studies. Thus, primarily the antiproliferative mode of action as well as the expected low systemic exposure after intravitreal administration have been taken into account for the low carcinogenic potential of ONS-5010.

2.4.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity studies were not performed with ONS-5010. The applicant's justification for not conducting such studies is based on the advanced age of the target patient population, low systemic exposure after intravitreal administration, the known mode of action of bevacizumab as well as the complex role of VEGF in the reproductive system.

The applicant provided published data that point towards a decrease in ovarian weight as well as missing corpora lutea when 10 mg/kg bevacizumab were intravenously administered to monkeys for 13 weeks. No such findings were made in the study provided with ONS-1045 which is most probably due to the shorter duration.

No juvenile toxicity studies were conducted with ONS-5010 but the results of three published studies with bevacizumab were summarised. Overall, single or repeated intravitreal administration to newborn or 6-week old rabbits did not lead to any general or ocular adverse effects.

2.4.4.6. Toxicokinetic data

Toxicokinetic analysis of data obtained in the scope of the GLP-compliant RDT study in cynomolgus monkeys revealed clearly lower C_{max} values after the first administration (day 1) in male and female animals that received ONS-1045 as compared to C_{max} values on day 25. As opposed to that, C_{max} values in animals that

received Avastin were rather constant between day 1 and day 25. With regard to AUC_{48} day 1 values were slightly lower in animals of the ONS-1045 group whereas day 25 values were lower in the Avastin group. In both treatment groups female animals had a slightly higher exposure than male animals. The applicant further provided data on clinical exposure that point towards a 1500 times higher exposure after intravenous application of Avastin in comparison to intravitreal administration.

2.4.4.7. Local Tolerance

No product-specific studies on local tolerance were conducted but the applicant argued with sufficient existing literature proving the tolerability of bevacizumab after intravitreal administration.

2.4.5. Ecotoxicity/environmental risk assessment

The applicant did not conduct ERA studies but provided a justification based on the classification of bevacizumab as a protein and, therefore, consisting of natural amino acids. Thus, ONS-5010 is not likely to exert an environmental risk.

2.4.6. Discussion on non-clinical aspects

Pharmacodynamics

Overall, the functional *in vitro* assays conducted with ONS-1045, presented in the interim quality data summary report (RPT-0175), demonstrate the ability of bevacizumab to bind to its target antigen (VEGF) and, on the other hand, bevacizumab's Fab-associated functions, inhibition of VEGF-mediated angiogenesis by reduced cell proliferation. Primary pharmacodynamics *in vitro assays* with ONS-1045 were performed side-by-side in comparison to EU- and US-approved bevacizumab (Avastin). To note, an adequate and thorough comparability assessment of these studies was not possible at the time of the initial marketing authorisation application due to the lack of detailed study reports for each *in vitro* assay and insufficient information provided in the interim report (RPT-0175) e.g. in regard to used batches, specification limits and recorded data. Concerns regarding the comparability exercise were addressed in the quality part, therefore, please refer to the quality section for further details. In addition, a wide variety of literature references including *in vitro* and *in vivo* studies relevant to retinal indications was submitted with the dossier, supporting the supposed mode of action of bevacizumab, being a monoclonal antibody against VEGF. Functional *in vitro* assays with ONS-1045 were conducted by the applicant and provided in Module 3 of this marketing authorisation application. The functional assays included two neutralisation assays (a HUVEC cell-based and a KDR/NFAT-RE HEK293-VEGF neutralisation assay), VEGF binding assays (by ELISA and SPR), and Fc-mediated binding assays (by SPR for FcRs and by ELISA for C1q). A cell-based assay was also performed to assess the antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activity of ONS-5010. Please refer to the quality assessment for further details.

It is accepted, that the cardiovascular safety assessment was incorporated into the repeat-dose toxicity study conducted in cynomolgus monkeys. No treatment related effects were observed for any cardiovascular safety parameters. For a more detailed assessment of this *in vivo* study, please refer to the toxicology part of this report. No further safety pharmacology assessment was initially submitted by the applicant, but a thorough discussion on safety pharmacology of bevacizumab, especially in regard to the central nervous system (CNS), was provided as response to the questions raised during assessment. Therefore, the conclusion of the

applicant, that a risk of neurotoxicity associated with the use of Lytenava in adult patients is considered to be very unlikely, is comprehensible and accepted.

In general, drug interactions are not expected; neither locally, because the intravitreal administration of bevacizumab is routinely not combined with other ocular treatments, nor systemically due to the low levels of drug reaching the systemic circulation from the treated eye. Therefore, no further non-clinical data on pharmacodynamics drug interactions are required.

To conclude, from a non-clinical perspective, the pharmacodynamic properties of bevacizumab gamma, being a monoclonal antibody against VEGF and thus blocking its biological activity, have been supported by the means of published literature and functional *in vitro* assays conducted with ONS-1045 (RPT-0175) and ONS-5010 (please refer to Module 3). Given that no uncertainties regarding the safety or functionality of ONS-5010 have been identified neither in clinical studies nor in the quality comparability exercise, the non-clinical data generated with ONS-1045 and ONS-5010 together with the provided literature data are considered sufficient.

Pharmacokinetics

Overall, published studies on PK are considered as general information regarding bevacizumab but not product-specific to Lytenava.

Toxicology

A GLP-compliant repeat dose toxicity study in monkeys revealed that repeated intravenous administration of doses of 50 mg/kg Avastin or ONS-1045 to monkeys for 4 weeks was in general well tolerated except for physeal dysplasia that was found in all male animals of both treatment groups. Physeal dysplasia in immature bone is a known and reversible effect of bevacizumab (Peraza et al., 2018) or VEGF-inhibition in general (Gerber et al., 1999) and related to the mode of action. Although no differences in systemic toxicology were revealed in the scope of the repeat-dose toxicity study it is noted that the specific intended route of administration for ONS-1045 has not been taken into account. Potential toxicities of bevacizumab administered intravitreally were covered by a summary of published studies. No adverse effects were observed in rodents, whereas an increase in retinal apoptosis as well as vitreous inflammatory infiltration were noted in rabbits. Intravitreal administration of bevacizumab to monkeys did not reveal any toxicological effects.

The applicant was asked to establish the relevance of the published study by Sakurai et al. (2009), considering the treatment regimen used in the monkey study, including the dosages and frequency of administration, and how it compares to the treatment regimens used in clinical studies. In the response the applicant clarified that the dosing frequency of intravitreally administered bevacizumab in Sakurai's juvenile monkey study differs from the treatment regime of Lytenava, since a single dose was administered. In the Lytenava clinical studies, NORSE ONE and NORSE TWO, only monthly dosing for up to 12 months was performed. The applicant pointed out, that the aims of this animal study were simply to establish the tolerability of bevacizumab in monkeys in order to support ongoing clinical use of intravitreally injected Avastin and was not designed to mimic the clinical dosing regimen.

In this study the vitreous volume of monkey eyes was calculated as half that of human eyes. As a result, the intravitreal concentrations of bevacizumab in the monkey eyes injected with the 6.25 and 12.5 mg doses were equivalent to 10 and 20 times the current clinical dose of 1.25 mg bevacizumab, respectively. The large safety margin supports the tolerability of intravitreal use of bevacizumab in humans.

In addition, an update of the literature summary in regard to available intravitreal repeat dose studies in monkeys was requested. In the response, applicant updated the literature summary with relevant intravitreal repeat dose and single dose studies in monkeys (Pereza et al, 2023; Olvera-Montano O, et al, 2019). These scientific articles provide further reassurance for the safety and tolerability of intravitreal bevacizumab at a clinically relevant dose.

Slight differences were observed regarding toxicokinetics between ONS-10455010 and Avastin over time in monkeys intravenously administered over 4 weeks. However, the kinetics of bevacizumab are already sufficiently known from clinical studies and the systemic exposure after intravitreal administration is assumed to be very low as demonstrated in clinical studies.

With regard to developmental toxicity the argumentation that predominantly post-menopausal women might be treated with Lytenava is acknowledged yet has to be treated with caution as no age-restriction is currently laid down in the label. It is further agreed that, as clinically demonstrated by the applicant, the systemic exposure after intravitreal injection is substantially lower than after intravenous administration. Nevertheless, reports claiming that relevant systemic exposure capable of exerting pharmacological effects can be reached after intravitreal injection of bevacizumab exist (Phadke et al., 2021). The reproductive risk of bevacizumab can, however, be derived from the mechanism of action which is regarded sufficient to communicate the risk as laid down in ICH Guidelines S5 "Reproductive toxicology: Detection of Toxicity to Reproduction for Human Pharmaceuticals" (EMA/CHMP/ICH/544278/1998) and S6 (R1) "Preclinical safety evaluation of biotechnology-derived pharmaceuticals" (EMA/CHMP/ICH/731268/1998). It is therefore agreed to communicate the risk in the label of Lytenava without the need of definitive product-specific studies.

Regarding local tolerance the applicant's argumentation that sufficient data in this respect have been published for bevacizumab can be followed, however, local tolerance is expected to be evaluated in a product- and not class-specific manner. Published studies on bevacizumab are therefore regarded as supportive. Nevertheless, no additional data are requested in view of the availability of clinical data.

The omission of definitive studies on genotoxicity, carcinogenicity and juvenile toxicity has been well justified and is acceptable.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Lytenava is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

The CHMP considers the product approvable from a non-clinical perspective.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

	Study type	Subjects/patients	N	Design
CHDR1427_ONS-1045-001	PK	HV, male	135	Single center, double blind, randomized, single dose, parallel group
NORSE ONE (ONS-5010-001)	E/S	patients	31 Lytenava, 30 ranibizumab	Multicenter, randomized, double-masked, active controlled
NORSE TWO (ONS-5010-002)	E/S	patients	113 Lytenava, 115 ranibizumab	Multicenter, randomized, double-masked, active controlled
NORSE THREE (ONS-5010-003)	S	patients	197	Prospective, multicenter, open label, nonrandomized
NORSE SEVEN (ONS-5010-007)	S	patients	120 planned	Prospective, multicenter, open label, nonrandomized

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Introduction

A total of 3 studies (one Phase 1 and two Phase 3) were conducted in which either healthy subjects (Phase 1 study) or subjects with nAMD (both Phase 3 NORSE studies) contributed to the analysis of PK and/or immunogenicity of ONS-5010.

Study CHDR1427_ONS-1045-001, which was conducted in the Netherlands, was designed to define the PK of ONS-1045 (the IV dosage form of ONS-5010 delivered at a concentration of 100 mg/4 mL) in comparison with the EU and US reference forms of Avastin and to demonstrate PK bioequivalence of ONS-1045 to the EU and US forms of Avastin. Considering the global development programme for ONS-5010, both EU and US forms of Avastin were selected for this comparison.

The study was a single centre, double-blind, randomised, single-dose, 3-arm parallel study. Healthy subjects who met the entry criteria were randomised to 1 of 3 study drug groups. After a single 2.0 mg/kg IV infusion of study drug, safety, immunogenicity, and PK data were collected and reviewed for a total of 98 days after study drug administration. The duration of the study for each subject was approximately 18 weeks, which included 4 weeks for screening and approximately 14 weeks for PK, immunogenicity, and safety assessments. The study will be separately presented and discussed under Bioequivalence.

PK in the target population was investigated in a small proportion of patients from studies NORSE ONE and NORSE TWO following a single intravitreal administration of ONS-5010. Due to the similarity in study designs and sample collection time points, the PK and ADA data from the plasma sample analyses in Phase 3 Study ONS-5010-001 and Phase 3 Study ONS- 5010-002 were pooled. A sample size of up to 14 subjects from both studies, ie, 10% of the subjects receiving ONS-5010, was considered adequate to be a representative sample. From these patients, serum samples for analysis of ONS-5010 concentration were collected daily up to day 4.

2.5.2.2. Pharmacokinetics

The applicant has established and validated a chemo-luminescence based analytical method to detect ONS-5010 in human serum samples. Serum samples containing ONS-5010 are pre-incubated with biotin- and SULFO-labelled, bevacizumab specific antibodies of different specificities. ONS-5010 in samples forms a bridge between both antibodies and is then captured on streptavidin coated plates and detected by a chemiluminescent signal, proportional to the amount of analyte present in the sample. Sample receipt, sample analysis, results and evaluation procedures were well documented. Reproducibility was confirmed by incurred sample reanalysis of a sufficient amount of samples. Validity of results and of the method for its intended use was confirmed in the range of 2-128 ng/ml in serum matrix.

Bioequivalence of ONS-1045 vs EU and US Avastin

The Phase 1 Study CHDR1427_ONS-1045-001, which was conducted in the Netherlands, was designed to define the PK of ONS-1045 (the IV dosage form of ONS-5010 delivered at a concentration of 100 mg/4 mL) in comparison with the EU and US reference forms of Avastin and to demonstrate PK bioequivalence of ONS-1045 to the EU and US Avastin products.

Study design

This was a single centre, double-blind, randomised, single-dose, 3-arm parallel study.

Study centre: Centre for Human Drug Research (CHDR), Zernikedreef 8, 2333 CL Leiden, The Netherlands

Subjects who met the entry criteria were randomised to one of 3 treatment arms. After a single 2.0 mg/kg i.v. infusion, safety, immunogenicity, and pharmacokinetic data were collected and reviewed for a total of 98 days after dose administration.

The total duration of the study for each subject was approximately 18 weeks–- broken down into the following study phases:

Screening: up to 28 days before dosing;

Treatment and study assessments: days 1 to 71 (inpatient/outpatient time);

Final follow-up visit including final study assessments: 14 weeks after dose administration (day 99).

Outlook Therapeutics' (previously known as Oncobiologics) clinical development plan includes a global submission strategy for ONS-1045. Outlook Therapeutics proposed a 3-arm study with parallel groups; ONS-1045 compared to the two reference forms of registered Avastin, the US and EU formulations, respectively. The aim was to demonstrate and prove PK biosimilarity between these two reference products of Avastin and Outlook Therapeutic" bevacizumab gamma. The rationale for including both US and EU reference products was that both the US FDA and the EMA requested PK biosimilarity to be demonstrated between ONS-1045 and the Avastin reference product that is registered in their respective territory.

The parallel design was proposed due to the estimated long half-life of bevacizumab of approximately 20 days as well as to avoid the potential influence of immunogenicity upon multiple dosing.

Healthy volunteers were selected as the subject population as a sensitive PK population that is more homogeneous than a patient population. The subject population reduced potential variability in PK since target-mediated clearance is less important than in patients. Additionally, in the light of the bevacizumab safety profile, it was anticipated that the use of a dose less than half of the lowest recommended therapeutic dose according to Avastin SmPC would be well tolerated by healthy volunteers. Indeed, the most frequent adverse reactions that were seen at higher doses were reversible upon bevacizumab treatment cessation. In addition, hypertension and proteinuria that occurred in patients receiving multiple higher doses were likely to be dose- dependent. The study included careful in-unit and post-confinement monitoring of the participating male volunteers.

Males only were enrolled in this Phase I PK biosimilarity study due to the following reasons:

1. the incidence of ovarian failure was higher in premenopausal women (34%) receiving Avastin, and

2. the fact that male volunteers represent the most homogeneous population for a PK bioequivalence study. For safety reasons, a limit in age from 18 to 55 years (inclusive) was selected.

Study participants

135 healthy adult males aged 18 to 55 years of age, moderate smoker and/or non-smoker.

Inclusion Criteria (complete list)

Subjects had to meet all of the following criteria to be included in the study:

1. Male, moderate smoker (no more than 9 cigarettes or equivalent daily) or non-smoker, ≥18 and ≤55 years of age, with BMI ≥18.5 and ≤30.0 kg/m2 and body weight ≥55.0 kg and ≤90.0 kg.
2. Healthy as defined by:
    a. the absence of clinically significant illness and surgery within 4 weeks prior to dosing. Inclusion pre-dosing was at the discretion of the investigator.
    b. the absence of clinically significant history of neurological, endocrinal, cardiovascular, pulmonary, haematological, immunologic, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease which, in the opinion of the investigator, would put the subject at risk by participation in the protocol.
    c. vital signs including temperature, and ECG did not show medically meaningful abnormalities.
    d. all laboratory results (haematology, biochemistry, and urinalysis screen) within normal ranges or with slight abnormalities that were assessed as non-significant by the investigator.
    e. physical examination did not reveal any medically relevant findings.
3. Subject had to be able to participate for the duration of the entire study and willing to give informed consent and to comply with the study regulations/ protocol.

Exclusion Criteria (complete list)

Subjects to whom any of the following applies would be excluded from the study:

1. Any clinically significant abnormality or abnormal laboratory test results found during medical screening or positive test for hepatitis B, hepatitis C, or HIV found during medical screening.
2. Presence of signs and symptoms of congestive heart failure or any other medical cardiac condition predisposing to heart failure.
3. History of myocardial infarction or unstable angina, or any cardiac abnormalities (e.g. signs of hypertrophic cardiomyopathy).
4. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to dose administration.
5. Major surgical procedure, open biopsy, or significant traumatic injury within 30 days prior to dosing; anticipation of need for a major surgical procedure during the course of the study.

6. Minor surgical procedures such as fine needle aspirations or core biopsies within 7 days prior to dose administration.
7. Presence of serious, non-healing wound, recent wound for which the healing process is not completed, ulcer, or bone fracture.
8. Evidence of bleeding diathesis or coagulopathy.
9. Clinically significant peripheral vascular disease.
10. History of stroke.
11. Active infection requiring antibiotics on dosing day.
12. Grade > 1 peripheral neuropathy (as defined by the NCI CTCAE, v3.0).
13. Known hypersensitivity or history of anaphylactoid reaction(s) to bevacizumab or its excipients.
14. Documented history of allergies to any medication.
15. Clinically significant electrocardiogram (ECG) abnormalities or vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, heart rate less than 40 or over 100 bpm) at screening.
16. History of significant alcohol abuse within one year prior to screening or positive alcohol breath test at screening.
17. History of significant drug abuse within one year prior to screening or a positive urine drug screen at screening.
18. Use of bevacizumab for a medical condition or in the context of a previous clinical trial.
19. Participation in another clinical study involving the administration of an investigational drug within 3 months prior to the start of this study or participation in more than 4 trials per annum.
20. Use of medication other than topical products without significant systemic absorption:
    a. prescription medication within 14 days prior to dose administration;
    b. sporadic use of over-the-counter products including natural health products (e.g. food supplements and herbal supplements) within 7 days prior to the first dosing, with the exception of the occasional use of acetaminophen (up to 2 g daily), or regular use of over-the-counter products for at least three months prior to dose administration.
    c. a depot injection or an implant of any drug within 3 months prior to dose administration.
    d. use of organotoxic drugs within 3 months before study start, or use of drugs with a well-defined potential for toxicity to a major organ system (for example chloramphenicol, which may cause bone marrow suppression).
21. Donation of plasma within 14 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening) within 3 months.
22. Haemoglobin <8 mM and haematocrit <0.37 L/L at screening.
23. Urine protein:creatinine ratio outside normal laboratory range at screening.

24. Any condition that in the opinion of the investigator might jeopardise the subject's health and/or well-being.

Prescription and over-the-counter medications were prohibited throughout the study. No concomitant drug therapy was allowed during the study except one(s) required for the medical management of an AE. Any concomitant medication use other than the occasional use of paracetamol/acetaminophen was evaluated on a case-by-case basis by the Principal Investigator or a physician. All concomitant medication use was documented.

Subjects were required to abstain from:

- food containing poppy seeds within 24 hours prior to screening and admission;
- natural health products (including food supplements, herbal supplements, etc.) from 7 days prior to dosing until after the last pharmacokinetic blood sample collection.

In addition, subjects were required to abstain from using soft or hard drugs from screening and throughout the study, and from smoking from at least 2 hours prior to dosing until 4 hours post-dose. Subjects were not allowed to smoke more than 9 cigarettes or equivalent per day.

Consumption of alcohol-based products was prohibited from 24 hours prior to screening and admission until after the 24-hour post-dose blood sample collection.

For safety reasons, subjects were required to remain on the bed during dose administration until 4 hours after the start of the infusion. However, failure of subjects to comply with these requirements did not constitute a deviation from the protocol if it was deemed medically necessary, procedurally required, or to go to the bathroom. When appropriate, subjects were accompanied by a staff member during ambulations. Vigorous activity was prohibited at all times during the confinement.

Subjects were required to use contraception until 3 months after dose administration and to avoid any sperm donation during this time period. It is known that Avastin could have an effect on a pregnancy and possibly also on breast milk. Men who wanted to participate in the study had to take all possible precautions to prevent pregnancy of their partners from the moment of medical screening till 3 months after administration of the investigational product or Avastin (condom and spermicidal crème or contraceptive such as hormonal oral contraceptives or an intra-uterine device for their partner).

Treatments

All healthy volunteers were randomised to one of the three treatment arms, and received a single dose (2.0 mg/kg) of either the test product ONS-1045 or one of the two reference products of Avastin (US or EU form), all administered according to CHDR's standard operation procedures (SOP) as a single i.v. infusion over 40 minutes in 50 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

All doses were prepared by the Pharmacy of Leiden University Medical Centre. The concentration of the final bevacizumab solution was kept within the range of 1.4 mg/mL to 16.5 mg/mL.

As there was no preservative in the medicinal products, admixed solutions were to be used immediately. If necessary, diluted drug was stored between 2 and 8°C and used within 12 hours of preparation.

Products administered:

Test Product:	ONS-1045 (bevacizumab, Oncobiologics, Inc., USA) 100 mg/4mL, single use vials
Reference Product 1:	Avastin (US-licensed bevacizumab, Genentech, USA) 100 mg/4mL, single use vials
Reference Product 2:	Avastin (EU-licensed bevacizumab, Roche, Switzerland) 100 mg/4mL, single use vials

Objectives

The primary objective was to demonstrate pharmacokinetic biosimilarity of ONS-1045 to the EU- and US-licensed product of Avastin following a single 2.0 mg/kg i.v. infusion, in healthy male adult subjects.

Two secondary objectives were defined:

1. To evaluate the safety, tolerability, and immunogenicity of ONS-1045 and the EU- and US-licensed product of Avastin following a single 2.0 mg/kg i.v. infusion in healthy adult male subjects.

2. To evaluate pharmacokinetic biosimilarity of the EU- to the US-licensed product of Avastin following a single 2.0 mg/kg intravenous (i.v.) infusion, in healthy male adult subjects.

Outcomes/endpoints

Primary endpoint:

AUC_{0-inf}: area under the concentration-time curve from time zero to infinity (extrapolated), calculated as $AUC_{0-t} + C_t/k_{el}$, where: C_t = the last non-zero concentration

Secondary endpoints:

- AUC_{0-t}: area under the concentration-time curve from time zero to the last non-zero concentration
- C_{max}: maximum observed concentration
- t_{max}: time of observed C_{max}
- k_{el}: apparent terminal elimination rate constant
- $t_{½\ el}$: apparent terminal half-life, calculated as $ln(2)/k_{el}$
- CL: apparent body clearance, calculated as $Dose/AUC_{0-inf}$

- V_d: apparent volume of distribution, calculated as Dose/(k_{el} x AUC_{0-inf})

PK blood sampling timepoints: pre-dose (0 hour) and 20 min (mid-infusion), 40 min (end of infusion), 50 min, 1, 2, 3, 4, 5, 8, 16, 24, 48, 96, 144, 192, 240, and 336 hours post-dose, followed by 9 weekly blood samplings (Days 22, 29, 36, 43, 50, 57, 64, 71, and 99) for a total duration of 14 weeks.

Sample size (determination of sample size as presented in CSR, in line with SAP)

The sample size required for the Phase I PK (bioequivalence study) was based on the expected variability of the PK parameters of bevacizumab. However, limited information was available from the literature regarding this variability. In Table 1PK, which is taken from the EMA Avastin EPAR–- Scientific Discussion, the bevacizumab PK parameters studies conducted as part of the clinical development of Avastin are summarised. When considering studies performed with doses varying from 1 to 10 mg/kg, which are more relevant in the context of the dose to be used in the ONS-1045 Phase I study, the AUC0-inf CV values ranged from 15% to 55%, with a mean of 30%.

It is of note, however, that these studies included very low numbers of patients, with some receiving concomitant chemotherapy treatments. In addition, more extensive sampling was made only in Phase I study AVF0737g, (which included only 5 patients at each dose level). In the remaining studies mainly peak and trough bevacizumab concentrations were determined, which may affect the variability of the measured PK parameters. The PK of bevacizumab, given with either capecitabine and oxaliplatin (XELOX) or with 5-fluorouracil/folinic acid and oxaliplatin (FOLFOX-4), was more recently evaluated at steady state in 37 patients with metastatic colorectal cancer (Zhi et al., 2011). CVs of 15% and 30% were reported for the AUC parameter, for the XELOX and FOLFOX-4 treatment arms, respectively.

In another study evaluating the PK of bevacizumab in 39 Chinese patients with advanced cancer, CVs of 22% and 25% were reported for AUC after single doses of 5 mg/kg and 10 mg/kg, respectively (Wu et al., 2010). It is of note that the CVs of Cmax were much lower (13% and 15% for doses of 5 mg/kg and 10 mg/kg), which suggests that CV of AUCinf could be considered for sample size estimation. This might be one of the most relevant studies from a sample size assessment perspective, considering that single-dose PK data was reported, and that the number of patients was reasonable. In addition, three Phase 1 bioequivalence studies are currently reported in ClinicalTrials.gov:

1. Study to Compare and Evaluate the Pharmacokinetic (PK) and Safety Profile of Bevacizumab Biosimilar (BEVZ92) Versus Bevacizumab (AVASTIN) as First-line Treatment in Patients with Metastatic Colorectal Cancer (mCRC) Sponsor: mAbxienc
   - e S.A
   - Dose: 5 mg/kg every 2 weeks (multiple-dose study)
   - Number of patients: 100 (50 patients per treatment)

11. 2. A Pharmacokinetic Study Comparing PF-06439535 and Bevacizumab in Healthy Male Volunteers (REFLECTIONS B739-01)
    - Sponsor: Pfizer
    - Dose: single dose of 5mg/kg
    - Number of subjects: 96 subjects (32 per treatment)

11. 3. Pharmacokinetics and Safety Study of BI 695502 in Healthy Subjects

- Sponsor: Boehringer Ingelheim
- Dose: single IV infusion (dose not reported)
- Number of subjects: 30 per treatment arm)

The assumptions that were used for the above-mentioned protocols for sample size determination are unknown, and no results were published. However, sample sizes reported in these studies suggest that a CV of about 35% was assumed by mAbxience (study in cancer patients), while CV values around 25% would have been assumed by Pfizer and Boehringer Ingelheim for their healthy volunteers studies (assuming a power of 80%, and not taking into consideration the drop-out rate). The variability expected in healthy volunteers would likely be lower than that in cancer patients, considering that healthy subjects would constitute a much more homogenous population.

Based on a 25% coefficient of variation for bevacizumab AUC and assuming a ratio of AUC between 0.95-1.05 and a power of at least 90%, 37 evaluable subjects per group for a total of 111 subjects were required to show pharmacokinetic biosimilarity. Accounting for a dropout rate of about 20%, 8 additional subjects were enrolled into each group. The study enrolled a total sample size of 135, i.e. 45 subjects per group, randomly assigned to one of the 3 treatment arms.

Table 1PK: Bevacizumab pharmacokinetic parameters studies in the original clinical development program from the EU Avastin EPAR

Protocol No., Phase, Study Objective	N	Chemo.	Dose Group (mg/kg)	CL (mL/day/kg)	V_c (mL/kg)	V_{ss} (mL/kg)	$t_{1/2}$ alpha (days)	$t_{1/2}$ beta [a] (days)	MRT (days)	AUC_{inf} (µg•day/mL)
AVF0737g	5	NA	0.1	9.29	48.0	50.1	NA	5.21	7.40	18.5
Phase I, Dose			q 1 week	±7.07	±17.4	±17.0		±2.41	±3.44	±14.3
escalation	5	NA	0.3	5.07	48.6	60.3	1.90	10.4	13.9	68.7
			q 1 week	±2.39	±13.0	±7.30	±0.283	±5.34	±6.11	±26.8
	5	NA	1.0	3.27	37.9	60.4	1.30	14.7	19.9	322
			q 1 week	±0.81	±7.77	±18.8	±0.535	±6.92	±9.25	±84.0
	5	NA	3.0	3.65	41.4	53.4	0.844	12.8	18.1	1073
			q 1 week	±2.10	±12.0	±12.0	±0.143	±6.60	±9.36	±595
	5	NA	10	2.75	43.5	53.0	2.17	14.2	19.3	3730
			q 1 week	±0.47	±12.6	±10.9	±0.573	±3.36	±3.18	±722
AVF0761g	3	Doxorubicin	3	3.74	64.8	NA	NA	12.1	17.4	814
Phase I, solid			q 1 week	±0.555	±8.68			±0.603	±0.854	±122
tumours	4	Carboplatin/paclitaxel	3	2.48	51.7	NA	NA	14.2	20.6	1243
			q 1 week	±0.436	±14.0			±1.55	±2.26	±241
	4	5-FU/FA	3	3.28	56.0	NA	NA	12.51	18.1	966
			q 1 week	□0.857	±12.3			±4.41	±6.36	±256
AVF0775g	15	NA	10	2.71	46.1	NA	NA	12.7	18.3	3963
Ph. II, HRPC			q 2 week	±0.746	±5.54			±3.93	±5.67	±1112
AVF0776g	17	NA	3	2.95	39.0	NA	NA	9.78	14.1	1146
Phase II,			q 2 week	1.29	±9.45			±2.22	±3.20	±374
Efficacy in	41		10	2.74	40.1	NA	NA	10.79	15.6	4047
MBC			q 2 week	±1.11	±9.58			±2.72	±3.91	±1243
	16		20	3.15	39.0	NA	NA	8.85	12.8	6696
			q 2 week	±0.75	±7.28			±1.93	±2.79	±1600
AVF0757g	30	Paclitaxel/	7.5	2.98	42.9	NA	NA	11.2	16.2	2950
Phase II		carboplatin	q 3 week	±1.39	±9.10			±3.55	±5.12	±1085
NSCLC	32	Paclitaxel/	15	2.75	39.4	NA	NA	10.7	15.5	6162
		carboplatin	q 3 week	±1.16	±8.69			±2.64	±3.81	±1897
AVF0780g	34	5-FU/FA	5	2.79	45.4	NA	NA	12.0	17.3	2009
Phase II, CR			q 2 week	±0.849	±9.02			±3.22	±4.65	±653
	28	5-FU/FA	10	2.78	46.1	NA	NA	12.0	17.4	3810
			q 2 week	±0.663	±8.84			±3.47	±5.00	±1002
AVF2107g	214 [b]	Arm 2:IFL	5	3.1 [c]	40.3 [c]	NA	NA	NA	13.1 [d]	1610 [e]
Phase III, CR		Arm 3: 5-FU/FA	q 2 week							
AVF2119g	19	Capecitabine	15	2.08	34.3	NA	NA	11.8	17.0	7640
Phase III, MBC			q 3 week	±0.513	±7.62			±2.82	±4.07	±1940

Abbreviations: 5-FU/FA, 5-fluorouracil/folinic acid; CR, colorectal carcinoma; HRPC, hormone-refractory prostate carcinoma; MBC, metastatic breast carcinoma; NA, not applicable; NSCLC, non small-cell–lung carcinoma

[a] $t_{1/2}$ beta when data fitted to two-compartment model or $t_{1/2}$ K_{10} when one-compartment model was used.

[b] Population PK parameter estimates based on n=214 from Arms 2 and 3.

[c] Parameters normalized to a 80-kg subject.

[d] MRT was calculated as 1/K (where K=clearance/volume).

[e] AUC was calculated as dose/clearance.

Randomisation

Test or reference products were administered according to the randomisation table which was prepared prior to the start of the study by the CHDR statistician, who was not involved in the conduct of the trial, by using SAS 9.1.3 for Windows (SAS Institute Inc., Cary, NC, USA).

The randomisation code was kept strictly confidential. The randomisation code was also not available for the Bioanalytical Laboratory until the clinical and analytical phases of the study had been completed. Sealed individual randomisation codes per subject were placed in a sealed envelope. The labelled 'emergency decoding envelopes' were kept in a safe, access- controlled cabinet at CHDR. Prefilled syringes of the product(s) were dispensed by the pharmacist according to the randomisation code.

Blinding (masking)

The main objective of this phase I trial was to demonstrate PK bioequivalence, i.e. similar PK between ONS-1045 and the US and EU reference products of Avastin. The safety of the test product (ONS-1045) was also compared to Avastin. The unblinded pharmacist dispensed study medication according to the randomisation sequence in an IV bag which was labelled with the subject's randomisation number only. All treatments looked alike and treatment allocation was thus concealed from all non-pharmacy staff.

The investigators, the laboratory staff and the healthy volunteers/trial subjects remained blinded to treatment allocation during the course of this study.

Statistical methods

Analysis Populations

The safety population is defined as all subjects who received the study medication.

The PK population will include all subjects completing the study, and for whom the PK profile can be adequately characterised. This covers adequate exposure to treatment (In case the dose administration is not completed within the infusion time of 40 minutes, the subject will not be included in the PK population for the secondary parameters Cmax and tmax; however, the subject will be included for the primary parameter AUC0-inf and the other secondary PK parameters. If the infusion is incomplete, the subject will not be included in the PK population.), availability of measurements, and absence of major protocol violation. Any subject with measurable pre-dose concentrations will be excluded from the pharmacokinetic population if the pre-dose concentration is greater than 5% of the Cmax value for this subject. Data (concentrations and pharmacokinetic parameters) from subjects excluded due to a pre-dose concentration greater than 5% of their Cmax or from subjects withdrawn due to AEs will be presented but excluded from descriptive statistics.

Demographics and Baseline Characteristics

The descriptive statistics (mean, median, standard deviation [SD], minimum [Min], maximum [Max], and sample size) were to be calculated for continuous variables (age, body mass index [BMI], height, and weight). Frequency counts and percentages were to be tabulated for categorical variables (age group, gender, ethnicity, and race). Results were to be presented overall and by treatment for each study population. All demographic characteristics will be listed by subject.

Statistical analysis methods for PK parameters

The PK population was to be used for PK analyses.

A total of 27 blood samples were to be collected for assessment of serum concentrations of ONS-1045 and reference bevacizumab: pre-dose (0 hour) and 20 min (mid-infusion), 40 min (end of infusion), 50 min, 1, 2, 3, 4, 5, 8, 16, 24 [Day 2], 48 [Day 3], 96 [Day 5], 144 [Day 7], 192 [Day 9], 240 [Day 11], and 336 [Day 15] hours post-dose, followed by 9 blood samplings (Days 22 [504h], 29 [672h], 36 [840h], 43 [1008h], 50 [1176h], 57 [1344h], 64 [1512h], 71 [1680h], and 99 [2352h]) for a total duration of 14 weeks.

The individual serum concentrations of bevacizumab were to be used to calculate the following pharmacokinetic parameters for each subject by standard non-compartmental methods:

Primary parameter:

AUC_{0-inf}: area under the concentration-time curve from time zero to infinity (extrapolated), calculated as $AUC_{0-t}+C_t/k_{el,}$ where: C_t = the last non-zero concentration.

Secondary parameters:

AUC_{0-t}: area under the concentration-time curve from time zero to the last non-zero concentration.

C_{max}: maximum observed concentration.

t_{max}: time of observed C_{max}.

$t_{½\ el}$: terminal half-life, calculated as $ln(2)/k_{el}$.

k_{el}: terminal elimination rate constant. This parameter is the negative of the estimated slope of the linear regression of the ln-transformed concentration versus time profile in the terminal elimination phase. At least 3 concentration points will be used in estimating k_{el}.

CL: body clearance, calculated as $Dose/AUC_{0-inf}$.

V_d: volume of distribution, calculated as $Dose/(k_{el} \times AUC_{0-inf})$.

The calculation of AUC will be done using the linear trapezoidal method.

The timepoint where ln-linear k_{el} calculation begins ($k_{el\ Lower}$), the actual sampling time of the last non-zero concentration used to estimate the k_{el} ($K_{el\ Upper}$) and the correlation coefficient (Corr) from the linear regression for the elimination rate constant calculation were to be reported.

Some PK parameters may not be calculated for all or some subjects, at the discretion of the inVentiv pharmacokineticist, if the concentration data is not deemed to be amenable to evaluation. Explanations for PK parameters that could not be estimated were to be provided in the report.

Summary statistics were to be used to describe the pharmacokinetic profile of bevacizumab. Individual and mean serum concentration versus time curves were to be presented for both linear and semi-log scales. Descriptive statistics (arithmetic and geometric means, standard deviation (SD), coefficient of variation (CV [%]), min., max., and median) of the serum concentrations versus time were to be presented as well as for the pharmacokinetic parameters.

Using GLM procedure in SAS®, ANOVA will be performed on untransformed t_{max}, k_{el} and $t_{½\ el}$, and on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. The statistical model was planned to include Treatment. Total CV% was to be estimated for AUC_{0-inf} and C_{max}. The ratio of means (A/B and B/C) and 90% geometric confidence interval for the ratio of means, based on least-squares means from the ANOVA of the ln-transformed data, was to be calculated for AUC_{0-inf}, and C_{max}.

A separate ANOVA was to be performed using data from Treatments A (ONS-1045) and C (EU-Avastin) only to determine the ratio of means (A/C) and 90% confidence interval for the ratio of means for ln-transformed AUC_{0-inf}, and C_{max}.

As the subjects were to be dosed in multiple small groups, no group term was planned to be included in the statistical model.

Wilcoxon's test using data from Treatments A and C only were to be performed on t_{max}.

Participant flow

In total, 202 subjects were assessed for eligibility after signing informed consent, of whom 43 did not meet the entry criteria (please refer to Appendix B for an overview of the exclusion reason). Additionally, 24 eligible subjects were not enrolled, mainly because the dosing group in which they were available to participate was already full.

One hundred and thirty-five participants were enrolled in the trial (Table 2PK) and received a single dose of 2.0 mg/kg of Avastin US (reference 1), Avastin EU (reference 2), or ONS-1045 (test), 45 per treatment. Five (3.7%) subjects (#2, #13, #77, #84, #85) withdrew consent for personal reasons and did not complete the study: 2 on Avastin US, 1 on Avastin EU, 2 on ONS-1045.

Table 2PK: Subject disposition

Summary of Subject Disposition

	ONS-1045 2.0 mg/kg (Test)	Avastin® US 2.0 mg/kg (Reference 1)	Avastin® EU 2.0 mg/kg (Reference 2)	Overall
Screened	-	-	-	202
Screening Failures[1, 2]	-	-	-	43 (21.3)
Not Enrolled[1, 3]	-	-	-	24 (11.9)
Enrolled[1,4]	-	-	-	135 (66.8)
Randomized	45	45	45	135
Dosed[5]	45 (100)	45 (100)	45 (100)	135 (100)
Completed the Study[5]	43 (95.6)	43 (95.6)	44 (97.8)	130 (96.3)
Withdrawals	2	2	1	5
Primary Reason for Discontinuation:				
Adverse Event[6]	0	0	0	0
Death[6]	0	0	0	0
Protocol Violation[6]	0	0	0	0
Lost to Follow-up[6]	0	0	0	0
Study Terminated by Sponsor[6]	0	0	0	0
Non-Compliance with Study Drug[6]	0	0	0	0
Withdrawal by Subject[6]	2 (100)	2 (100)	1 (100)	5 (100)
Physician Decision[6]	0	0	0	0
Other[6]	0	0	0	0

[1]Percentage based on the number of screened subjects within each cohort or overall, as appropriate.
[2] Screening failures include volunteers who did not meet project criteria.
[3]Not enrolled include volunteers who were judged eligible but decided not to participate on study or who were not selected to participate in the study since there was already a sufficient number of subjects.
[4]Enrolled include volunteers who were judged eligible and accepted to participate in the trial after having signed the approved final version of the study informed consent form.
[5]Percentage based on the number of randomized subjects within each cohort or overall, as appropriate.
[6]Percentage based on the number of withdrawal subjects within each cohort or overall, as appropriate.
Data Source : Subject Disposition - Not Randomized and Subject Disposition - Randomized listings

Recruitment

Subject screening procedures will be performed within 28 days preceding administration of study medication. Subjects must provide written informed consent prior to study-related procedures.

Subject screening procedures will include: demographic data, medical and medication histories, physical examination, body measurements, ECG (12-lead), vital signs (blood pressure, heart rate, and respiratory

rate), temperature, haematology, HIV, hepatitis B and C tests, biochemistry, urinalysis, alcohol breath test, and urine drug screen.

First dosing took place on 12 January 2015, last dosing on 06 March 2015.

Conduct of the study

Study protocol: V3 dated 19-Jun-2015

Protocol history:

V1 dated 13-Nov-2014

V2 dated 10-Dec-2014 with sentinel dosing groups added per IEC request, also additional minor changes were made for clarification/accuracy

V3 dated 19-Jun-2015 with updates regarding schedule of events to clarify urine biobank sample timepoints and weight measurements, clarified 24h urine collection, detailed timepoints for heart rate and blood pressure on day 1, and updated legend scheme in schedule of events

Changes in the planned analyses

The SAP (Appendix A, section 8) described two changes from the protocol:

- As per EMA guidance [Guideline on the Investigation of Bioequivalence. London, 20 January 2010. (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev.1/Corr**)]: "In studies with more than two treatment arms (e.g. a three period study including two references, one from EU and another from USA, or a four period study including test and reference in fed and fasted states), the analysis for each comparison should be conducted excluding the data from the treatments that are not relevant for the comparison in question". Therefore, a separate ANOVA will be performed for the A versus C comparison, to determine the ratio (A/C) and 90% confidence interval for the ratio for ln-transformed AUC0-inf, and Cmax.
- The following sentence in the definition of the pharmacokinetic population was changed from: "*This covers adequate exposure to treatment (in case the dose administration is not completed within the infusion time of 40 minutes, the subject will not be included in the PK population), availability of measurements, and absence of major protocol violation." to: "*This covers adequate exposure to treatment (In case the dose administration is not completed within the infusion time of 40 minutes, the subject will be not be included in the PK population for the secondary parameters Cmax and tmax; however the subject will be included for the primary parameter AUC0- inf and the other secondary PK parameters. If the infusion is incomplete, the subject will not be included in the PK population.), availability of measurements, and absence of major protocol violation."

Baseline data

Table 3PK: Summary of demographic characteristics of subjects included in the PK population for primary parameter ($AUC_{0\text{-}inf}$) and secondary parameters (except C_{max} and t_{max})

Category	Statistic		Treatment			Overall (N=130)
			ONS-1045 2.0 mg/kg (Test) (N=44)	Avastin US 2.0 mg/kg (Reference 1) (N=43)	Avastin EU 2.0 mg/kg (Reference 2) (N=43)	
Age (years)	N		44	43	43	130
	Mean		25.5	27.4	26.0	26.3
	Std. Dev.		8.6	9.3	9.1	9.0
	Median		22.5	24.0	22.0	23.0
	Min., Max.		18, 55	18, 52	18, 53	18, 55
Age Groups	18-40	n (%)	41 (93.2)	39 (90.7)	38 (88.4)	118 (90.8)
	41-55	n (%)	3 (6.8)	4 (9.3)	5 (11.6)	12 (9.2)
Gender	Female	n	0	0	0	0
	Male	n (%)	44 (100)	43 (100)	43 (100)	130 (100)
Race	White	n (%)	37 (84.1)	33 (76.7)	35 (81.4)	105 (80.8)
	Black or Afr. American	n (%)	0	3 (7.0)	2 (4.7)	5 (3.8)
	Asian	n (%)	3 (6.8)	0	1 (2.3)	4 (3.1)
	Hispanic or Latino	n (%)	0	0	1 (2.3)	1 (0.8)
	Pacifique Islander	n (%)	1 (2.3)	0	0	1 (0.8)
	Multiple	n (%)	1 (2.3)	4 (9.3)	2 (4.7)	7 (5.4)
	Other	n (%)	2 (4.5)	3 (7.0)	2 (4.7)	7 (5.4)
Height (cm)	N		44	43	43	130
	Mean		181.22	181.40	182.12	181.57
	Std. Dev.		6.73	7.12	7.36	7.03
	Median		181.20	181.10	181.70	181.35
	Min., Max.		168.2, 192.1	162.6, 193.4	168.6, 198.5	162.6, 198.5
Weight (kg)	N		44	43	43	130
	Mean		75.108	75.299	76.423	75.606
	Std. Dev.		7.944	9.228	6.414	7.905
	Median		75.425	77.150	76.550	76.450
	Min., Max.		54.45, 89.65	54.95, 89.65	63.70, 88.65	54.45, 89.65
BMI (kg/m^2)	N		44	43	43	130
	Mean		22.89	22.88	23.15	22.97
	Std. Dev.		2.31	2.50	2.67	2.48
	Median		22.95	22.60	22.80	22.85
	Min., Max.		18.7, 27.7	18.5, 30.0	19.0, 28.7	18.5, 30.0

n (%): Number and percent of subjects.
N: Number of subjects dosed.
BMI: Body mass index.
Screening data was used to generate this table.
Data source: Demographics and Subject Disposition- Randomized

Table 4PK: Summary of demographic characteristics of subjects included in the PK population for secondary parameters (C_{max} and t_{max})

Category	Statistic		Treatment			Overall (N=119)
			ONS-1045 2.0 mg/kg (Test) (N=40)	Avastin US 2.0 mg/kg (Reference 1) (N=42)	Avastin EU 2.0 mg/kg (Reference 2) (N=37)	
Age (years)	N		40	42	37	119
	Mean		26.0	27.0	27.0	26.7
	Std. Dev.		8.9	8.5	9.7	9.0
	Median		22.5	24.5	22.0	24.0
	Min., Max.		19, 55	18, 52	18, 53	18, 55
Age Groups	18-40	n (%)	37 (92.5)	39 (92.9)	32 (86.5)	108 (90.8)
	41-55	n (%)	3 (7.5)	3 (7.1)	5 (13.5)	11 (9.2)
Gender	Female	n	0	0	0	0
	Male	n (%)	40 (100)	42 (100)	37 (100)	119 (100)
Race	White	n (%)	34 (85.0)	32 (76.2)	30 (81.1)	96 (80.7)
	Black or Afr. American	n (%)	0	3 (7.1)	1 (2.7)	4 (3.4)
	Asian	n (%)	3 (7.5)	0	1 (2.7)	4 (3.4)
	Hispanic or Latino	n (%)	0	0	1 (2.7)	1 (0.8)
	Pacifique Islander	n (%)	1 (2.5)	0	0	1 (0.8)
	Multiple	n (%)	0	4 (9.5)	2 (5.4)	6 (5.0)
	Other	n (%)	2 (5.0)	3 (7.1)	2 (5.4)	7 (5.9)
Height (cm)	N		40	42	37	119
	Mean		181.85	181.77	182.36	181.98
	Std. Dev.		6.71	7.38	7.62	7.18
	Median		183.10	181.70	181.70	181.80
	Min., Max.		168.2, 192.1	162.6, 193.4	168.6, 198.5	162.6, 198.5
Weight (kg)	N		40	42	37	119
	Mean		75.204	74.999	77.127	75.729
	Std. Dev.		8.139	9.187	6.730	8.120
	Median		74.525	76.500	77.650	76.550
	Min., Max.		54.45, 89.65	54.95, 89.65	63.70, 88.65	54.45, 89.65
BMI (kg/m^2)	N		40	42	37	119
	Mean		22.75	22.70	23.31	22.91
	Std. Dev.		2.29	2.48	2.78	2.51
	Median		22.90	22.30	22.90	22.80
	Min., Max.		18.7, 27.7	18.5, 30.0	19.0, 28.7	18.5, 30.0

n (%): Number and percent of subjects.
N: Number of subjects dosed.
BMI: Body mass index.
Screening data was used to generate this table.
Data source: Demographics and Subject Disposition- Randomized

Numbers analysed

All subjects completing the study and for whom the PK profile can be adequately characterised according to the definitions given below were included in the PK population.

Adequate characterisation covers adequate exposure to treatment (if the dose administration was not completed within the infusion time of 40 minutes, the subject was not included in the PK population for the secondary parameters C_{max} and T_{max}; however, the subject was included for the primary parameter $AUC_{0\text{-}inf}$ and the other secondary PK parameters. If the infusion was incomplete, the subject was not included in the PK population), availability of measurements, and absence of major protocol violation.

Any subject with measurable pre-dose concentrations will be excluded from the pharmacokinetic population if the pre-dose concentration is greater than 5% of the Cmax value for this subject.

Data (concentrations and pharmacokinetic parameters) from subjects excluded due to a pre-dose concentration greater than 5% of their C_{max} or from subjects withdrawn due to AEs were be presented but excluded from descriptive statistics.

Although subjects 002, 013, 077, 084, and 085 withdrew from the study, they were included in the PK population.

135 subjects were enrolled and dosed in the current study. Of these, 133 completed the study and/or have adequate characterisation of the PK profile and were therefore included in the pharmacokinetic population.

The number of subjects included in the PK population for each treatment is detailed below for the primary and secondary endpoints.

Table 5PK: Disposition of subjects for PK population by treatment and PK parameter

ONS-1045 (A)	**Avastin (US) (B)**	**Avastin (EU) (C)**
Total N = 44	Total N = 45	Total N = 44
Primary: AUC_{0-inf} and Secondary: AUC_{0-t}, $T_{½\ el}$, K_{el}, CL, V_d		
N = 44	N = 43 (Subjects 084 and 085 were excluded)	N = 43 (Subject 077 was excluded)
Secondary: C_{max} and T_{max}		
N = 40 (Subjects 094, 103, 126, and 135 were excluded)	N = 42 (Subjects 076, 092, and 111 were excluded)	N = 37 (Subjects 072, 073, 087, 110, 113,121, and 124 were excluded)

Outcomes and estimation

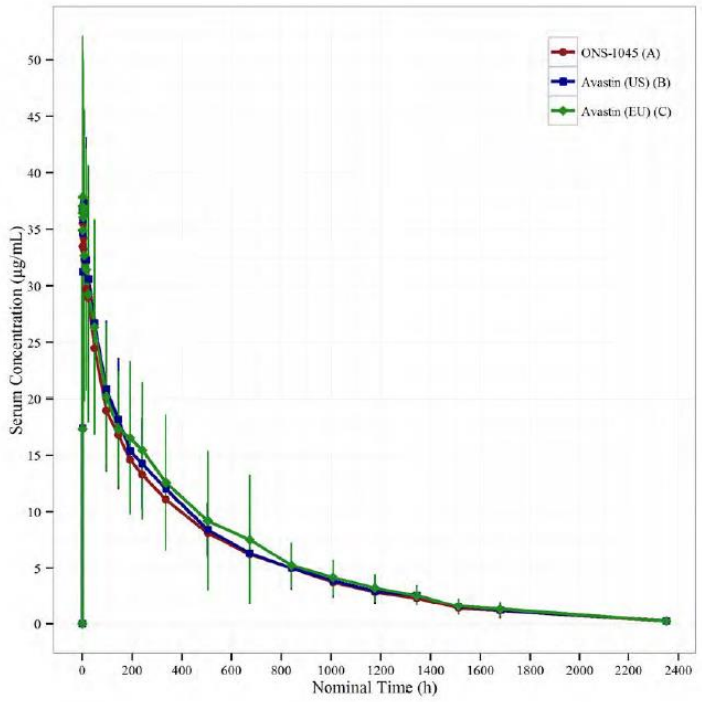
Pharmacokinetic Results

The pharmacokinetic profile following administration of 2.0 mg/kg bevacizumab could be described as an initial rapid increase during infusion, which continued until tmax was reached with a median at 3, 3, and 2 hours respectively for Avastin US, Avastin EU, and ONS-1045, although quite some inter-subject variability was observed with tmax ranging from 20 minutes to 16 hours (Appendix A). Thereafter, the concentration declined seemingly log-linear, though at lower concentrations (~2 µg/mL) non-linear elimination similar to other monoclonal antibodies could be discerned, resulting from target-mediated drug disposition.

The profiles for Avastin US, Avastin EU, and ONS-1045 were similar in shape and overlapping (Figure 2PK).

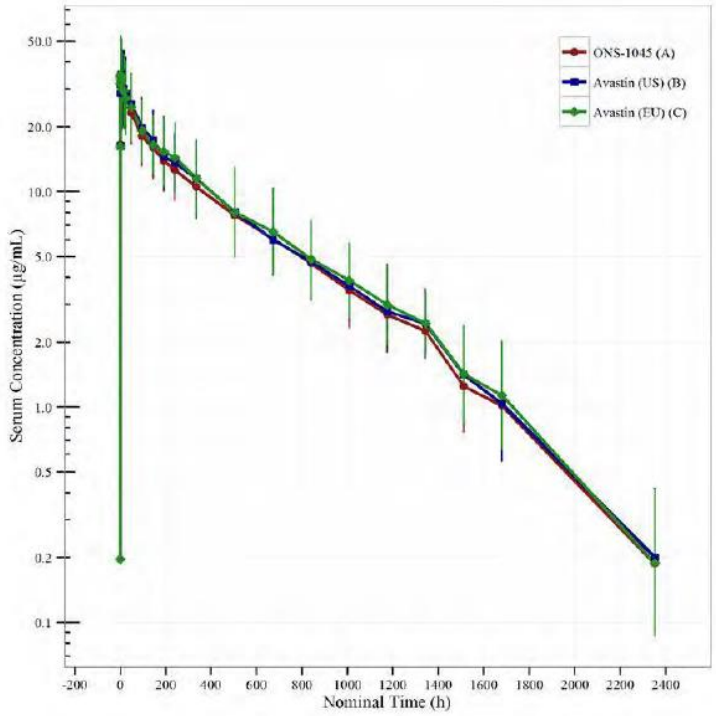
Figure 1PK: Mean (±SD) Bevacizumab serum concentration - linear scale

Figure 5.3.1-1: Mean (±SD) Bevacizumab Serum Concentration - Linear Scale



Source: Figure 7.2-136a

Figure 2PK: Mean (±SD) Bevacizumab Serum Concentration - log Scale



Mean (SD) bevacizumab serum concentrations on semi-log scale
Source: Appendix A

Mean values for pharmacokinetic parameters obtained are summarised below.

Table 6PK: Summary of PK parameters

Table 5.3.2-1: Descriptive Statistics Summary of Bevacizumab Serum Pharmacokinetic Parameters

	ONS-1045 (A)				Avastin (US) (B)				Avastin (EU) (C)			
Parameter (units)	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**
AUC_{0-t} (h*ug/mL)	44	12148.42	2521.60	20.76	43	13165.20	3093.45	23.50	43	13594.89	4189.55	30.82
AUC_{0-inf} (h*ug/mL)	44	12315.33	2568.05	20.85	43	13288.48	3126.98	23.53	43	13698.38	4208.82	30.72
Residual area (%)	44	1.29	2.41	187.18	43	0.91	0.80	87.96	43	0.77	0.56	72.93
C_{max} (ug/mL)	40	40.25	8.63	21.44	42	42.37	10.38	24.51	37	44.69	14.58	32.62
$T_{½ el}$ (h)	44	306.50	70.34	22.95	43	298.02	57.29	19.22	43	290.44	56.90	19.59
K_{el} (/h)	44	0.0024	0.0004	18.4227	43	0.0024	0.0005	18.9892	43	0.0025	0.0007	26.4818
Correlation	44	-0.9639	0.0468	-4.8573	43	-0.9759	0.0296	-3.0322	43	-0.9700	0.0397	-4.0925
$K_{el\ Lower}$ (h)	44	1300	160	12.3	43	1330	57.8	4.34	43	1330	61.6	4.63
$K_{el\ Upper}$ (h)	44	2310	218	9.43	43	2360	42.9	1.82	43	2350	30.1	1.28
CL (mL/h)	44	0.1702	0.0395	23.1926	43	0.1601	0.0438	27.3274	43	0.1588	0.0457	28.7485
V_d (mL)	44	73.4712	16.0581	21.8564	43	68.1841	20.3795	29.8889	43	65.4788	20.6238	31.4969
Parameter (units)	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
T_{max} (h)	40	2.00	0.667	8.00	42	3.00	0.367	16.0	37	3.00	0.667	16.0

Source: Tables 7.1-4, 7.1-5, and 7.1-6.

The least-squares means ratios ONS-1045 (A) / US-Avastin (B) and US-Avastin (B) / EU-Avastin (C), the 90% geometric confidence intervals, and pooled CV were determined for AUC0-inf, and Cmax. The results of these calculations are summarised below.

Table 7PK: Inferential Results for the Comparison of ONS-1045 vs US-Avastin and US-Avastin vs EU-Avastin

Parameter	Treatment Comparisons	Ratio[1]	90% Geometric C.I.[2]		Pooled CV
			Lower	Upper	
AUC_{0-inf}	Test(A) – Reference 1(B)	93.31%	85.18%	102.21%	26.08%
	Reference 1(B) – Reference 2(C)	98.34%	89.73%	107.78%	
C_{max}	Test(A) – Reference 1(B)	95.85%	86.60%	106.09%	28.24%
	Reference 1(B) – Reference 2(C)	96.47%	86.98%	106.99%	

[1] Calculated using least-squares means according to the formula: $e^{(DIFFERENCE)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.
Source: Tables 7.1-10 and 7.1-14.

The least-squares means ratio ONS-1045 (A) / EU-Avastin (C), the 90% geometric confidence intervals, and pooled CV were determined for AUC_{0-inf}, and C_{max}. The results of these calculations are summarised below.

Table 8PK: Inferential Results for the Comparison of ONS-1045 vs EU-Avastin

Parameter	Treatment Comparisons	Ratio[1]	90% Geometric C.I.[2]		Pooled CV
			Lower	Upper	
AUC_{0-inf}	Test(A) – Reference 2(C)	91.76%	83.67%	100.64%	26.33%
C_{max}	Test(A) – Reference 2(C)	92.47%	83.16%	102.81%	28.47%

[1] Calculated using least-squares means according to the formula: $e^{(DIFFERENCE)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.
Source: Tables 7.1-12 and 7.1-16.

The ratios of the geometric means (90% CI) for the natural log-transformed AUCinf values were as follows:

- 91.76% (83.67%-100.64%) for ONS-1045/Avastin EU
- 93.31% (85.18%-102.21%) for ONS-1045/Avastin US

Since both of the 90% CIs for AUCinf were fully enclosed within the predefined acceptance margins of 80.00%-125.00%, bioequivalence was demonstrated for this endpoint.

Separately the ratios of the geometric means (90% CI) for the natural log-transformed Cmax values were as follows:

- 92.47% (83.16%-102.81%) for ONS-1045/Avastin EU
- 95.85% (86.60%-106.09%) for ONS-1045/Avastin US

Again, since both 90% CIs for Cmax were fully enclosed within the predefined acceptance margins 80.00%-125.00%, bioequivalence was demonstrated for this endpoint.

In addition, the EU form and US form of Avastin were shown to be bioequivalent. For Avastin EU vs Avastin US, the ratios of the geometric means (90% CI) for the natural log-transformed AUCinf and Cmax values were as follows:

AUCinf: 98.34% (89.73%-107.78%) for Avastin US/Avastin EU

Cmax: 96.47% (86.98%-106.99%) for Avastin US/Avastin EU

Since both 90% CIs for Cmax were fully enclosed within the predefined acceptance margins 80.00%-125.00%, bioequivalence was demonstrated for this endpoint.

No statistically significant difference between Avastin EU, Avastin US, and ONS-1045 were found with regard to any other PK parameters (Tmax, AUC0-t, AUC0-inf, Cmax, Tmax, T½ el, and Kel). Additional statistical analyses of Cmax and Tmax, including for subjects who had an infusion duration > 40 minutes, yielded virtually identical results, further supporting bioequivalence on these parameters.

The additional statistical analysis for Cmax and tmax, including also the subjects with an infusion duration >40 minutes, gave virtually identical results, further supporting bioequivalence on these parameters.

Absorption, Distribution, and Elimination following IVT administration

PK following intravitreal injection was investigated in a small subset of patients from studies NORSE ONE and NORSE TWO. Due to the similarity in study designs and sample collection time points, PK data from the plasma sample analyses in Phase 3 Study ONS-5010-001 and Phase 3 Study ONS-5010-002 were pooled. A sample size of up to 14 subjects from both studies, i.e. 10% of the subjects receiving ONS-5010, was considered adequate to be a representative sample.

In both studies, serum samples for analysis of ONS-5010 concentration were collected prior to injection of study drug on Day 0, and post-injection on Days 1, 2, 3, and 4.

11 subjects from study ONS-5010-001 and 3 subjects from study ONS-5010-002 randomised to the ONS-5010 group who received ONS-5010 treatment in the study eye only, with no anti-VEGF treatment of any kind in the fellow eye, underwent serum sampling for pharmacokinetic (PK) testing.

There were 14 subjects (11 from ONS-5010-001 and 3 from ONS-5010-002) who were included in the PK Population and in PK analysis.

In total, PK parameters (C_{max}, T_{max} and AUC_{0-t}) were generated for 11 subjects and there were no PK parameters generated for 3 subjects (201601-0008, 201805-0003 and 201812-0006) from ONS-5010-001 due to incomplete profile. Terminal elimination rate constant (h_z) and its dependent parameters ($t_{1/2}$, AUC_{0-inf}, CL/F and Vz/F) were not reported for all 11 subjects as they could not be reliably estimated based on the following reliability criteria: a) The regression contains data from less than 3 different time points in the terminal phase excluding C_{max}; b) If the determination coefficient (r^2) for h_z is =< 0.80.

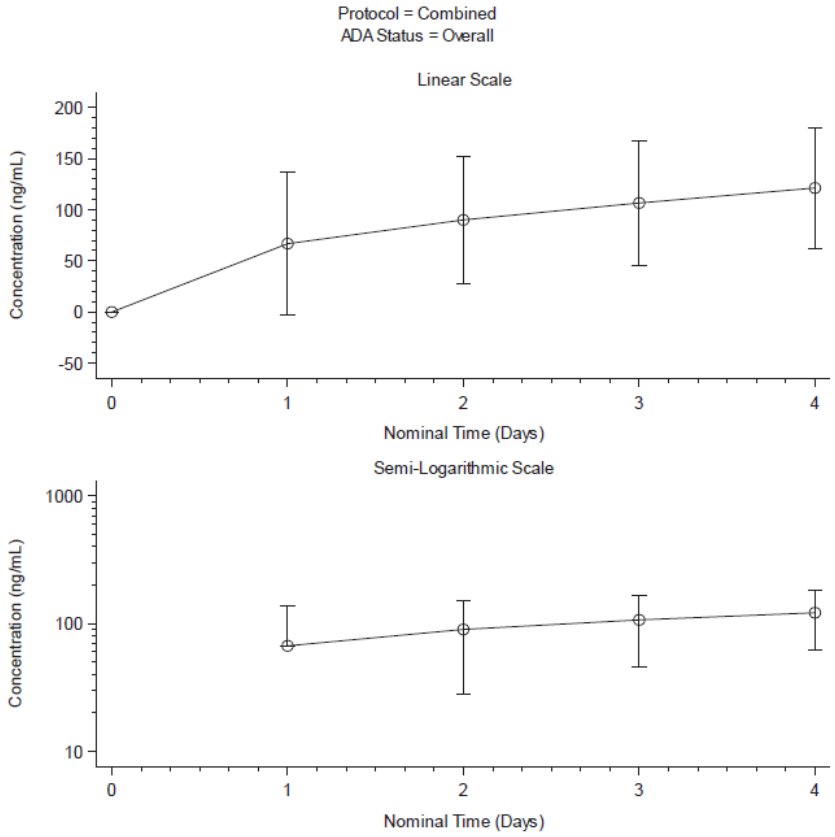
Following intravitreal administration of a single 1.25 mg dose of ONS-5010, mean serum concentrations of ONS-5010 gradually increased with time.

The geometric mean Cmax of ONS-5010 was 108 ng/mL, which was reached at a median Tmax of approximately 91.80 hours (3.83 days) post-injection. The geometric mean total serum exposure (AUC0-t) of

ONS-5010 was 6520 h•ng/mL. The inter-subject variability expressed by the geometric mean %CV was slightly high, with values of 68.9% for Cmax and 81.2% for AUC0-t. The serum PK parameters estimated for ONS-5010 are summarised in the below figure.

The inter-subject variability expressed by the geometric mean %CV was slightly high, with values of 68.9% for Cmax and 81.2% for AUC0-t.

Figure 3PK: Mean (±SD) Serum Concentrations of ONS-5010 vs Time (PK Population)



Note: Fourteen subjects were included in this plot.

Source: Figure 14.2.1.

Table 9PK: Integrated Analysis: Summary of Serum Pharmacokinetic Parameters for ONS-5010 (PK Population)

Summary Statistic	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (h•ng/mL)
n	11	11	11
Mean (SD)	127 (72.0)	NC (NC)	8090 (5610)
%CV	56.9	NC	69.3
Geometric Mean (%CV)	108 (68.9)	NC (NC)	6520 (81.2)
Median	109	91.80	7330
Minimum	33.0	21.78	1670
Maximum	270	101.77	21600

%CV = coefficient of variation; AUC_{0-t} = area under the concentration-time curve extrapolated from time zero to the last quantifiable concentration; C_{max} = maximum drug concentration; PK = pharmacokinetic; SD = standard deviation; T_{max} = time of maximum concentration
The integrated analysis included results from Study ONS-5010-001 and Study ONS-5010-002.
Source: PK Report ONS-5010-001/ONS-5010-002, Table 14.2.2

Dose proportionality and time dependencies

Neither data on dose proportionality nor time dependency were investigated in the clinical programme of Lytenava.

Special populations

No data on special populations was provided in the dossier.

Pharmacokinetic interaction studies

No formal interaction studies have been conducted.

Pharmacokinetics using human biomaterials

No reports of studies pertinent to pharmacokinetics using human biomaterials were provided in the dossier.

2.5.2.3. Pharmacodynamics

No clinical studies investigating the pharmacodynamics of Lytenava were conducted. Data on the pharmacodynamic properties of Lytenava were provided as part of the non-clinical module and are discussed in the non-clinical section of this overview document.

Mechanism of action

The primary mechanism of action of bevacizumab is based on its ability to prevent the binding of VEGF to the receptors Flt-1 and KDR and thus inhibit VEGF/VEGFR mediated endothelial cell proliferation and angiogenesis. Inhibition of angiogenesis inhibits the growth of abnormal blood vessels.

The mechanism of action was investigated in non-clinical studies and further information is presented and discussed in the non-clinical section of this overview document.

Primary and Secondary pharmacology

No data on clinical pharmacodynamics of Lytenava were submitted with this MAA.

2.5.1. Discussion on clinical pharmacology

The clinical pharmacology programme for Lytenava comprises data from a total of 3 studies.

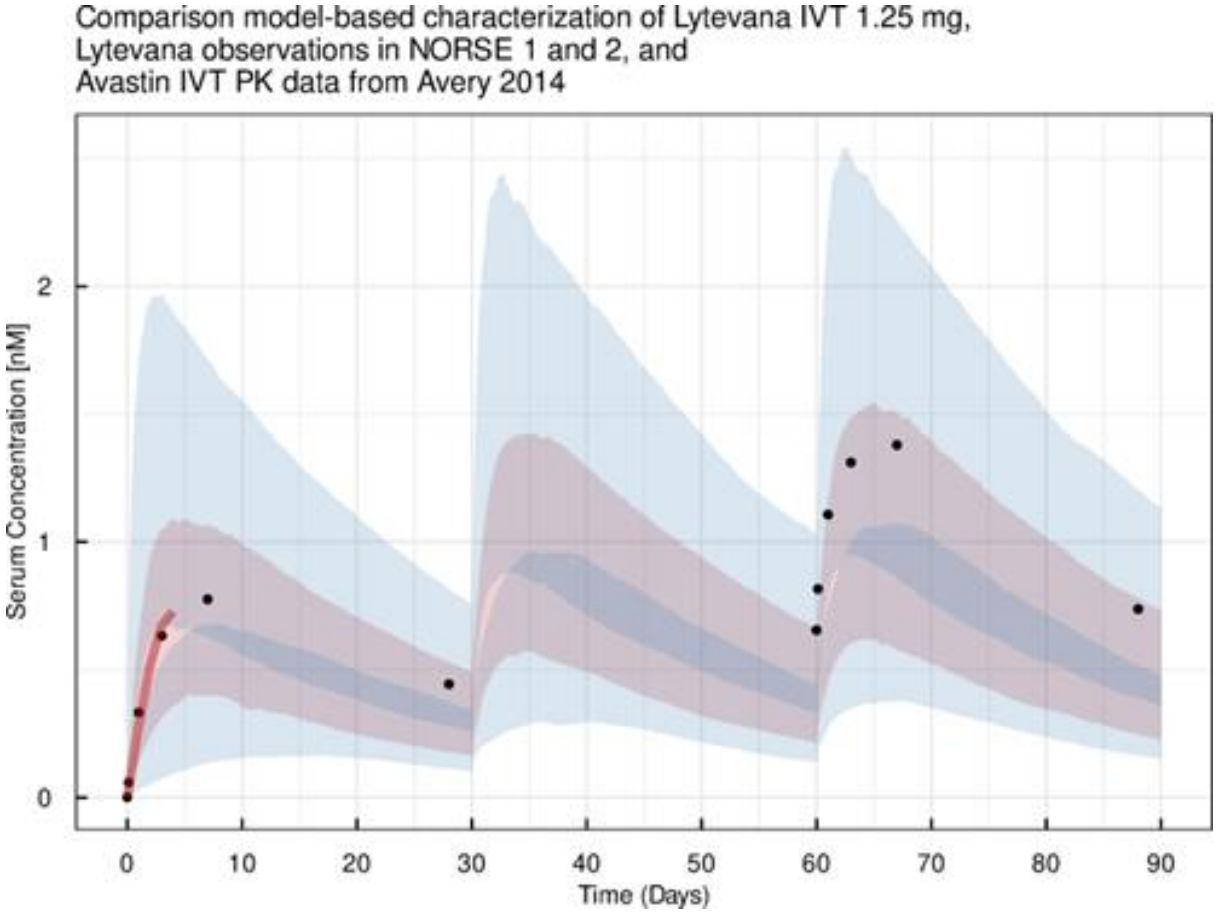
PK following a single intravitreal injection was evaluated in a pooled subpopulation of patients from two Phase 3 E/S studies (ONS-5010-001 and ONS-5010-002). Additionally, a Phase 1 comparative PK study (CHDR14427_ONS-1045-001) was conducted to define the PK of an IV formulation of Lytenava (ONS-1045) in comparison with the EU and US reference forms of Avastin after IV administration, and further to demonstrate PK equivalence of intravenous ONS-1045 to EU and US reference forms of Avastin.

Only limited data newly generated with Lytenava on absorption, bioavailability, distribution, and elimination following intravitreal administration was provided in the dossier.

Serum levels following a single IVT injection of Lytenava were investigated in a total of 14 patients (11 subjects from study ONS-5010-001 and 3 subjects from study ONS-5010-002) over the course of 4 days post administration. In total, PK parameters (C_{max}, T_{max} and AUC_{0-t}) were generated for 11 subjects. Terminal elimination rate constant and its dependent parameters ($t_{1/2}$, AUC_{0-inf}, CL/F and Vz/F) were not reported for any subjects as they could not be reliably estimated. The selected sampling duration of only 4 days raised a question of whether systemic accumulation could be ruled out from the data. In order to provide more insight into potential systemic accumulation following repeat IVT dosing, the applicant provided data generated using a PK model using a) Lytenava PK data following IV administration from the BE study CHDR1427_ONS-1045-001 and b) data following IV administration combined with data following IVT administration from studies NORSE 1 and NORSE 2. According to the presented results, a serum steady-state of less than two-fold across the exposure metrics Cmax and Cavg would be reached before the 12th dosing interval, likely around the 5th dosing interval. The approach is generally considered informative, however, clear limitations of the used PK model are noted. Since for IVT Lytenava no pharmacologically relevant parameters like Cmax, Tmax were characterised due to insufficient sampling timepoints, only very limited data could be entered into the model. While a linear PK model was considered adequate for the majority of data points, the last IV data point at 98 days post dose in study CHDR1427_ONS-1045-001 was not captured adequately. Further the population predictions seem to plateau and could not adequately represent higher concentrations.

A comparison with Avastin data from a publication by Avery et al. 2014 (see below) showed that although the model predictions seem to follow the same profile, the model predictions are generally lower compared to the Avery et al. data.

Figure 2: Visual predictive check for 1.25 mg ONS-5010 repeated dose compared to Avery 2014 and median NORSE 1+2 IVT data for the selected linear model based on all data



Shaded areas correspond to the 95% confidence intervals of the 5th –blue - lower), 50th (red), and 95th (blue -upper) percentiles. Black dots correspond to digitised Avastin IVT mean data from Avery et al 2014. The bold red line corresponds to the binned median of the NORSE 1 and 2 data.

It is however not known whether this indicates a difference between Lytenava and Avastin used in Avery et al. or a limitation of the PK model based on Lytenava data, or simply, interstudy variability as also observed in the efficacy results between NORSE TWO and other studies with anti-VEGF treatments in the target indication. Given the results of the BE study, the limited data available, and since the model seems to underestimate higher exposure levels, the second possibility seems more reasonable. It therefore seems likely that steady-state concentrations might be higher than predicted by the model. While the newly provided data cannot be considered a full characterisation of Lytenava PK, the provided PK model estimations are considered informative. According to the model, serum steady-state is reached within a reasonable time frame and at serum levels comparably lower than what is expected from intravenously administered bevacizumab in oncological settings (factor >500). Since higher levels are very likely and cannot be reliably estimated, uncertainties still remain. However, given that the expected serum levels at steady state are far

below levels reached via IV administration, no relevant safety issues are anticipated. No further questions are raised in this regard.

Further, no information regarding PK following repeat IVT dosing with Lytenava was provided. Respective data was therefore considered missing from the dossier and was requested as part of the questions raised during assessment. The issue could not be resolved with the first set of responses, and the importance of thorough characterisation of systemic accumulation of ONS-5010 following IVT administration was underlined, as additional information from the literature showed an increased risk from IVT bevacizumab compared to other IVT anti-VEGFs for various safety endpoints, e.g. major bleeding events and all-cause death (Kang 2023). With the second set of responses, concerns regarding insufficient bridging to Avastin were largely resolved by the bridging exercise provided by the applicant, thus making possible the use of bibliographic Avastin data as additional evidence. In order to provide more insight into potential systemic accumulation following repeat IVT dosing, the applicant provided data generated using a PK model using a) Lytenava PK data following IV administration from BE study CHDR1427 ONS-1045-001 and b) data following IV administration combined with data following IVT administration from studies NORSE ONE and NORSE TWO. According to the presented results, a serum steady-state of less than two-fold across the exposure metrics Cmax and Cavg would be reached before the 12th dosing interval, likely around the 5th dosing interval. While clear limitations of the used PK model were noted, the approach was generally considered informative. According to the model, serum steady-state is reached within a reasonable time frame and at serum levels considerably lower than what is expected from intravenously administered bevacizumab in oncological settings (factor >500). Since it is considered likely that predicted steady-state levels were underpredicted and cannot be reliably estimated from the PK model, uncertainties remain and were considered for B/R assessment.

No PK data from special populations was provided. The applicant was therefore asked to discuss relevant covariates and their potential impact on PK in subpopulations. As part of the responses, the applicant identified body weight and gender as relevant covariates affecting the clearance and volume of distribution for Avastin. Given the local administration of ONS-5010 it was deemed rather unlikely that these covariates would have strong impacts on intravitreal PK.

CHDR14427_ONS-1045-001: IV Bioequivalence study

The comparative PK study (CHDR14427_ONS-1045-001) was designed as a single centre, double-blind, randomised, single-dose, 3-arm parallel study conducted in the Netherlands. The primary objective was demonstration of PK equivalence of the intravenous formulation of Lytenava ONS-1045 to the EU- and US-licensed product of Avastin following a single 2.0 mg/kg iv infusion in healthy male adult subjects. In this study, one primary PK endpoint (AUC0-inf) and an array of secondary PK endpoints (including AUC0-t, Cmax, tmax, kel, t½ el, CL, and Vd) were used. The overall study design and the selected population were appropriate. Demographic and baseline characteristics were balanced between the three treatment arms.

Equivalence in PK of ONS-1045 and EU and US sourced Avastin was demonstrated, as the 90% confidence intervals for the ratios of the pairwise comparisons of AUC0-inf were within the pre-specified acceptance range of 0.8 – 1.25. The ratio for the pairwise comparison for ONS-1045 vs EU-Avastin was 0.9176 (CI: 0.8367, 1.0064), for ONS-1045 vs US-Avastin it was 0.9331 (CI: 0.8518, 1.0221), and for US-Avastin vs EU-Avastin it was 0.9834 (CI: 0.8973, 1.0778). Also, the ratios for the pairwise comparisons of the secondary endpoint Cmax were fully enclosed within the acceptance range of 0.8 – 1.25. The ratio for the pairwise comparison in Cmax for ONS-1045 vs EU-Avastin was 0.9247 (CI: 0,8316, 1,0281), for ONS-1045 vs US-

Avastin it was 0.9585 (CI: 0.8660, 1.0609), and for US-Avastin vs EU-Avastin it was 0.9647 (CI: 0.8698, 1.0699).

Further secondary EPs (tmax, kel, t1/2 el, CL, Vd) were supportive of these results. In total, mean concentration-time profiles as well as the results for secondary endpoints suggest similarity in PK for ONS-1045 and US-/EU-Avastin.

2.5.2. Conclusions on clinical pharmacology

From the presented data on PK following administration of the IV formulation ONS-1045, equivalent pharmacokinetics between ONS-1045 and EU and US Avastin can be concluded.

Lytenava PK data following intravitreal administration was insufficiently characterised, as the provided newly generated data with Lytenava were inconclusive. No clinical studies investigating the pharmacodynamics of Lytenava were conducted. The mechanism of action of bevacizumab is established in the literature and was investigated in non-clinical studies. No clinical studies investigating the relationship between plasma concentration and its effect were conducted.

However, based on the bridging exercise provided by the applicant, which was found acceptable, use of bibliographic data from off-label Avastin as additional evidence was possible, and concerns regarding e.g. systemic accumulation could be resolved.

2.5.3. Clinical efficacy

Table 1. Studies Contributing to the Efficacy Evaluation of ONS-5010

Study Identifier (Study Phase)	Study Title	Study Design and Population	Treatment Groups (Number of Subjects)	Dosing Regimen	Primary Efficacy Endpoint
ONS-5010-001 (NORSE ONE) Safety and Efficacy (Phase 3)	A Clinical Effectiveness, Multicenter, Randomized, Double-Masked, Controlled Study of the Efficacy and Safety of ONS-5010 in Subjects with Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD)	Multicenter, randomized, double-masked, controlled, 12 month efficacy and safety study intravitreally administered ONS-5010; subjects must have been at least 50 years of age with active primary or recurrent subfoveal CNV lesions, with or without a classic CNV component, secondary to AMD in the study eye	ONS-5010 (31) Ranibizumab (30)	ONS-5010: Administered at a dose of 1.25 mg by intravitreal injection in the study eye every month for 12 months Ranibizumab: Administered at a dose of 0.5 mg by intravitreal injection in the study eye every month for 3 months (ie, on Days 0, 30, and 60) followed by every 90 days (ie, on Days 150 and 240)	Proportion of subjects who gained ≥ 15 letters in BCVA from baseline to 11 months
ONS-5010-002 (NORSE TWO) Safety and Efficacy (Pivotal Phase 3)	A Clinical Effectiveness, Multicenter, Randomized, Double-Masked, Controlled Study of the Efficacy and Safety of ONS-5010 in Subjects with Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD)	Multicenter, randomized, double-masked, controlled, 12 month efficacy and safety study intravitreally administered ONS-5010; subjects must have been at least 50 years of age with active primary subfoveal CNV lesions, with or without a classic CNV component, secondary to AMD in the study eye	ONS-5010 (113) Ranibizumab (115)	ONS-5010: Administered at a dose of 1.25 mg by intravitreal injection in the study eye every month for 12 months Ranibizumab: Administered at a dose of 0.5 mg by intravitreal injection in the study eye every month for 3 months (ie, on Days 0, 30, and 60) followed by every 90 days (ie, on Days 150 and 240)	Proportion of subjects who gained ≥ 15 letters in BCVA from baseline to 11 months

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization

Lytenava has been presented with a dossier containing two clinical trials and a range of literature references. While the literature references offer some supportive evidence, state of the art clinical trials are the gold standard when it comes to evaluating the efficacy and safety of new treatments, as they involve rigorous scientific methods. Literature references, on the other hand, may be more subjective in selection and

publication, less complete and less rigorous in their evaluation of treatment outcomes. The literature references nevertheless provide additional context and background information, while they on their own do not carry the same weight as the clinical trial data. For the literature references no study protocol and report are available, just publications that provide a basic summary, as opposed to the possibility of an in depth assessment based on the totality of data generated in a clinical trial.

Only the two efficacy trials (NORSE ONE and NORSE TWO) are considered pivotal for establishing efficacy and safety of ONS-5010 in this MAA. Literature data is regarded as supportive with this respect.

2.5.3.1. Main study(ies)

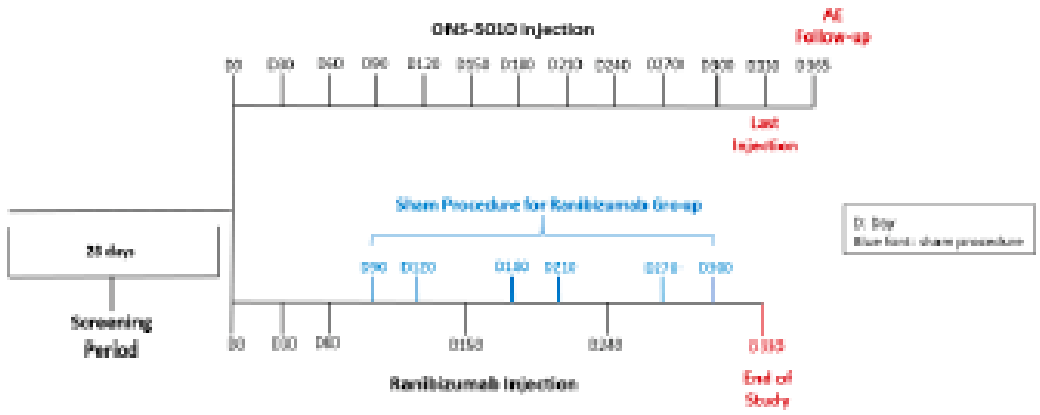
ONS-5010-002 (NORSE TWO) and ONS-5010-001 (NORSE ONE) were similarly designed multicentre, randomised, double-masked, controlled Phase 3 studies that evaluated the efficacy and safety of intravitreally administered ONS-5010. Both studies were conducted in accordance to Good Clinical Practice. The key differences between the NORSE ONE and NORSE TWO patient populations were: (1) both treatment-naïve and previously treated subjects were included in NORSE ONE, but only treatment-naïve in NORSE TWO; and (2) baseline visual acuity was 20/40 to 20/320 in NORSE ONE, but 20/50 to 20/320 in NORSE TWO.

Following a screening period of up to 28 days in both studies, eligible subjects were randomised in a 1:1 ratio to receive ONS-5010 or ranibizumab in the study eye. Note that only 1 eye was designated as the study eye and the injection was performed by an unmasked physician. Prior to randomisation, the investigator was to receive and review clinical laboratory tests for eligibility and also to receive confirmation of subject eligibility from the medical image reviewer.

In the Phase 3 studies ONS-5010-001 and ONS-5010-002, ONS-5010 was given in the same posology and dose as has been used off-label for the off-label IV preparations of Avastin. Subjects randomised to receive ONS-5010 were administered a monthly intravitreal injection of 1.25 mg of ONS-5010 in the study eye for up to 12 months. Subjects randomised to ranibizumab received 0.5 mg of ranibizumab by intravitreal injection in the study eye every month for 3 months (ie, on Days 0, 30, and 60) followed by 2 additional injections, 90-days apart, on Days 150 and 240. Subjects in the ranibizumab group underwent sham procedures at visits when they did not receive an active (ranibizumab) injection.

In each study, the last planned study visit differed depending on which study drug group the subject was randomised to, concluding at Day 330 for subjects in the ranibizumab group and at Day 365 for subjects in the ONS-5010 group; following the last study visit, all subjects reverted to the investigator’s standard of care.

Figure 1. Studies ONS-5010-002 and ONS-5010-001: Study Schematic



The efficacy assessments were conducted throughout the dosing and evaluation phases of each study. For subjects in both the ONS-5010 and ranibizumab groups, evaluation period for efficacy was 11 months (through Day 330); note that safety was assessed for 12 months (through Day 365) in the ONS-5010 group. In both studies, the determination of efficacy was based on best-corrected visual acuity (BCVA) (test distance of 4 m using certified lanes) assessments and measurements of central foveal thickness (CFT) by spectral domain-optical coherence tomography (SD-OCT). Measurements of BCVA were obtained for each eye separately prior to study drug injection and any assessments requiring dilation. The number of letters read correctly (for each eye) based on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart was recorded at all study visits. Imaging by SD-OCT was performed.

Study ONS-5010-001

A total of 61 subjects were randomised in this study at 8 study centres across Australia. Of the 61 subjects who were randomised, 45 (73.8%) completed the study (ONS-5010-001 CSR Table 14.1.1). The 3 most frequently reported reasons for study discontinuation were withdrawal of consent (13.1%), sponsor decision (6.6%), and a decrease from baseline in BCVA of ≥ 15 letters (4.9%).

All 61 randomised subjects were included in the ITT population (31 subjects in the ONS-5010 group and 30 subjects in the ranibizumab group) and 44 subjects were included in the PP population (20 and 24 subjects in the ONS-5010 and ranibizumab groups, respectively). To be eligible for the study, subjects must have been at least 50 years of age and had active primary or recurrent subfoveal CNV lesions, with or without a classic CNV component, secondary to AMD in the study eye. The subjects must have had a BCVA, using ETDRS charts, of 25 to 70 letters read (approximately equivalent to 20/40 to 20/320 Snellen) in the study eye, along with the presence of active leakage on fluorescein angiogram involving the fovea and oedema involving the fovea as measured by central subfield foveal thickness on SD-OCT, and the absence of scarring, or atrophy.

The subjects in the ITT population had a mean age of 78.6 years (range = 61-97 years) (Table 8). Overall, 60.7% of the subjects were female and all subjects (100.0%) identified as not Hispanic or Latino; most subjects were white (95.1%). With the exception of more female than male subjects in the ONS-5010 group compared with equal percentages of male and female subjects in the ranibizumab group, the demographic characteristics were similar between study drug groups.

At baseline, the mean BCVA was 60.0 letters (range = 30-73 letters), which was similar in both study drug groups (61.6 and 58.4 letters, respectively, in the ONS-5010 and ranibizumab groups) (Table 9). Overall, a larger percentage of subjects had a baseline BCVA ≥ 55 letters than had a baseline BCVA ≤ 54 letters (72.1% vs 27.9%, respectively). Most subjects (40 [65.5%]) overall reported having prior treatment with anti-VEGF therapy; however, this was driven by the larger number of treatment experienced subjects in the ONS-5010 group. In the ranibizumab group, treatment naive and treatment experienced subjects were equally represented (50.0% each), whereas in the ONS-5010 group, a greater percentage of subjects received prior anti-VEGF treatment than subjects who were treatment naive (80.6% vs 19.4%, respectively).

Study ONS-5010-002

All 228 randomised subjects were included in the ITT population (113 subjects in the ONS-5010 group and 115 subjects in the ranibizumab group) and 163 subjects were included in the PP population (85 and 78 subjects in the ONS-5010 and ranibizumab groups, respectively) (ONS-5010-002 CSR Table 14.1.1).

To be eligible for the study, subjects must have been at least 50 years of age and had active primary subfoveal CNV lesions, with or without a classic CNV component, secondary to AMD in the study eye. Subjects must have had BCVA, using ETDRS charts, of 25 to 67 letters read (approximately equivalent to 20/50 to 20/320 Snellen) in the study eye, along with the presence of active leakage on fluorescein angiogram involving the fovea and oedema involving the fovea as measured by central subfield foveal thickness on SD-OCT, and the absence of scarring, fibrosis, or atrophy involving the central foveal zone (inner most ring on SD-OCT).

The subjects in the ITT population had a mean age of 78.9 years (range = 54-98 years) (Table 6). Overall, 59.6% of the subjects were female and 94.3% identified as not Hispanic or Latino; most subjects were white (97.8%). Overall, the demographic characteristics were similar between study drug groups.

At baseline, the mean BCVA was 51.6 letters (range = 20-73 letters), with a slightly larger percentage of subjects having a BCVA ≥ 55 letters than subjects having a baseline BCVA ≤ 54 letters (54.4% vs 45.6%, respectively) (Table 7). Most subjects (219 [96.1%]) did not have prior treatment with anti-VEGF therapy. The mean CFT at baseline was 430.0 µm (range = 181-926 µm) in the ONS-5010 group and 423.7 µm (range = 173-769 µm) in the ranibizumab group. Overall, the demographic and other baseline characteristics were generally similar across the treatment groups.

Overall, both pivotal trials include patients who are considered relevant for the desired indication "treatment of wet AMD" The key differences between the NORSE ONE and NORSE TWO patient populations were: both treatment-naïve and previously treated subjects were included in NORSE ONE, but mostly treatment-naïve in NORSE TWO; and baseline visual acuity was 20/40 to 20/320 in NORSE ONE, but 20/50 to 20/320 in NORSE TWO.

Treatments

The comparator product in both studies, ranibizumab (Lucentis), is approved for use in the treatment of nAMD, macular oedema following retinal vein occlusion, diabetic macular oedema, diabetic retinopathy, and myopic CNV. There are multiple dosing regimens that are approved for the treatment of AMD, including the ranibizumab dosing regimen as evaluated in the PIER and EXCITE clinical studies (Regillo 2008, Schmidt-Erfurth 2011). The ranibizumab dosing regimen used in the PIER study encompasses an initial 3 loading doses of ranibizumab injected once a month followed by an injection on a quarterly basis.

In the two Phase 3 studies ONS-5010-001 and ONS-5010-002, subjects randomised to ONS-5010 received study drug every month for up to 12 months. Subjects randomised to ranibizumab received study drug every month for 3 months followed by 2 additional injections, 90-days apart. To ensure masking of the study drugs, at visits when subjects in the ranibizumab group were not scheduled to receive an active injection, a sham procedure was conducted. At each study centre, an injecting physician was unmasked to the study drug assignment; this investigator performed the ONS-5010 or ranibizumab (or sham) preparation and injection at each relevant study visit. A separate investigator referred to as the evaluating investigator, was fully masked to the study drug assignment; this investigator conducted all ocular assessments at every study visit.

Objectives

The primary objectives of study ONS-5010-001 and study ONS-5010-002 were to evaluate the efficacy of intravitreal injections of ONS-5010 1.25 mg administered monthly compared with ranibizumab 0.5 mg injections administered as 3 doses and then quarterly in subjects with primary subfoveal choroidal neovascularisation (CNV) with or without a classic CNV component secondary to AMD, as measured by the difference in proportion of subjects who gain ≥15 letters in best corrected visual acuity (BCVA) at 11 months as well as the safety and tolerability of intravitreal injections of ONS-5010 administered monthly from baseline to 12 months (see discussion of clinical safety). The rationale of measuring BCVA at 11 months was not understood and the applicant was asked to argument. The applicant responded referencing to an efficacy plateau after 3 months, so that a longer evaluation period of 12 months was not expected to provide additional clinically relevant and meaningful information. The argument is not completely agreed and this is considered a source of uncertainty for the estimate of efficacy.

The secondary objectives were a further evaluation of the efficacy of intravitreal injections of ONS-5010 as compared with ranibizumab in preventing vision loss as measured by the following:

- The mean change in BCVA from baseline to 11 months
- The proportion of subjects who gain ≥5 letters in visual acuity at 11 months compared with baseline
- The proportion of subjects who gain ≥10 letters in visual acuity at 11 months compared with baseline
- The proportion of subjects who lose fewer than 15 letters in visual acuity at 11 months compared with baseline
- The proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 11 months

Outcomes/endpoints

Primary and secondary endpoints are the same in study ONS-5010-001 and ONS-5010-002.

The primary efficacy endpoint is the proportion of subjects gain ≥15 letters in the BCVA score at 11 months compared with baseline, where BCVA is based on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity assessment.

The secondary efficacy endpoints include the following:

- The mean change from baseline in BCVA score from baseline to 11 months
- The proportion of subjects who gain ≥5 letters in the BCVA score at 11 months compared with baseline
- The proportion of subjects who gain ≥10 letters in the BCVA score at 11 months compared with baseline
- The proportion of subjects who lose fewer than 15 letters in the BCVA score at 11 months compared with baseline
- Proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 11 months

Sample size

For the NORSE ONE Phase 3 study a sample size of 50 subjects (25 per treatment arm) was considered adequate. This sample size was based on the primary efficacy endpoint of the proportion of subjects who gained ≥ 15 letters in visual acuity at 11 months, with a treatment effect for the difference in proportions between ONS-5010 (assumed proportion 55%) and ranibizumab (assumed proportion 14%) of 41%. The power was set to 80%, using a 1-sided alpha of 0.025.

For the NORSE TWO Phase 3 study a sample size of 220 subjects (110 per treatment arm) was considered adequate. This sample size was based on the primary endpoint of the proportion of subjects who gain ≥15 letters in visual acuity at 11 months, with a treatment effect for the difference in proportions between ONS-5010 (assumed proportion 32%) and ranibizumab (assumed proportion 14%) of 18%. The power was set to 90%, using a one-sided α=0.025.

Randomisation and blinding (masking)

In both studies (NORSE ONE and NORSE TWO) eligible subjects were randomised in a 1:1 ratio to receive either ONS-5010 at a dose of 1.25 mg monthly or Ranibizumab at a dose of 0.5 mg monthly for the first three doses followed by 2 further doses every 90 days.

The randomisation was conducted centrally using an interactive web response system. Study drug was assigned according to a randomisation scheme generated by an independent, unmasked statistician.

Only those subjects who were randomised but discontinued the study prior to receiving study drug may have been replaced.

Both, the NORSE ONE and NORSE TWO study used a masking procedure as follows:

At least 1 investigator was designated as the evaluating investigator and was masked to the study drug assignment; this investigator conducted all ocular assessments. Due to the presentation of the compound (colour) and needle type required, at least 1 other investigator, designated as the injecting physician, was unmasked to the study drug assignment; this investigator performed the ONS-5010 or ranibizumab (or sham) preparation and injection. At least 1 study coordinator was also unmasked for study drug preparation if needed, for study drug accountability, and for assistance during the injection procedure.

The BCVA examiner, image photographer and grader, subjects, evaluating investigator (ophthalmologist), and additional study centre staff, and sponsor, were masked to study drug assignment, along with a masked study coordinator and masked contract research organisation personnel. The injecting investigator was unmasked to study group assignment, along with unmasked study coordinators and unmasked clinical research associates. Finally, a designated unmasked data manager oversaw drug randomisation; all other data managers were masked.

If unmasking became necessary (i.e., in the event of a medical emergency, where the identity of the study drug had to be known to properly treat the subject), then the study drug assignment for the unmasked subject was only to be revealed by a qualified designee with approval from the sponsor’s medical monitor or designee. In the event of any unmasking, the principal investigator was to record the date and reason for study drug unmasking in the subject’s electronic case report form (eCRF).

In the absence of a medical emergency, the masked randomisation was not to be revealed at the study level until database lock.

Statistical methods

All efficacy analyses were performed on the intent-to-treat (ITT) population. The ITT population included all randomised subjects. For efficacy analyses, subjects were analysed in the treatment group to which they were randomised. Results based on the ITT population were considered primary for drawing efficacy conclusions.

The Per-Protocol (PP) population is defined as all subjects who are included in the ITT population, who have at least 1 post-dose BCVA score, and who are compliant with all critical study criteria.

Subjects with major protocol violations, identified prior to unmasking of the study, were excluded from the PP population. A protocol deviation occurred when the participant, investigator, or the sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, participant safety and primary endpoint criteria. When a protocol deviation occurs, it was discussed with the investigator and a Protocol Deviation Form detailing the deviation was generated.

Selected efficacy analyses were performed on the PP population and were considered supportive of the primary results based on the ITT population analyses.

The primary efficacy analysis employed a Fisher's Exact test to assess a significant difference in the proportion of subjects who gain ≥15 letters in visual acuity between ONS-5010 and Ranibizumab.

Efficacy analysis of the secondary endpoints

A Trimmed Means statistical approach was used for the first secondary efficacy analysis (mean change from baseline). Two methods of trimming were used, a fixed approach and an adaptive approach. Due to its ease of interpretability, i.e. a comparison of the better halves of each group, the fixed method was treated as the first secondary analysis method.

For the fixed approach, the best 50% of observations in both the active and control arms were subset. For the calculation of the median, dropouts were included as observations worse than the median.

For the adaptive approach, first the proportions of subjects who dropped out of the control and treatment arms were identified. This greater proportion of the two arms was then used as the percentile floor in which observations must be better. Those observations that were not better than the floor were trimmed (removed). Dropouts were again included in the calculation of the percentile floor value as values worse than the percentile.

After trimming was done, an ANCOVA was used again on the two analysis sets to find an observed treatment effect. To determine the p-value and 95% CI, 10,000 permutations of the data have been run and the trimming methodology was repeated. The number of permutations that result in an effect size greater than the observed effect size divided by the number of permutations was the p-value. The 95% CI was calculated using the 2.5 and 97.5 percentiles of the permutation distribution.

The remaining proportional secondary analyses were performed using Fisher's exact test to compare the ONS-5010 and ranibizumab groups.

Intercurrent Events and Missing Data

Subjects who discontinued study treatment and received rescue/prohibited therapy or discontinued from study due to lack-of-efficacy or adverse event, were included in analyses for the primary efficacy endpoint

(and proportional secondary endpoints) as a non-responder. Subjects who discontinued for other reasons and had a missing 11-month BCVA score were treated as missing.

Subjects who discontinued study treatment and did not receive any rescue/prohibited therapy, and were willing to remain in the study, were followed and evaluated for efficacy through the end of study. These subjects were included in the analysis of the primary and secondary efficacy endpoints.

Complementary and Sensitivity Analyses to the first secondary endpoint

As complements to the first secondary efficacy analysis, the following statistical methods were used:

1. The *first complementary analysis* was performed using an ANCOVA model with treatment group as the fixed effect and the baseline BCVA as a continuous covariate.
2. The *second complementary analysis* employed the multiple imputation method that replaces each missing 11-month BCVA value with a set of plausible values that represents the uncertainty of the correct value based on the observed time matched data at all other visits. The multiple imputation was completed by two steps (1) imputing these intermittent missing data using Markov chain Monte Carlo (MCMC) methods to get a monotone missingness data pattern; (2) then using regression method to impute missing data. This method of imputation makes the assumption that missing data are missing at random (MAR).
3. The *third complementary analysis* was performed on BCVA over time, using repeated measures, mixed model methodology. This analysis was used to determine any potential treatment group differences in the pattern of change in BCVA over time. Change from baseline in BCVA score was modelled using treatment, visit, and an interaction term of treatment and visit, as fixed effects.

In order to further assess the effect of missing data, the following sensitivity analyses were performed on the first secondary efficacy endpoint (i.e., the mean change from baseline in BCVA to 11 months). These analyses included an ANCOVA with study drug and stratification as factors and study baseline value as a covariate. Pairwise comparisons were made between the ONS-5010 and ranibizumab groups.

Sensitivity analyses to assess the impact of missing data were evaluated as follows:

1. Last observation carried forward (LOCF) – missing 11-month BCVA data were imputed using the last post dose time matched data values.
2. Multiple Imputation by washout – for missing Month 11 values for the ONS-5010 group, each missing value was replaced with a set of plausible values that represented the uncertainty of the correct value based on the observed time matched data for the ranibizumab group at all other visits; this was a conservative approach, since it assumed missing data in the ONS-5010 group would be similar to the results in the ranibizumab group subsequent to unavailability, thereby diminishing the difference between the ONS-5010 and ranibizumab results.
3. Completer's analysis – including only those subjects who had complete Month 11 results.
4. Jump to reference imputation – for the change in the ONS-5010 treatment group for any missing individual subject's 11-month BCVA data of the ranibizumab group mean at Month 11 was used for imputation.

Multiplicity

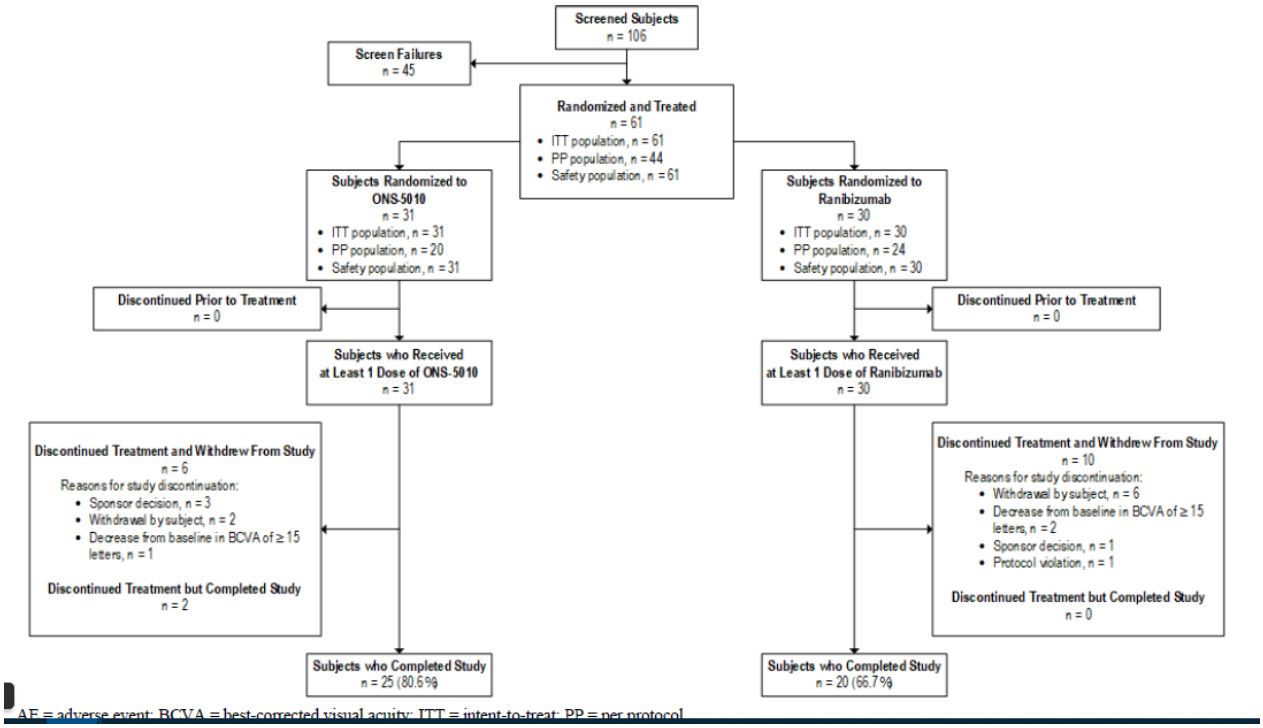
A hierarchical testing method was used to control the Type 1 error at an overall 2-sided alpha level of 0.05. If statistical significance was declared for the primary efficacy endpoint, formal hypothesis testing was conducted for the key secondary and other secondary efficacy endpoints in sequence until a nonsignificant result was reached. The significance testing for secondary endpoints was conducted in the same order listed under Section "3.3.1.4. Outcomes/endpoints", where each successive endpoint analysis was considered significant only if the prior analysis in the hierarchy was significant.

Of note, hierarchy testing applied only to the primary and secondary endpoints analysed using the ITT population. All other p-values, after a nonsignificant p-value was reached, were considered nominal; this also included p-values from endpoints not included in the fixed-sequence testing strategy.

Results

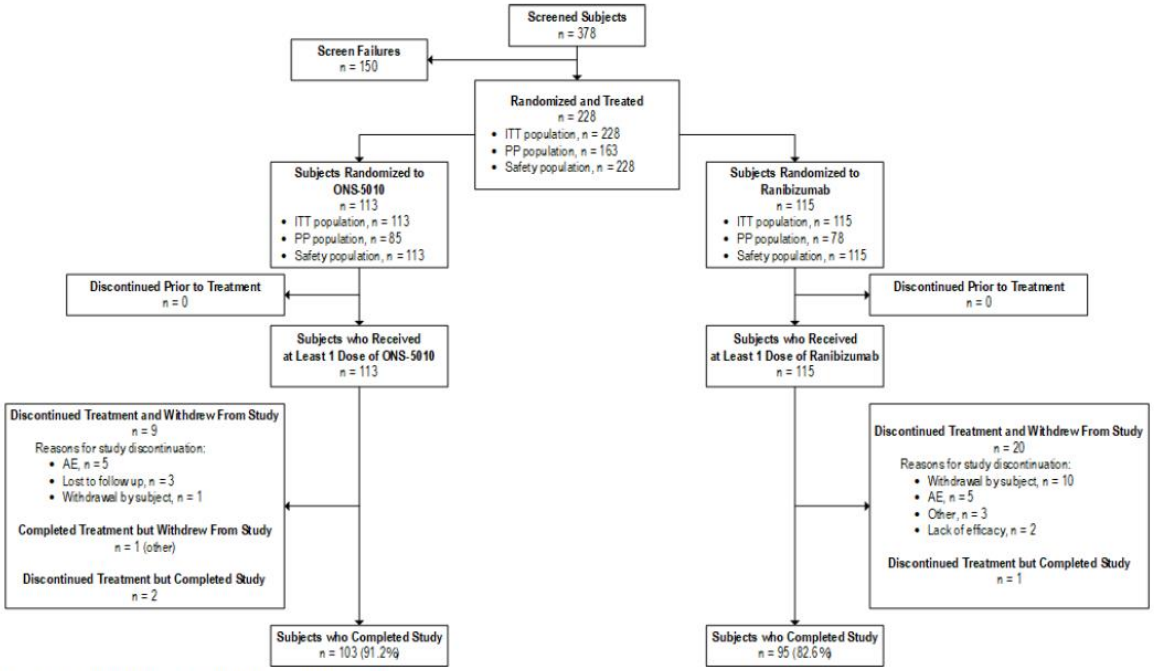
Participant flow

Figure 2. Study ONS-5010-001: Subject Disposition



AE = adverse event; BCVA = best-corrected visual acuity; ITT = intent-to-treat; PP = per protocol

Figure 2. **Study ONS-5010-002: Subject Disposition**



AE = adverse event; ITT = intent-to-treat; PP = per protocol
Source: Table 14.1.1 and Listing 16.2.1.1

Recruitment

Study ONS-5010-001

Date first subject randomised: 24 September 2018

Date last subject completed: 13 August 2020

Study ONS-5010-002

Date first subject randomised: 15 July 2019

Date last subject completed: 08 July 2021

Study ONS-5010-001

Overall, 61 subjects met the entry criteria and were randomised in the study. All randomised subjects received at least 1 dose of their assigned study drug, including 31 subjects in the ONS-5010 group and 30 subjects in the ranibizumab group.

Of the 61 subjects who were randomised, 45 (73.8%) completed the study. The rate of study completion was higher in the ONS-5010 group (25 of 31 subjects [80.6%]) compared with the ranibizumab group (20 of 30 subjects [66.7%]).

Study ONS-5010-002
A total of 378 subjects were screened for the study, of whom 150 were screen failures.
Overall, 228 subjects met the entry criteria and were randomised in the study. All randomised

subjects received at least 1 dose of their assigned study drug, including 113 subjects in the ONS-5010 group and 115 subjects in the ranibizumab group.
Of the 228 subjects who were randomised, 198 (86.8%) completed the study. The rate of study completion was higher in the ONS-5010 group (103 of 113 subjects [91.2%]) compared with the ranibizumab group (95 of 115 subjects [82.6%]).

No abnormalities or imbalances were noted in the participant flow of both studies.

Conduct of the study

NORSE ONE

The original protocol was dated 22 May 2018 and was amended 8 times over the course of the study. In addition to the amendments, a note to file on the use of image reviewers was provided to the study centres to document that, while the protocol initially allowed for inclusion/exclusion criteria of subjects based upon ophthalmic imaging as assessed by the investigator, it was determined necessary to have an independent review of a potential subject's images prior to enrolment/randomisation. Disruptions to the study conduct due to the COVID-19 pandemic did not seem to affect the safety of subjects, the assessment of the study objectives, or the integrity and quality of the data collected.

NORSE TWO:

The original protocol was approved on 19 November 2018 and was amended 6 times over the course of the study. The final approved protocol is Version 6.0, dated 20 December 2019. Disruptions to the study conduct due to the COVID-19 pandemic did not affect the safety of subjects, the assessment of the study objectives, or the integrity and quality of the data collected. Changes made to the protocol are broadly understandable.

Baseline data

Table 8. Study ONS-5010-001: Key Demographic Characteristics (ITT Population)

Parameter	Ranibizumab (N = 30)	ONS-5010 (N = 31)	Overall (N = 61)
Sex, n (%)			
Male	15 (50.0)	9 (29.0)	24 (39.3)
Female	15 (50.0)	22 (71.0)	37 (60.7)
Study eye, n (%)			
Right eye	16 (53.3)	13 (41.9)	29 (47.5)
Left eye	14 (46.7)	18 (58.1)	32 (52.5)
Age at screening (years), n	30	31	61
Mean (SD)	78.5 (5.51)	78.7 (8.05)	78.6 (6.87)
Median	78.0	77.0	78.0
Min, max	70, 90	61, 97	61, 97
Weight (kg), n	30	31	61
Mean (SD)	72.24 (17.538)	72.07 (16.345)	72.16 (16.800)
Median	68.50	68.00	68.00
Min, max	50.0, 129.4	49.5, 130.0	49.5, 130.0
BMI (kg/m^2), n	30	31	61
Mean (SD)	25.633 (6.1316)	27.316 (5.2785)	26.488 (5.7291)
Median	24.340	26.840	25.400
Min, max	18.48, 50.55	17.96, 41.83	17.96, 50.55
Race, n (%)			
White	29 (96.7)	29 (93.5)	58 (95.1)
Asian	1 (3.3)	1 (3.2)	2 (3.3)
Black or African American	0	0	0
Native Hawaiian or Pacific Islander	0	0	0
American Indian or Alaskan Native	0	0	0
Other	0	1 (3.2)	1 (1.6)
Ethnicity, n (%)			
Not Hispanic or Latino	30 (100.0)	31 (100.0)	61 (100.0)

BMI = body mass index; ITT = intent-to-treat; max = maximum; min = minimum; SD = standard deviation
Source: ONS-5010-001 Table 14.1.2

Table 6. Study ONS-5010-002: Key Demographic Characteristics (ITT Population)

Parameter	Ranibizumab (N = 115)	ONS-5010 (N = 113)	Overall (N = 228)
Sex, n (%)			
Male	46 (40.0)	46 (40.7)	92 (40.4)
Female	69 (60.0)	67 (59.3)	136 (59.6)
Study eye, n (%)			
Right eye	51 (44.3)	49 (43.4)	100 (43.9)
Left eye	64 (55.7)	64 (56.6)	128 (56.1)
Age at screening (years), n	115	113	228
Mean (SD)	79.1 (8.49)	78.8 (8.30)	78.9 (8.38)
Median	80.0	79.0	79.0
Min, max	55, 98	54, 97	54, 98
Weight (kg), n	114	113	227
Mean (SD)	76.17 (19.743)	76.98 (17.099)	76.57 (18.438)
Median	73.50	78.40	76.00
Min, max	41.6, 133.8	42.6, 140.6	41.6, 140.6
BMI (kg/m^2), n	114	113	227
Mean (SD)	27.677 (6.1729)	28.187 (5.7548)	27.931 (5.9607)
Median	26.960	27.660	27.390
Min, max	17.05, 55.66	16.79, 51.01	16.79, 55.66
Race, n (%)			
White	113 (98.3)	110 (97.3)	223 (97.8)
Asian	1 (0.9)	1 (0.9)	2 (0.9)
Black or African American	0	2 (1.8)	2 (0.9)
Native Hawaiian or Pacific Islander	0	0	0
American Indian or Alaskan Native	0	0	0
Other	1 (0.9)	0	1 (0.4)

BMI = body mass index; ITT = intent-to-treat; max = maximum; min = minimum; SD = standard deviation
Source: ONS-5010-002 Table 14.1.2

Table 9. Study ONS-5010-001: Baseline Disease Characteristics in the Study Eye (ITT Population)

Parameter	Ranibizumab (N = 30)	ONS-5010 (N = 31)	Overall (N = 61)
AMD diagnosis, n (%)			
Yes	30 (100.0)	31 (100.0)	61 (100.0)

No	0	0	0
Prior anti-VEGF treatment, n (%)			
Yes	15 (50.0)	25 (80.6)	40 (65.6)
No	15 (50.0)	6 (19.4)	21 (34.4)
Baseline BCVA			
Mean (SD)	58.4 (11.73)	61.6 (11.74)	60.0 (11.75)
Median	60.0	68.0	65.0
Min, max	30, 70	30, 73	30, 73
≤ 54 letters, n (%)	9 (30.0)	8 (25.8)	17 (27.9)
≥ 55 letters, n (%)	21 (70.0)	23 (74.2)	44 (72.1)
Baseline BCVA (treatment naïve subjects)			
n	15	6	21
Mean (SD)	60.2 (10.93)	60.3 (15.33)	60.2 (11.93)
Median	60.0	65.0	63.0
Min, max	30, 70	30, 72	30, 72
≤ 67 letters, n (%)	10 (33.3)	4 (12.9)	14 (23.0)
≥ 68 letters, n (%)	5 (16.7)	2 (6.5)	7 (11.5)
Baseline BCVA (previously treated subjects)			
n	15	25	40
Mean (SD)	56.5 (12.57)	62.0 (11.08)	59.9 (11.81)
Median	59.0	68.0	65.0
Min, max	31, 70	33, 73	31, 73
≤ 67 letters, n (%)	11 (36.7)	11 (35.5)	22 (36.1)
≥ 68 letters, n (%)	4 (13.3)	14 (45.2)	18 (29.5)
Baseline CFT, µm (treatment naïve subjects)			
Mean (SD)	373.5 (75.16)	393.8 (86.61)	379.3 (76.93)
Median	344.0	384.0	361.0
Min, max	257, 508	303, 545	257, 545
Baseline CFT, µm (previously treated subjects)			
Mean (SD)	313.8 (120.32)	296.5 (65.07)	303.0 (88.74)
Median	293.0	284.0	284.5
Min, max	108, 519	215, 429	108, 519

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CFT = central foveal thickness; ITT = intent-to-treat; max = maximum; min = minimum; SD = standard deviation

Source: Table 14.1.3

Table 7. Study ONS-5010-002: Baseline Disease Characteristics in the Study Eye (ITT Population)

Parameter	Ranibizumab (N = 115)	ONS-5010 (N = 113)	Overall (N = 228)
AMD diagnosis, n (%)			
Yes	115 (100.0)	113 (100.0)	228 (100.0)
No	0	0	0
Prior anti-VEGF treatment, n (%)			
Yes	5 (4.3)[a]	4 (3.5)[a]	9 (3.9)[a]
No	110 (95.7)	109 (96.5)	219 (96.1)
Baseline BCVA, n (%)			
Mean (SD)	51.1 (12.96)	52.1 (12.16)	51.6 (12.55)
Median	56.0	56.0	56.0
Min, max	20, 73	25, 68	20, 73
≤ 54 letters	55 (47.8)	49 (43.4)	104 (45.6)
≥ 55 letters	60 (52.2)	64 (56.6)	124 (54.4)
Baseline CFT, µm			
Mean (SD)	423.7 (114.77)	430.0 (150.85)	426.8 (133.61)
Median	422.0	392.0	403.5
Min, max	173, 769	181, 926	173, 926
Baseline BCVA (treatment naive subjects)			
n	110	109	219
Mean (SD)	51.1 (13.12)	52.2 (12.16)	51.6 (12.63)
Median	56.0	56.0	56.0
Min, max	20, 73	25, 68	20, 73
Baseline BCVA (previously treated subjects)			
n	5	4	9
Mean (SD)	52.6 (9.71)	51.8 (13.96)	52.2 (10.97)
Median	54.0	58.0	56.0
Min, max	37, 62	31, 60	31, 62

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CFT = central foveal thickness; ITT = intent-to-treat; max = maximum; min = minimum; SD = standard deviation

a Subjects were enrolled prior to amendment 4 of the protocol.

Source: ONS-5010-002 Table 14.1.3

Numbers analysed

NORSE ONE

All 61 randomised subjects were included in the ITT and safety populations. A total of 44 subjects (72.1%) were included in the PP population (20 of 31 subjects [64.5%] in the ONS-5010 group and 24 of 30 subjects [80.0%] in the ranibizumab group) (Table 7).

Table 7. Study ONS-5010-001: Study Populations (All Randomized Subjects)

Subject Populations	Ranibizumab (N = 30) n (%)	ONS-5010 (N = 31) n (%)	Total (N = 61) n (%)
Intent-to-treat[a]	30 (100.0)	31 (100.0)	61 (100.0)
Per protocol[b]	24 (80.0)	20 (64.5)	44 (72.1)
Safety[c]	30 (100.0)	31 (100.0)	61 (100.0)

Percentages are based on the number randomized. The table excludes reasons for discontinuation if no subject in either treatment group discontinued for the specific reason.

A The intent-to-treat (ITT) population included all randomized subjects.

B The per protocol population included all subjects in the ITT population who had at least 1 postdose best-corrected visual acuity assessment, and who were compliant with all critical study criteria.

C The safety population included all subjects who were randomized and who received at least 1 dose of study drug during the treatment period.

Source: Table 14.1.1

NORSE TWO

All 228 randomised subjects were included in the ITT and safety populations. A total of 163 subjects (71.5%) were included in the PP population (85 of 113 subjects [75.2%] in the ONS-5010 group and 78 of 115 subjects [67.8%] in the ranibizumab group)

Table 6. Study ONS-5010-002: Study Populations (All Randomized Subjects)

Subject Populations	Ranibizumab (N = 115) n (%)	ONS-5010 (N = 113) n (%)	Total (N = 228) n (%)
Intent-to-treat[a]	115 (100.0)	113 (100.0)	228 (100.0)
Per protocol[b]	78 (67.8)	85 (75.2)	163 (71.5)
Safety[c]	115 (100.0)	113 (100.0)	228 (100.0)

Percentages are based on the number randomized. The table excludes reasons for discontinuation if no subject in either treatment group discontinued for the specific reason.

a The intent-to-treat (ITT) population included all randomized subjects.

b The per protocol population included all subjects in the ITT population who had at least 1 postdose best-corrected visual acuity assessment, and who were compliant with all critical study criteria.

c The safety population included all subjects who were randomized and who received at least 1 dose of study drug during the treatment period.

Source: Table 14.1.1

Outcomes and estimation

Efficacy Analyses in Study ONS-5010-001 (NORSE ONE) Primary Analysis

The study did not meet its primary efficacy endpoint, the proportion of subjects achieving an increase of ≥ 15 letters in BCVA from baseline to 11 months (7.7% vs 20.8%, respectively, in the ONS-5010 and ranibizumab groups, with a risk difference of −0.1314 [95% CI = −0.3550, 0.0765]; p = 0.2387)

Table 14. Study ONS-5010-001: Primary Efficacy Endpoint - Subjects Gaining ≥ 15 Letters from Baseline to 11 Months (ITT Population)

	Ranibizumab (N = 30)	ONS-5010 (N = 31)
Number of subjects, n/N (%)	5/24 (20.8)	2/26 (7.7)
Risk difference		−0.1314
95% CI[a]		(−0.3550, 0.0765)
p-value[b]		0.2387

CI = confidence interval; ITT = intent-to-treat; n = number of subjects with ≥ 15 letter increase; N = number of subjects with Month 11 assessment

a. Exact 95% CI for risk difference

b. P-value from Fisher's exact test. A hierarchical testing method was used to control Type 1 error at an overall 2-sided 0.05 level.

Subjects who received rescue/prohibited therapy or withdrew from study drug administration due to an adverse event or lack of efficacy were considered nonresponders. Subjects who had missing month 11-month values and did not receive rescue/prohibited therapy or withdrew from study drug administration due to an adverse event or lack of efficacy were treated as missing.

Source: ONS-5010-001 Table 14.2.1.1A

Secondary Measures

As the treatment group difference in the analysis of the primary efficacy endpoint was not significant, the fixed-sequence testing was stopped. No inferential conclusions could therefore be drawn regarding the secondary efficacy endpoints.

Table 17. Study ONS-5010-001: Secondary Efficacy Endpoints – Responder Analyses (ITT Population)

Parameter, n/N (%)	Ranibizumab (N = 30)	ONS-5010 (N = 31)
Subjects gaining ≥ 5 letters from baseline at 11 months, n/N (%)	11/24 (45.8)	11/26 (42.3)
Risk difference		−0.0353
95% CI[a]		(−0.3101, 0.2544)
p-value[b]		1.0000
Subjects gaining ≥ 10 letters from baseline at 11 months, n/N (%)	9/24 (37.5)	3/26 (11.5)
Risk difference		−0.2596
95% CI[a]		(−0.4953, −0.0171)
p-value[b]		0.0475
Subjects losing < 15 letters from baseline at 11 months, n/N (%)	20/24 (83.3)	23/26 (88.5)
Risk difference		0.0513
95% CI[a]		(−0.1616, 0.2702)
p-value[b]		0.6971
Subjects with a visual acuity Snellen equivalent of 20/200 or worse at 11 months, n/N (%)[c]	5/24 (20.8)	4/26 (15.4)
Risk difference		−0.0545
95% CI[a]		(−0.2922,0.1777)
p-value[b]		0.7210

CI = confidence interval; ITT = intent-to-treat; n = number of subjects meeting criterion, N = number of subjects with Month 11 assessment

a Exact 95% CI for risk difference.

b P-value from Fisher's exact test. A hierarchical testing method was used to control Type 1 error at an overall 2-sided alpha of 0.05.

c 20/200 is the visual acuity Snellen equivalent of 35 letters.

Subjects who received rescue/prohibited therapy or withdrew from study drug administration due to an adverse event or lack of efficacy were considered nonresponders. Subjects who had missing 11-month values and did not receive rescue/prohibited therapy or withdrew from study drug administration due to an adverse event or lack of efficacy were treated as missing.

Source: Table 14.2.2.6A

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Table 14.2.2.1A

First Secondary Efficacy Analysis - Trimmed Means Fixed Approach
(ITT Population)

Parameter	Statistic	Ranibizumab (N=30)	ONS-5010 (N=31)
BCVA Score Change from Baseline to 11 Months [1]	n	20	23
	Mean (SD)	8.0 (9.30)	3.2 (8.33)
	Median	8.0	4.0
	Min, Max	-5, 27	-14, 20
LS Means (Q1, Q3) [2]		9.441 (8.417, 10.530)	9.187 (8.215, 10.265)
(95% CI)		(6.104, 12.301)	(5.949, 11.934)
LS Means Difference			-0.254
(95% CI)			(-6.236, 5.764)
p-value			0.7411

Note: BCVA = Best Corrected Visual Acuity.
Note: The trimmed means fixed approach compares the 50% best (> median) observations in each treatment arm. Those observations with missing data at 11 months had values worse than the median imputed to calculate the adjusted median in which the best 50% were subset. Observations are ranked based on baseline adjusted 11-month scores. The p-value to test the LS Means difference was determined by taking the proportion of values in a 10,000 permutation distribution more extreme than the observed effect. The 95% CI surrounding the LS means difference was determined by taking the 2.5 and 97.5 percentiles from the same permutation distribution. The PROC MULTTEST procedure in SAS v9.4 was used to produce one dataset containing 10,000 permutated treatment effects. The procedure used seed 2250.
[1] Summary statistics based on observed changes from baseline to 11 months.
[2] Q1 = 25th percentile, Q3 = 75th percentile.
Reference Listing: 16.2.6.1

Date of data extract: 26AUG2020

Table 14.2.2.2A

Second Secondary Efficacy Analysis - Trimmed Means Adaptive Approach
(ITT Population)

Parameter	Statistic	Ranibizumab (N=30)	ONS-5010 (N=31)
BCVA Score Change from Baseline to 11 Months [1]	n	20	23
	Mean (SD)	8.0 (9.30)	3.2 (8.33)
	Median	8.0	4.0
	Min, Max	-5, 27	-14, 20
LS Means (Q1, Q3) [2]		5.384 (4.435, 6.334)	6.253 (4.951, 7.482)
(95% CI)		(2.641, 8.152)	(2.814, 10.089)
LS Means Difference			0.868
(95% CI)			(-5.098, 6.982)
p-value			0.8352

Note: BCVA = Best Corrected Visual Acuity.
Note: The trimmed means adaptive approach assigns a percentile floor in the treatment arm based on the greatest proportion of dropouts observed between the two arms. Those observations with missing data at 11 months had values worse than the percentile floor imputed to calculate the adjusted floor in which the best observations were subset. Observations are ranked based on baseline adjusted 11-month scores. The p-value to test the LS Means difference was determined by taking the proportion of values in a 10,000 permutation distribution more extreme than the observed effect. The 95% CI surrounding the LS means difference was determined by taking the 2.5 and 97.5 percentiles from the same permutation distribution. The PROC MULTTEST procedure in SAS v9.4 was used to produce one dataset containing 10,000 permutated treatment effects. The procedure used seed 2830.
[1] Summary statistics based on observed changes from baseline to 11 months.
[2] Q1 = 25th percentile, Q3 = 75th percentile.
Reference Listing: 16.2.6.1

Protocol ONS-5010-001
Date of data extract: 26AUG2020

Table 14.2.3.2A

Sensitivity Analysis - Multiple Imputation by Washout
(ITT Population)

Parameter	Statistic	Ranibizumab (N=30)	ONS-5010 (N=31)
BCVA Score Change from Baseline to 11 Months [1]	n	20	23
	Mean (SD)	8.0 (9.30)	3.2 (8.33)
	Median	8.0	4.0
	Min, Max	-5, 27	-14, 20
LS Means (SE)		7.451 (2.1008)	5.903 (1.9216)
(95% CI)		(3.328, 11.573)	(2.135, 9.671)
LS Means Difference			-1.548 (2.9109)
(95% CI)			(-7.259, 4.163)
p-value [2]			0.5950

Note: BCVA = Best Corrected Visual Acuity.
Note: Missing 11-month values for the ONS-5010 treatment group will be replaced with a set of plausible values that represents the uncertainty of the correct value based on the observed time matched data for the ranibizumab group at all other visits.
[1] Summary statistics based on observed changes from baseline to 11 months.
[2] p-value using analysis of covariance (ANCOVA) with treatment as the factor and study baseline value as a covariate. The p-value is testing the difference in LS Means among the treatment arms.
Reference Listing: 16.2.6.1

Protocol ONS-5010-001
Date of data extract: 26AUG2020

Table 14.2.3.4A

Sensitivity Analysis - Jump to Reference
(ITT Population)

Parameter	Statistic	Ranibizumab (N=30)	ONS-5010 (N=31)
BCVA Score Change from Baseline to 11 Months [1]	n	30	31
	Mean (SD)	8.4 (9.86)	3.9 (9.14)
	Median	6.9	4.0
	Min, Max	-5, 32	-14, 28
LS Means (SE)		7.899 (1.6148)	4.433 (1.5883)
(95% CI)		(4.667, 11.132)	(1.254, 7.612)
LS Means Difference			-3.466 (2.2763)
(95% CI)			(-8.023, 1.090)
p-value [2]			0.1332

Note: BCVA = Best Corrected Visual Acuity.
Note: This method imputes the change in the ONS-5010 treatment group for any missing individual subject's 11-month BCVA data by the ranibizumab group mean at Month 11.
[1] Summary statistics based on changes from baseline to 11 months using jump to reference.
[2] p-value using analysis of covariance (ANCOVA) with treatment as the factor and study baseline value as a covariate. The p-value is testing the difference in LS Means among the treatment arms.
Reference Listing: 16.2.6.1

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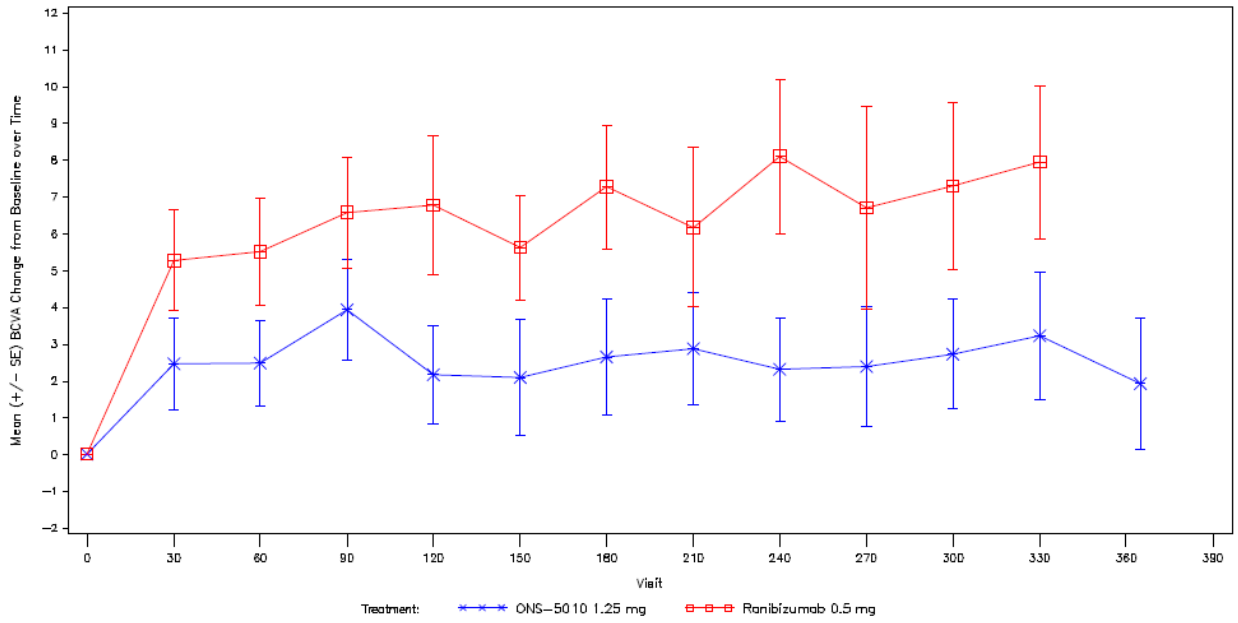
Date of data extract: 26AUG2020

Figure 14.2.2.5A

Mean (+/- SE) BCVA Change from Baseline over Time
(ITT Population)



Reference Listing: 16.2.6.1

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Exploratory Efficacy Analysis

In the ITT population, the LS mean (SE) change from baseline in CFT was −32.010 (20.9689) µm in the ONS-5010 group and −16.515 (23.0737) µm in the ranibizumab group (LS mean difference = −15.495; 95% CI = −78.601, 47.612); p = 0.6222) (Table 18). The results obtained in the PP population were consistent with those obtained in the ITT population.

Table 18. Study ONS-5010-001: Exploratory Efficacy Endpoint – Change in Central Foveal Thickness (µm) from Baseline to 11 Months (ITT Population)

	Ranibizumab (N = 30) n = 19	ONS-5010 (N = 31) n = 23
Mean (SD)	−17.9 (112.03)	−30.8 (93.98)
Median	−14.0	−23.0
Min, max	−209, 370	−284, 183
LS mean (SE)	−16.515 (23.0737)	−32.010 (20.9689)
95% CI	(−63.186, 30.156)	(−74.423, 10.404)
LS mean difference		−15.495 (31.1992)
95% CI		(−78.601, 47.612)
p-value[a]		0.6222

CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; n = number of subjects meeting criterion; LS = least squares; N = number of subjects with Month 11 assessment; SD = standard deviation; SE = standard error
Summary statistics are based on observed changes from baseline to 11 months.
a P-value using analysis of covariance with study drug group as a fixed effect and baseline BCVA as a continuous covariate. The p-value tested the difference in LS mean values between study drug groups.
Source: Table 14.2.4.1A

Study ONS-5010-002

Study ONS-5010-002 provided substantial evidence of clinical efficacy and met its primary efficacy endpoint, demonstrating that ONS-5010 was superior to ranibizumab, when ranibizumab was administered in a manner consistent with the PIER study dosing regimen, for the proportion of subjects achieving an increase of ≥ 15 letters in BCVA from baseline to 11 months. Specifically, in the ITT population, 45 subjects (41.7%) in the ONS-5010 group compared with 24 subjects (23.1%) in the ranibizumab group gained ≥ 15 letters from baseline to 11 months. The difference observed between the study drug groups was significant, with a risk difference of 0.1859 (95% CI = 0.0442, 0.3086; p = 0.0052) (Table 10). A graphical presentation of the percentage of subjects gaining ≥ 15 letters from baseline over time is shown in Figure 2.

The primary efficacy results obtained using the PP population were consistent with those observed in the ITT population, with 34 subjects (41.0%) in the ONS-5010 group and 18 subjects (24.7%) in the ranibizumab group gaining ≥ 15 letters in BCVA from baseline to 11 months; the difference between study drug groups strongly favoured ONS-5010, with a risk difference of 0.1631 (95% CI = 0.0120, 0.3083; p = 0.0409) (ONS-5010-002 CSR Table 14.2.1.1B).

Table 10. Study ONS-5010-002: Primary Efficacy Endpoint - Subjects Gaining ≥ 15 Letters from Baseline to 11 Months (ITT Population)

	Ranibizumab (N = 115)	ONS-5010 (N = 113)
Number of subjects, n/N (%)	24/104 (23.1)	45/108 (41.7)
Risk difference		0.1859
95% CI[a]		0.0442, 0.3086
p-value[b]		0.0052

CI = confidence interval; ITT = intent-to-treat; n = number of subjects with ≥ 15 letter increase; N = number of subjects with Month 11 assessment

a Exact 95% CI for risk difference

b P-value from Fisher's exact test. A hierarchical testing method was used to control Type 1 error at an overall 2-sided 0.05 level.

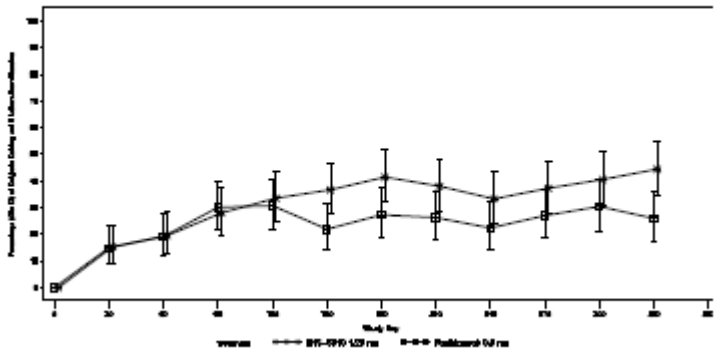
Subjects who received rescue/prohibited therapy or withdrew from study drug administration due to an adverse event or lack of efficacy were considered nonresponders. Subjects who had missing 11-month values and did not receive rescue/prohibited therapy or withdrew from study drug administration due to an adverse event or lack of efficacy were treated as missing.

Source: ONS-5010-002 Table 14.2.1.1A

Because the difference between study drug groups in the analysis of the primary efficacy endpoint was significant, the fixed-sequence testing continued with the analysis of the first secondary efficacy endpoint.

Overall, the difference between study drug groups was significant, favouring ONS-5010, for the first secondary efficacy endpoint (change from baseline in BCVA to 11 months) using both trimmed means approaches (Table 11). Since the trimmed mean approaches only compare the best remaining % after trimming and it is uncertain whether the results are representative for the entire sample, focus was placed on two further analyses using reference-based imputation. Thereby, the LS mean change in BCVA from baseline to 11 months using an ANCOVA with a multiple imputation by wash-out approach was 9.156 letters in the ONS-5010 group and 5.351 letters in the ranibizumab group (LS mean difference of 3.805 [95% CI = -0.016, 7.626]; p = 0.0510). Similarly, the LS mean change in BCVA from baseline to 11 months using the Jump-to-Reference imputation was 11.205 letters in the ONS-5010 group and 6.904 letters in the ranibizumab group (LS mean difference = 4.301 [95% CI = 0.934, 7.668]; p = 0.0125).

Figure 2. Study ONS-5010-002: Subjects Gaining ≥ 15 Letters from Baseline Over Time (ITT Population)



CI = confidence interval

Table 11. Study ONS-5010-002: Secondary Efficacy Endpoint – Best-Corrected Visual Acuity Change from Baseline to 11 Months by Trimmed Means Fixed and Adaptive Approaches (ITT Population)

	Ranibizumab (N = 115) n = 96	ONS-5010 (N = 113) n = 104
Mean (SD)	5.8 (14.80)	11.2 (12.19)
Median	6.0	12.0
Min, max	−42, 42	−47, 40
Trimmed Means Fixed Approach		
LS mean[a,b]	14.575	19.310
LS mean difference (95% CI)		4.735 (1.306, 8.163)
p-value		0.0035
Trimmed Means Adaptive Approach		
LS mean[a,c]	5.770	13.640
LS mean difference (95% CI)		7.870 (4.536, 12.599)
p-value		0.0001

CI = confidence interval; ITT = intent-to-treat; LS = least squares; max = maximum; min= minimum; SD = standard deviation
Summary statistics were based on observed changes in best-corrected visual acuity from baseline to 11 months. Observations were ranked based on baseline adjusted 11-month scores. The p-values to test the LS mean differences were determined by taking the proportions of values in a 10,000 permutation distribution more extreme than the observed effect. The 95% CI surrounding the LS mean difference was determined by adding the 2.5 and 97.5 percentiles from the same permutation distribution to the observed LS mean difference.

a The LS mean values and LS mean difference were estimated from and analysis of covariance model using the subset of values greater than the percentile floor.

b The trimmed means fixed approach compared the 50% best (> median) observations in each study drug group. Those observations with missing data at 11 months had values worse than the median imputed to calculate the adjusted median in which the best 50% were subset.

c The trimmed means adaptive approach assigns a percentile floor in the study drug group based on the greatest proportion of dropouts observed between the 2 groups. Those observations with missing data at 11 months had values worse than the percentile floor imputed to calculate the adjusted floor in which the best observations were subset.

Source: ONS-5010-002 Table14.2.2.1A and Table 14.2.2.2A

There was a significant difference favouring ONS-5010 when compared with ranibizumab in the sequential testing of the first 3 remaining secondary efficacy endpoints (ie, the proportions of subjects who gained ≥ 5 letters and ≥ 10 letters in BCVA from baseline to 11 months, and the proportion of subjects who lost < 15 letters in BCVA from baseline to 11 months) (Table 12). In the ONS-5010 group, 74 subjects (68.5%) gained ≥ 5 letters in BCVA, 61 subjects (56.5%) gained ≥ 10 letters in BCVA, and 101 subjects (93.5%) lost < 15 letters in BCVA from baseline to 11 months. In the ranibizumab group, 53 subjects (51.0%), 36 subjects (34.6%), and 86 subjects (82.7%) were included in the same respective BCVA responder categories. For each of these fixed-sequence secondary endpoints, the difference between study drug groups was significant ($p \leq 0.0185$). The proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 11 months (ie, the final secondary efficacy endpoint in the fixed-sequence) was lower in the ONS-5010 group (13.0% [14 subjects]) compared with the ranibizumab group (24.0% [25/104], p=0.0505).

Table 12. Study ONS-5010-002: Secondary Efficacy Endpoints – Responder Analyses (ITT Population)

Parameter, n/N (%)	Ranibizumab (N = 115)	ONS-5010 (N = 113)
Subjects gaining ≥ 5 letters from baseline at 11 months, n/N (%)	53/104 (51.0)	74/108 (68.5)
Risk difference		0.1756
95% CI[a]		0.0315, 0.3052
p-value[b]		0.0116
Subjects gaining ≥ 10 letters from baseline at 11 months, n/N (%)	36/104 (34.6)	61/108 (56.5)
Risk difference		0.2187
95% CI[a]		0.0726, 0.3487
p-value[b]		0.0016
Subjects losing < 15 letters from baseline at 11 months, n/N (%)	86/104 (82.7)	101/108 (93.5)
Risk difference		0.1083
95% CI[a]		0.0168, 0.2044
p-value[b]		0.0185
Subjects with a visual acuity Snellen equivalent of 20/200 or worse at 11 months, n/N (%)[c]	25/104 (24.0)	14/108 (13.0)
Risk difference		−0.1108
95% CI[a]		−0.2187, −0.0050
p-value[b]		0.0505

CI = confidence interval; ITT = intent-to-treat; n = number of subjects meeting criterion, N = number of subjects with Month 11 assessment

a Exact 95% CI for risk difference.

b P-value from Fisher's exact test. A hierarchical testing method was used to control Type 1 error at an overall 2-sided alpha of 0.05.

c 20/200 is the visual acuity Snellen equivalent of 35 letters.

Subjects who received rescue/prohibited therapy or withdrew from study drug administration due to an adverse event or lack of efficacy were considered nonresponders. Subjects who had missing 11-month values and did not receive rescue/prohibited therapy or withdrew from study drug administration due to an adverse event or lack of efficacy were treated as missing.

Source: ONS-5010-002 Table 14.2.2.6A

Table 13. Study ONS-5010-002: Secondary Efficacy Endpoint – First and Second Complementary Analyses of the Change in Best-Corrected Visual Acuity from Baseline to 11 Months (ITT Population)

BCVA Change from Baseline to 11 Months[a]	Ranibizumab (N = 115) n = 96	ONS-5010 (N = 113) n = 104
ANCOVA		
Mean (SD)	5.8 (14.80)	11.2 (12.19)
Median	6.0	12.0
Min, max	−42, 42	−47, 40
LS mean (SE)	5.807 (1.3519)	11.226 (1.2989)
95% CI	3.141, 8.473	8.665, 13.788
LS mean difference		5.419 (1.8748)
95% CI		1.722, 9.117
p-value[a]		0.0043
ANCOVA with multiple imputation[b]		
Mean (SD)	5.8 (14.80)	11.2 (12.19)
Median	6.0	12.0
Min, max	−42, 42	−47, 40
LS mean (SE)	5.131 (1.3632)	11.191 (1.3112)
95% CI	2.459, 7.803	8.621, 13.761
LS mean difference		6.060 (1.8927)
95% CI		2.350, 9.770
p-value[a]		0.0014

ANCOVA = analysis of covariance; BCVA = best-corrected visual acuity; CI = confidence interval; ITT = intent-to-treat; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SE = standard error

Summary statistics are based on observed changes from baseline to 11 months.

a P-value using an ANCOVA with study drug group as fixed effect and baseline BCVA as a continuous covariate. The p-value tested the difference in LS mean values between study drug groups.

b Missing 11-month BCVA values were replaced using the multiple imputation method with a set of plausible values that represented the uncertainty of the correct value based on the observed time matched data at all other visits. The multiple imputation was completed by 2 steps: (1) impute these intermittent missing data using Markov chain Monte Carlo methods to get a monotone missingness data pattern and, (2) use the regression method to impute missing data. This method of imputation assumed that missing data were missing at random.

c The 95% CIs and the p-values are based on the overall estimates from 100 imputations, testing the ONS-5010 group versus the ranibizumab group using the difference between Month 11 and baseline.

Source: ONS-5010-002 Table 14.2.2.4A and Table 14.2.2.5A

Across all sensitivity analyses of the first secondary efficacy endpoint, there was a consistently greater improvement in BCVA in the ONS-5010 group compared with the ranibizumab group at 11 months.

The efficacy analyses conducted using the PP population were generally similar to the analyses conducted using the ITT population, further confirming the efficacy conclusions of the study.

Ancillary analyses

Subgroup analyses are mainly of importance regarding NORSE ONE study, where the applicant postulates a difference between treated and treatment naïve patients.

While initially allowing both patient groups into the trial the applicant attributes its failure to the high and uneven proportion of previously treated patients in treatment arms.

Parameter	Ranibizumab (N = 30)	ONS-5010 (N = 31)
Prior anti-VEGF treatment, n (%)		
Yes	15 (50.0)	25 (80.6)
No	15 (50.0)	6 (19.4)

Table 16. Study ONS-5010-001: Treatment-Naïve Wet-AMD Subjects Achieving ≥ 15 Letters BCVA at Month 11

	ONS-5010	Ranibizumab
Subjects achieving ≥ 15 letters BCVA at Month 11	33%	28.6%

BCVA = best-corrected visual acuity; n = number of subjects with ≥ 15 letter increase; N = number of subjects with Month 11 assessment
Source: ONS-5010 Table 14.2.1.2A

Table 17. Study ONS-5010-001: Subjects with Baseline Visual Acuity of 20/50 or Worse Wet-AMD Subjects Achieving ≥ 15 Letters BCVA at Month 11

	ONS-5010	Ranibizumab
Proportion of Treatment-Naïve Subjects with Baseline Visual Acuity of 20/50 or worse (≤ 67 letters)	50%	40%

Source: ONS-5010 Table 14.2.1.3A

Table 18. Study ONS-5010-001: BCVA Score Change from Baseline to 11 Months

Baseline BCVA and prior treatment		Statistic	ONS-5010 (N=31)	Ranibizumab (N=30)
Treatment Naïve/ BCVA ≤ 67	BCVA Score Change from Baseline to 11 Months	n	4	7
		Mean	8.3	13.7

BCVA = best-corrected visual acuity; SD = standard deviation
Source: ONS-5010-001 Table 14.2.2.3E

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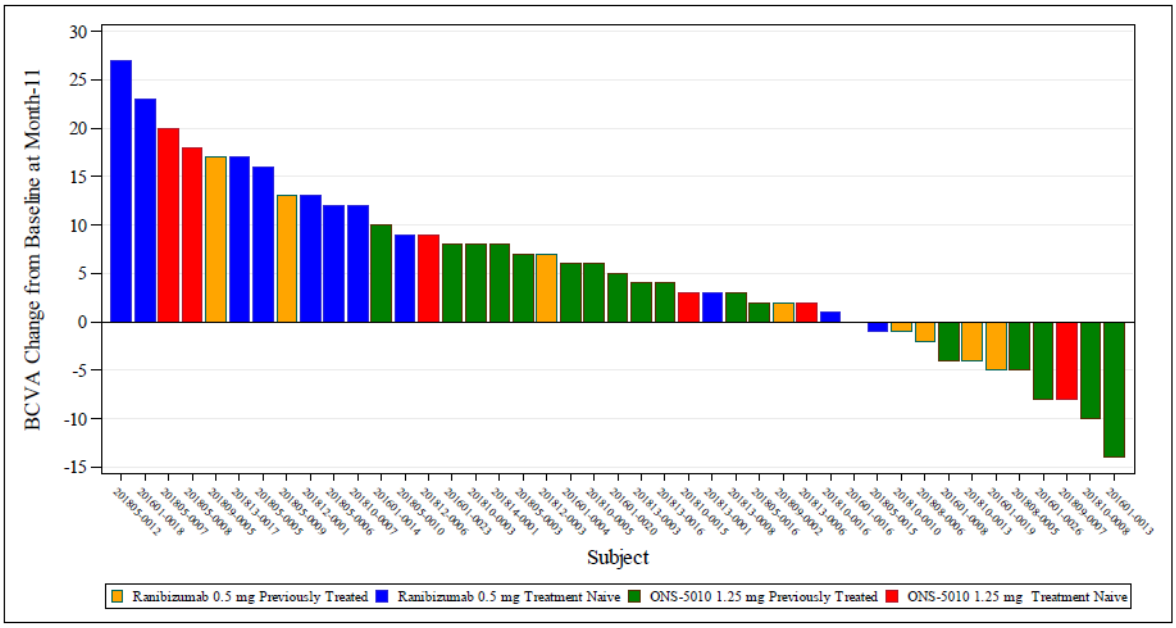
Figure 14.2.2.5C

Waterfall Plot of BCVA Change from Baseline at Day 330
(ITT Population)



Reference Listing: 16.2.6.1

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Subgroup analysis in treatment naïve patients also reveal no significant outcome in the primary measure.

A slight trend in favour of ONS-5010 cannot be considered indicative of superiority, and in pretreated patients, the trend seems to favour ranibizumab. In general numbers in subgroups are two small to derive any meaningful interpretation. Furthermore, the waterfall plot above indicates that previous treatment is no clear predictor of efficacy. While a general trend for better efficacy in treatment naïve patients (in both treatments) is in fact notable, efficacy on individual level seems not to be predictable.

Legal Blindness

In the ONS-5010 –002 study the proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 11 months (i.e., the final secondary efficacy endpoint in the fixed-sequence) was lower in the ONS-5010 group (13.0% [14/108 subjects]) compared with the ranibizumab group (24% [25/104 subjects]) according to Table 12, ITT population. Both Lytenava Phase-III studies present an outstandingly high proportion of legally blind subjects, independently of the treatment arm, even in the clinically superior active study drug group. The 8-10 times higher occurrence of legally blind patients at the efficacy evaluation checkpoints needed further clarification. In the response, the applicant clarified that subjects entered the NORSE studies with a relatively low visual acuity at baseline. Overall, 72.1% of subjects in NORSE ONE and 54.4% of subjects in NORSE TWO had a baseline BCVA of ≥ 55 letters, which is Snellen equivalent of 20/80 or better. The applicant provided a tabulated comparison of baseline and 11-month mean BVCA values as

well as the proportion of legally blind (Snellen 20/200) patients at 1 year of the NORSE ONE and NORSE TWO studies with off-label IVT Avastin studies CATT, IVAN and BRAMD as well as Lucentis clinical studies ANCHOR, MARINA and PIER. However, taking into consideration the MCID in BCVA in ETDRS letter scores, the mean baseline BCVA observed in NORSE ONE and NORSE TWO studies do not differ relevantly from those observed in all but one clinical study cited in the applicant's response (the only exception was the ANCHOR study). Therefore, the applicant's explanation that the remarkable differences observed in the ratio of legally blind patients at the end of NORSE ONE and NORSE TWO studies compared to literature data could be fully explained with the baseline BCVA differences, is not agreed.

In order to better contextualise the legally blind patients treated with LYTENAVA, a sensitivity analysis has been conducted.

In the pre-planned analysis of NORSE ONE, the proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 11 months was 15.4% (4/26) in the ONS-5010 group and 20.8% (5/24) in the ranibizumab group. Similar proportions were reported in the pre-planned analysis of NORSE TWO, with 13.0% (14/108 subjects) in the ONS-5010 group and 24% (25/104 subjects) the ranibizumab group with a 20/200 or worse visual acuity.

It should be noted that this analysis included subjects who were 35 letters or worse at the month 11 visit and missing month 11 data were handled based on the category of reason for discontinuation. Subjects who discontinued due to an AE, lack of efficacy, or use of rescue therapy were categorised as non-responders and included in the analysis, whereas subjects who discontinued for other reasons and had a missing Month 11 BCVA were treated as missing.

A sensitivity analysis was also presented where the ONS-5010 subjects with missing month 11 values who discontinued treatment for any reason are treated as non-responders and ranibizumab subjects, the response was determined from the multiply imputed month 11 BCVA value, i.e., impute-then-dichotomise. Multiple imputation was performed on all ranibizumab subjects under the assumption of missing at random. The response rate averaged over the 100 imputed datasets of subjects with a visual acuity Snellen equivalent of 20/200 or worse was 8.0% in the ONS-5010 arm (in line with the studies cited by the applicant) and 17.4% in the comparator arm. This analysis is however considered extremely conservative, as the treatment arms are treated differently and in favour of the control group. Altogether this post-hoc subset analysis with disproportionate handling of intercurrent events should thus not be overinterpreted and is therefore not further considered.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Title: A Clinical Effectiveness, Multicenter, Randomized, Double-Masked, Controlled Study of the Efficacy and Safety of ONS-5010 in Subjects with Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD)			
Study identifier	ONS-5010-001 (NORSE ONE); NCT03844074		
Design	This was a multi-centre, randomised, double-masked, controlled study performed in Australia that evaluated the efficacy and safety of intravitreally administered ONS-5010 in subjects with neovascular (wet) AMD. Eligible subjects were randomised in a 1:1 ratio to receive ONS-5010 or ranibizumab in the study eye. ONS-5010 was dosed monthly against ranibizumab (Lucentis) dosed according to the PIER regimen in the Lucentis labelling.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable not applicable
Hypothesis	Superiority		
Treatment groups	ONS-5010		Subjects randomised to receive ONS-5010 were administered a monthly intravitreal injection of 1.25 mg of ONS-5010 in the study eye for up to 12 months until study completion for a total of 12 intravitreal injections. A total of 31 subjects were randomised to the ONS-5010 group.
	Ranibizumab		Subjects randomised to ranibizumab, received 0.5 mg of ranibizumab by intravitreal injection in the study eye every month for 3 months (ie, on Days 0, 30, and 60) followed by 2 additional injections, 90-days apart, on Days 150 and 240. Subjects in the ranibizumab group underwent sham procedures at visits when they did not receive an active (ranibizumab) injection. Subjects in the ranibizumab group received a total of 11 procedures, 5 intravitreal injections and 6 sham procedures. A total of 30 subjects were randomised to the ranibizumab group.
Endpoints and definitions	Primary endpoint	≥ +15 letters BCVA	The proportion of subjects who gained ≥ 15 letters in BCVA from baseline to 11 months
	Secondary	Mean Change BCVA	The mean change from baseline in BCVA to 11 months

	Secondary	≥ +5 letters BCVA	The proportion of subjects who gained ≥ 5 letters in BCVA at 11 months compared with baseline
	Secondary	≥ +10 letters BCVA	The proportion of subjects who gained ≥ 10 letters in BCVA at 11 months compared with baseline
	Secondary	Loss of <15 letters BCVA	The proportion of subjects who lost fewer than 15 letters in BCVA at 11 months compared with baseline
	Secondary	20/200 or worse VA	The proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 11 months (legal blindness was defined as both eyes with 20/200 or worse)
Database lock	Efficacy database lock (month 11):29JUL2020 Safety database lock (month 12): 26AUG2020		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	The intent-to-treat (ITT) population included all randomised subjects. All efficacy analyses were performed on the ITT population, and subjects were analysed in the study drug group to which they were randomised. Results based on the ITT population were considered primary for drawing efficacy conclusions. All 61 randomised subjects received at least 1 dose of their assigned study drug and were included in the intent-to-treat (ITT) and safety populations. Subgroup populations: Among the randomised subjects, 21 subjects were naïve to nAMD treatment in the study eye (6 subjects in the ONS-5010 group and 15 in the ranibizumab group). Among the randomised subjects, 14 subjects were naïve to nAMD treatment and had a baseline BCVA of ≤ 67 letters read in the study eye, which correlated with the population of subjects planned for inclusion in a definitive Phase 3 study (4 subjects in the ONS-5010 group and 10 in the ranibizumab group). The per protocol (PP) population included all subjects in the ITT population who had at least 1 post-dose BCVA assessment and were compliant with all critical study criteria. Subjects with major protocol violations, identified prior to unmasking of the study, were excluded from the PP population. Where conducted, efficacy analyses based on the PP population were considered supportive of the primary analyses based on the ITT population. A total of 44 subjects (72.1%) were included in the PP population (20 of the 31 subjects [64.5%] in the ONS-5010 group and 24 of the 30 subjects [80.0%] in the ranibizumab group).		
Descriptive statistics and estimate variability	Treatment group	Ranibizumab	ONS-5010
	Number of subjects	30	31
	Primary: ≥ +15 letters BCVA (%)	20.8	7.7
	Primary: ≥ +15 letters BCVA – treatment naive (%)	28.6	33.3
	Primary: ≥ +15 letters BCVA – treatment naïve/ BCVA ≤ 67 (%)	40.0	50.0
	Secondary: Mean Change BCVA (mean)	8.0	3.2
	Standard deviation	9.30	8.33

	Secondary: Mean Change BCVA – treatment naive (mean [SD])	8.8 [9.66]	5.9 [6.54]
	Secondary: ≥ +5 letters BCVA (%)	45.8	42.3
	Secondary: ≥ +10 letters BCVA	37.5	11.5
	Secondary: Loss of <15 letters BCVA	83.3	88.5
	Secondary: 20/200 or worse VA	20.8	15.4
	Primary endpoint: ≥ +15 letters BCVA	Comparison groups	ONS-5010 - Ranibizumab
		Risk difference	-0.1314
		95% Confidence Interval	-0.3550, 0.0765
Effect estimate per comparison	Primary endpoint: ≥ +15 letters BCVA	P-value Fisher's exact test	0.2387
	Primary endpoint: ≥ +15 letters BCVA – treatment naive	Comparison groups	ONS-5010 - Ranibizumab
		Risk difference	0.0476
		95% Confidence Interval	-0.3678, 0.5164
	Primary endpoint: ≥ +15 letters BCVA – treatment naive	P-value Cochran-Mantel-Haenszel test	0.6635
		Comparison groups	ONS-5010 - Ranibizumab
	Primary endpoint: ≥ +15 letters BCVA – treatment naïve/ BCVA ≤ 67	Risk difference	0.1000
		95% Confidence Interval	-0.4520,0.6395
	Primary endpoint: ≥ +15 letters BCVA – treatment naïve/ BCVA ≤ 67	P-value Fisher's exact test	1.0000
		Comparison groups	ONS-5010 - Ranibizumab
		LS mean	Ranibizumab = 7.451

Secondary: Mean Change BCVA;	LS mean difference	-1.548
	95% Confidence Interval	−7.259, 4.163
MI by washout Approach	P-value ANCOVA	Not significant
Secondary: Mean Change BCVA; Jump-to-Reference Imputation	Comparison groups	ONS-5010 - Ranibizumab
	LS mean	Ranibizumab = 7.889
	LS mean difference	-3.466
Secondary: Mean Change BCVA; Jump-to-Reference Imputation	95% Confidence Interval	−8.023, 1.090
	P-value ANCOVA	Not significant
Secondary: Mean Change BCVA – treatment naïve;	Comparison groups	ONS-5010 - Ranibizumab
	LS mean	Ranibizumab = 8.803
ANCOVA Day 120 to Day 330	LS mean difference	-2.878
Secondary: Mean Change BCVA – treatment naïve;	95% Confidence Interval	-11.167, 5.411
	P-value ANCOVA	Not significant
ANCOVA Day 120 to Day 330	Comparison groups	ONS-5010 - Ranibizumab
Secondary: Mean Change BCVA – treatment naïve/	Difference	-2.054
	95% Confidence Interval	-16.334, 12.225
Secondary: Mean Change BCVA – treatment naïve/ BCVA ≤ 67;	P-value t-test	Not significant
	Comparison groups	ONS-5010 - Ranibizumab
ANCOVA Day 120 to Day 330	Risk difference	−0.0545
Secondary: 20/200 or worse VA	95% Confidence Interval	−0.2922, 0.1777
	P-value Fisher’s exact test	Not significant
Secondary: Mean Change BCVA – treatment naïve/ BCVA ≤ 67;		
ANCOVA Day 120 to Day 330		
Secondary: Mean Change BCVA – treatment naïve/		
Secondary: Mean Change BCVA –		

	treatment naïve/ BCVA ≤ 67; ANCOVA Day 120 to Day 330		

Title: A Clinical Effectiveness, Multicenter, Randomized, Double-Masked, Controlled Study of the Efficacy and Safety of ONS-5010 in Subjects with Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD)			
Study identifier	ONS-5010-002 (NORSE TWO); NCT03834753		
Design	This was a multi-centre, randomised, double-masked, adequate and well-controlled Phase 3 study performed in the US that evaluated the efficacy and safety of intravitreally administered ONS-5010 in subjects with neovascular (wet) AMD. Eligible subjects were randomised in a 1:1 ratio to receive ONS-5010 or ranibizumab in the study eye. ONS-5010 was dosed monthly against ranibizumab (Lucentis) dosed according to the PIER regimen in the Lucentis labelling.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable not applicable
Hypothesis	Superiority		
Treatment groups	ONS-5010		Subjects randomised to receive ONS-5010 were administered a monthly intravitreal injection of 1.25 mg of ONS-5010 in the study eye for up to 12 months until study completion for a total of 12 intravitreal injections. A total of 113 subjects were randomised to the ONS-5010 group.
	Ranibizumab		Subjects randomised to ranibizumab, received 0.5 mg of ranibizumab by intravitreal injection in the study eye every month for 3 months (ie, on Days 0, 30, and 60) followed by 2 additional injections, 90-days apart, on Days 150 and 240. Subjects in the ranibizumab group underwent sham procedures at visits when they did not receive an active (ranibizumab) injection. Subjects in the ranibizumab group received a total of 11 procedures, 5 intravitreal injections and 6 sham procedures. A total of 115 subjects were randomised to the ranibizumab group.
Endpoints and definitions	Primary endpoint	≥ +15 letters BCVA	The proportion of subjects who gained ≥ 15 letters in BCVA from baseline to 11 months
	Secondary	Mean Change BCVA	The mean change from baseline in BCVA to 11 months

	Secondary	≥ +5 letters BCVA	The proportion of subjects who gained ≥ 5 letters in BCVA at 11 months compared with baseline
	Secondary	≥ +10 letters BCVA	The proportion of subjects who gained ≥ 10 letters in BCVA at 11 months compared with baseline
	Secondary	Loss of <15 letters BCVA	The proportion of subjects who lost fewer than 15 letters in BCVA at 11 months compared with baseline
	Secondary	20/200 or worse VA	The proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 11 months (legal blindness was defined as both eyes with 20/200 or worse)

Database lock	Efficacy database lock (month 11):19JUL2021 Safety database lock (month 12): 31AUG2021

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	The intent-to-treat (ITT) population included all randomised subjects. All efficacy analyses were performed on the ITT population, and subjects were analysed in the study drug group to which they were randomised. Results based on the ITT population were considered primary for drawing efficacy conclusions. All 228 randomised subjects received at least 1 dose of their assigned study drug and were included in the intent-to-treat (ITT) and safety populations. The per protocol (PP) population included all subjects in the ITT population who had at least 1 postdose BCVA assessment and were compliant with all critical study criteria. Subjects with major protocol violations, identified prior to unmasking of the study, were excluded from the PP population. Where conducted, efficacy analyses based on the PP population were considered supportive of the primary analyses based on the ITT population. A total of 163 subjects (71.5%) were included in the per protocol (PP) population (85 of the 113 subjects [75.2%] in the ONS-5010 group and 78 of the 115 subjects [67.8%] in the ranibizumab group).

Descriptive statistics and estimate variability	Treatment group	Ranibizumab	ONS-5010
	Number of subjects	115	113
	Primary: ≥ +15 letters BCVA (%)	23.1	41.7

	Secondary: Mean Change BCVA (mean [SD])	5.8 [14.80]	11.2 [12.19]
	Secondary: ≥ +5 letters BCVA (%)	51.0	68.5
	Secondary: ≥ +10 letters BCVA	34.6	56.5
	Secondary: Loss of <15 letters BCVA	82.7	93.5
	Secondary: 20/200 or worse VA	24.0	13.0
Effect estimate per comparison	Primary endpoint: ≥ +15 letters BCVA	Comparison groups	ONS-5010 - Ranibizumab
		Risk difference	0.1859
		95% Confidence Interval	0.0442, 0.3086
		P-value Fisher's exact test	0.0052
	Secondary: Mean Change BCVA; MI by washout Approach	Comparison groups	ONS-5010 - Ranibizumab
		LS mean	Ranibizumab = 5.351 ONS-5010 = 9.156
		LS mean difference	3.805
		95% Confidence Interval	−0.016, 7.626
		P-value ANCOVA	0.0510; Not significant
	Secondary: Mean Change BCVA; Jump-to-Reference Imputation	Comparison groups	Ranibizumab ONS-5010
		LS mean	Ranibizumab = 6.904 ONS-5010 = 11.205
		LS mean difference	4.301

		95% Confidence Interval	0.934, 7.668
		P-value ANCOVA	0.0125
	Secondary: 20/200 or worse VA	Comparison groups	ONS-5010 - Ranibizumab
		Risk difference	−0.1108
		95% Confidence Interval	−0.2187, −0.0050
		P-value Fisher's exact test	0.0505

Notes	Among the 228 subjects who were randomised, 198 (86.8%) completed the study. The 3 most frequently reported reasons for study discontinuation were withdrawal of consent (4.8%), AE (3.5%), and other (1.8%). All 228 randomised subjects were included in the ITT and safety populations (113 subjects in the ONS-5010 group and 115 subjects in the ranibizumab group) and 163 subjects were included in the PP population (85 and 78 subjects in the ONS-5010 and ranibizumab groups, respectively).
Analysis description	

Primary analysis: ≥ +15 letters BCVA (prespecified)	The primary efficacy endpoint was the proportion of subjects who gained ⩾ 15 letters in BCVA from baseline to 11 months, where BCVA was based on the ETDRS chart, analysed as a dichotomous variable. The difference in the proportion of subjects who gained ⩾ 15 letters in visual acuity between the ONS-5010 and ranibizumab groups was analysed using a Fisher's exact test. The difference in proportions and the associated 95% CI was reported. Subjects who discontinued due to an AE, lack of efficacy, or use of rescue therapy were categorised as non-responders, whereas subjects who discontinued for other reasons and had a missing Month 11 BCVA were treated as missing. Overall, within the protocol prescribed dosing regimen, efficacy for ONS-5010 was demonstrated, with ONS-5010 being superior to ranibizumab (administered in a manner consistent with the PIER study dosing regimen) for the proportion of subjects achieving an increase of ⩾ 15 letters in BCVA from baseline to 11 months. Specifically, in the ITT population, 45 subjects (41.7%) in the ONS-5010 group compared with 24 subjects (23.1%) in the ranibizumab group gained ⩾ 15 letters from baseline to 11 months. The difference observed between the study drug groups was significant, with a risk difference of 0.1859 (95% CI = 0.0442, 0.3086; p = 0.0052).

First Secondary analysis: Mean Change BCVA (prespecified)	Because the difference between study drug groups in the analysis of the primary efficacy endpoint was significant, the fixed-sequence testing continued with the analysis of the first secondary efficacy endpoint. The first secondary efficacy endpoint (change from baseline in BCVA to 11 months) was analysed using both fixed and adaptive approaches to a trimmed means method of analysis. Complementary analyses to the first secondary analysis included an analysis of covariance (ANCOVA) model, with study drug group as a fixed effect and the baseline BCVA as a continuous covariate; an ANCOVA employing a multiple imputation method; and a repeated measures analysis of the change in BCVA from baseline over time. Following the success of the primary efficacy endpoint analysis, the secondary efficacy endpoints were tested sequentially. The study met the first of its secondary efficacy endpoints, change from baseline in BCVA to 11 months. Specifically, for subjects in the ITT population who had a BCVA assessment at Month 11, the LS mean change in BCVA from baseline to 11 months using a trimmed means fixed approach was 19.310 letters in the ONS-5010 group and 14.575 letters in the ranibizumab group. The difference observed between study drug groups was significant, with an LS mean difference of 4.735 (95% CI = 1.306, 8.163; p = 0.0035). However, the trimmed mean analyses are not well understood and it is not clear under which assumptions valid inferences are provided that are representative for the entire population rather than the best remaining % after trimming. Based on the set of further analyses the results of the sensitivity analyses using reference-based imputation are the most promising, although the imputation based on information derived from an active treatment arm (i.e. ranibizumab treated subjects) might also be a too optimistic estimation for the missing data in the ONS-5010 arm. Until more reliable results based on requested analyses can be used, the results retrieved from the reference based analyses are considered the most relevant. Where the LS mean change in BCVA from baseline to 11 months using MI by washout approach was 9.156 letters in the ONS-5010 group and 5.351 letters in the ranibizumab group (LS mean difference of 3.805 [95% CI = -0.016, 7.626]; p = 0.051) and where the LS mean using the Jump-to-Reference imputation was 11.205 letters in the ONS-5010 group and 6.904 letters in the ranibizumab group (LS mean difference of 4.301 [95% CI = 0.934, 7.668]; p = 0.0125).

2.5.3.2. Clinical studies in special populations

The applicant provided primary efficacy measures on elderly participating in clinical trials (pooled NORSE ONE and NORSE TWO) per age subgroup.

Table below: Primary Efficacy Analysis by Age Subgroup in Pooled NORSE ONE and NORSE TWO, Subjects Gaining ≥15 Letters from Baseline to 11 Months (ITT Population)

	Age <65 years	**Age 65-74**	**Age 75-84**	**Age 85+**
Number of subjects[1] n/N (%)				
Ranibizumab (N=145)	4/5 (80.0)	10/31 (32.3)	10/56 (17.9)	5/36 (13.9)
ONS-5010 (N=144)	3/6 (50.0)	13/33 (39.4)	20/56 (35.7)	11/39 (28.2)

Note: Those subjects who received rescue/prohibited therapy or discontinued treatment due to adverse event or lack-of-efficacy are treated as non-responders. Those subjects who have missing 11-month values and did not receive rescue/prohibited therapy or discontinued treatment due to adverse event or lack-of-efficacy are treated as missing.

[1] n = number of subjects with >=15 letter increase, N = number of subjects with Month 11 assessment. Percentages based on N.

Source: Appendix 1-Q31 Adhoc Table 4.1.1a

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

No pooled efficacy analysis across NORSE ONE and NORSE TWO has been performed.

2.5.3.4. Supportive study(ies)

Supportive data was provided for this full-mixed application based on Article 8(3) of Directive 2001/83 and the requirements provided in Annex I to the Directive. These references include data on the efficacy and safety of anti-VEGF therapy and the mechanism of action, and provide information on the historical off-label use of anti-VEGF treatment for nAMD. In particular, literature reports comparing efficacy of bevacizumab to ranibizumab in wAMD, literature reports on the efficacy of approved ophthalmic anti-VEGF products, and literature reports on historical use of bevacizumab as off-label treatment for wAMD were provided in the dossier.

The applicant considers three studies especially meaningful to support the MAA of Lytenava (studies IVAN, CATT, BRAMD), each of which include results of comparative trials of bevacizumab and ranibizumab with continuous monthly intravitreal administration comparable to the bevacizumab administration regimen applied in the NORSE ONE and NORSE TWO studies. The bevacizumab product administered in all three trials was Avastin.

Literature reports comparing efficacy of bevacizumab to ranibizumab in wAMD

The applicant cites 9 randomised clinical studies designed to directly compare bevacizumab and ranibizumab in patients with AMD to support the dossier of Lytenava on the basis of a full-mixed application according to Article 8(3) of Directive 2001/83. Of these studies, only three evaluated a bevacizumab treatment regimen similar to the one used in studies ONS-5010-001 and ONS-5010-002 (monthly intravitreal injections) and the

applicant therefore classified these three trials – IVAN, CATT, and BRAMD – as most meaningful for the comparison with the efficacy and safety results obtained in the ONS-5010 studies.

CATT study

The "Comparison of AMD Treatment Trials" (CATT) was planned as a set of multicentre randomised clinical trials of treatment for AMD. In the cited trial (CATT: Lucentis-Avastin Trial), a comparison between bevacizumab and ranibizumab was conducted.

CATT was a randomised multicentre, single-blind, non-inferiority trial. 1208 patients with neovascular AMD were enrolled in the US at 44 clinical sites and allocated to either bevacizumab or ranibizumab on either a monthly schedule or as needed with monthly evaluation. Eligibility criteria included an age of 50 years or older, previously untreated active choroidal neovascularisation due to AMD, and visual acuity between 20/25 and 20/320. To establish presence of active choroidal neovascularisation, presence of leakage (as seen on fluorescein angiography) and of fluid (as seen on OCT) was required Inclusion criteria were neovascularisation, fluid, or haemorrhage under the fovea. Patients were randomly assigned to one of the four study groups (bevacizumab or ranibizumab, either monthly or as needed schedule). The administered dose was either 0.50 mg ranibizumab or 1.25 mg bevacizumab. The primary outcome was the mean change in visual acuity at 1 year, with a non-inferiority limit of 5 letters on the eye chart. Secondary endpoints included proportion of patients with change in visual acuity of 15 letters or more, number of injections, change in fluid and foveal thickness on OCT, change in lesion size on fluorescein angiography, and incidence of ocular and systemic adverse events.

Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm, P = 0.03 by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab (P>0.20). The proportion of patients with serious systemic adverse events (primarily hospitalisations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

At 1 year, the study concluded that bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events were considered to require further study.

IVAN study

Also the "Inhibition of VEGF in Age-related choroidal Neovascularisation" (IVAN) trial was designed to compare bevacizumab and ranibizumab as treatments for neovascular age-related macular degeneration with different regimens.

The study was a randomised multicentre, 2×2 factorial, non-inferiority trial. Adults aged at least 50 years with active, previously untreated neovascular age-related macular degeneration and a best corrected distance visual acuity (BCVA) of at least 25 letters were recruited from 23 hospitals in the UK. Participants were randomly assigned (1:1:1:1) to intravitreal injections of ranibizumab (0.5 mg) or bevacizumab (1.25

mg) in continuous (every month) or discontinuous (as needed) regimens, with monthly review. Diagnosis was confirmed by fluorescein angiography. Study participants and clinical assessors were masked to drug allocation. Allocation to continuous or discontinuous treatment was masked up to 3 months, at which point investigators and participants were unmasked. As in CATT, drug doses were 0.5 mg ranibizumab or 1.25 mg bevacizumab. The primary outcome was BCVA at 2 years (interim analysis after 1 year), with a prespecified non-inferiority limit of 3.5 letters. The primary safety outcome was arterial thrombotic event or hospital admission for heart failure. Secondary outcome measures include adverse effects, EQ-5D (generic health-related quality of life assessment), contrast sensitivity, near visual acuity and reading index, lesion morphology and metrics from angiograms and OCTs, and serum VEGF levels. Analyses were by modified intention to treat.

628 patients underwent randomisation, 18 were withdrawn. 610 received study drugs (314 ranibizumab; 296 bevacizumab) and were included in analyses. 525 participants reached the visit at 2 years: 134 ranibizumab in continuous regimen, 137 ranibizumab in discontinuous regimen, 127 bevacizumab in continuous regimen, and 127 bevacizumab in discontinuous regimen.

At 1 year, the increase in mean BCVA from baseline was 4.7 versus 6.4 letters, respectively, in the bevacizumab and ranibizumab groups. At this time point, 40 of 274 subjects (14.6%) in the bevacizumab group and 64 of 287 subjects (22.3%) in the ranibizumab group had gained ≥ 15 letters from baseline in BCVA. The mean decrease from baseline in foveal thickness, as measured by OCT, was −139 μm in the bevacizumab group and −155 μm in the ranibizumab group. The median number of treatments was 11 in the bevacizumab group and 10 in the ranibizumab group.

At 2 years, for BCVA bevacizumab was neither non-inferior nor inferior to ranibizumab (mean difference −1.37 letters, 95% CI −3.75 to 1.01; p=0.26). Discontinuous treatment was neither non-inferior nor inferior to continuous treatment (−1.63 letters, –4.01 to 0.75; p=0.18). Frequency of arterial thrombotic events or hospital admission for heart failure did not differ between groups given ranibizumab (20 [6%] of 314 participants) and bevacizumab (12 [4%] of 296; odds ratio [OR] 1.69, 95% CI 0.80–3.57; p=0.16), or those given continuous (12 [4%] of 308) and discontinuous treatment (20 [7%] of 302; 0.56, 0.27–1.19; p=0.13). Mortality was lower with continuous than discontinuous treatment (OR 0.47, 95% CI 0.22–1.03; p=0.05), but did not differ by drug group (0.96, 0.46–2.02; p=0.91).

The study concluded that bevacizumab and ranibizumab exert similar efficacy. Reduction in the frequency of retreatment resulted in a small loss of efficacy irrespective of drug. Safety was worse when treatment was administered discontinuously.

BRAMD study

The “Bevacizumab and Ranibizumab in exudative AMD” Study also compared the effectiveness of bevacizumab and ranibizumab in the treatment of exudative AMD.

This was a randomised, multicentre, controlled, triple-masked non-inferiority trial. 327 patients were recruited at 5 academic medical centres in the Netherlands. Patients were 60 years of age or older, with primary or recurrent sub- or juxtafoveal choroidal neovascularisation (CNV) secondary to AMD with a total area of CNV < 12 disc areas and a BCVA score between 20 and 78 letters on an ETDRS-like chart in the study eye. Decisions about eligibility were made based on fluorescein angiograms, fundus photography, and SD-OCT.

Patients were administered monthly intravitreal injections with 1.25 mg bevacizumab or 0.5 mg ranibizumab during one year. Intention to treat with last observation carried forward analysis was performed. The primary outcome was the change in BCVA in the study eye from baseline to 12 months. The non-inferiority margin was 4 letters. Secondary endpoints included proportion of patients with a loss of BCVA less than 15 letters from baseline at 12 months, proportion of patients with a loss or gain of BCVA less than 15 letters from baseline at 12 months, proportion of patients with 15 letters loss or more of BCVA from baseline at 12 months, proportion of patients with 15 letters gain or more of BCVA from baseline at 12 months, absolute and percentage change in CRT as measured by SD-OCT at 4 and 12 months, proportion of dropouts before the final 12 months assessments, proportion of switchers after the third injection, occurrence of (serious) adverse events during the 12 months of the study.

The mean gain in BCVA was 5.1 (±14.1) letters in the bevacizumab group (n = 161) and 6.4 (±12.2) letters in the ranibizumab group (n = 166) (p = 0.37). The lower limit of the 95% confidence interval of the difference in BCVA gain was 3.72. The response to bevacizumab was more varied; 24% of patients showed a gain of 15 letters, 11% a loss of 15 letters and 65% a gain or loss < 15 letters compared to 19%, 5% and 76% respectively for ranibizumab (p = 0.038). No significant differences in absolute CRT and CRT change (p = 0.13) or in the presence of subretinal or intraretinal fluid (p = 0.14 and 0.10, respectively) were observed. However, the presence of any fluid on SD-OCT (subretinal and/or intraretinal) differed significantly (p = 0.020), with definite fluid on SD-OCT in 45% of the patients for bevacizumab versus 31% for ranibizumab. The occurrence of serious adverse events and adverse events was similar, with 34 SAEs and 256 AEs in the bevacizumab group and 37 SAEs and 299 AEs in the ranibizumab group (p = 0.87 and p = 0.48, respectively).

Patient populations recruited appear similar for CATT (50 years or older, previously untreated active choroidal neovascularisation due to AMD, visual acuity between 20/25 and 20/320) and IVAN (50 years or older, previously untreated nAMD and a BCVA of at least 25 letters). In BRAMD, a different patient population was recruited, as recruitment was not restricted to treatment-naïve patients.

Baseline characteristics of patients were mostly evenly distributed amongst treatment arms of the respective study, with only minor deviations noted. No concerns regarding study integrity arise from these minor differences detected. More women than men were recruited in all three studies (overall approximately 59% females, 41% males) corresponding to higher risk for the disease associated with female gender.

The selected primary efficacy endpoints are considered informative for all three studies (change in BCVA after 1 year for CATT and BRAMD, after 2 years for IVAN). The secondary endpoints included both functional and anatomical parameters and are considered adequate to enable a comprehensive comparison of the treatments. Quality of life assessment was additionally investigated in IVAN using the EQ-5D questionnaire and showed no differences for bevacizumab and ranibizumab, as well as the two treatment regimens applied.

The overall study designs of the studies are considered appropriate for the comparison of both medicinal products (CATT, IVAN, BRAMD) and administration schemes (CATT, IVAN), and the overall quality of the three studies is considered high. In a Cochrane review article by Solomon et al. from 2019, which investigated the ocular and systemic effects of intravitreal anti-VEGF injections for wAMD, the overall risk for bias in studies CATT and IVAN was considered low (BRAMD not included in the article).

In the largest study provided (CATT), RBZ and BCZ exerted similar effects on VA when administered according to the same schedule (8.5 vs 8.0 letters improvement with monthly administration, 6.8 vs 5.9 letters with as needed administration). Similar results were reported from the IVAN study, where the difference in BCVA gain at 1 year was approximately 2 letters in favour of ranibizumab. At 2 years,

bevacizumab was found to neither be non-inferior with a non-inferiority margin of 3.5 letters, nor inferior (IVAN). In the third study, BRAMD, after 1 year, ranibizumab led to a 6.4 letter improvement compared to 5.1 letters in the bevacizumab treatment group.

Differences between treatments were detected in the effects on fovea thickness. In CATT, the largest decrease in foveal thickness was reported from monthly treatment with ranibizumab (mean difference −196±11 µm), followed by ranibizumab as needed (mean difference −168±11 µm). The effect achieved by bevacizumab was smaller: monthly treatment led to a decrease of −164±11 µm, with bevacizumab as needed −152±11 µm were reported. In the IVAN study, the effect on total thickness at the fovea was also shown to be significant in a pooled analysis in favour of ranibizumab (22 µm, 95% CI: 3.94, 40.1). Further, a significant difference of 26.2 µm was reported favouring continuous treatment (95% CI: 8.14, 44.2). In BRAMD, a trend in mean change in central retinal thickness was also detected in favour of ranibizumab, however without statistical significance (-32% change in ranibizumab treated patients vs -30% in bevacizumab treated patients.

Generally, the effect on visual acuity was numerically larger with ranibizumab in all studies submitted. While all three studies concluded on comparable efficacy for ranibizumab and bevacizumab nonetheless, a tendency in favour of ranibizumab was evident in all comparisons. This tendency is also described in a meta-analysis of 1 year outcomes conducted in the 1 year IVAN report (Chakravarthy 2012), which reports an overall tendency in favour of ranibizumab.

Reduction in CRT was more pronounced with ranibizumab treatment at 1 year in all three studies. Also, fluid on OCT was detected in a substantially higher percentage of patients receiving bevacizumab than in those receiving ranibizumab. As stated by the authors of the BRAMD study, so far there is no explanation for this observation and more research is warranted and effect differences between treatment arms in these parameters would be of high interest in the current MAA.

Regarding safety, no significant differences between treatments were detected in the rates of mortality, myocardial infarction, and stroke. In CATT, more serious systemic AEs were reported with bevacizumab, however, this effect was not seen in IVAN study, which reported comparable rates of serious systemic AEs between treatment arms.

Overall, the submitted studies support use of bevacizumab (Avastin) in a nAMD population.

In a provided study investigating the efficacy and safety of ONS-5010 (NORSE TWO), bevacizumab was reported to be superior to ranibizumab in a treatment naïve wAMD population. This result is in contradiction to the results from CATT, IVAN, and BRAMD, where clear trends in favour of ranibizumab were detected in all three studies and for most parameters evaluated. It is noted that in NORSE TWO different administration schemes were used for the bevacizumab and ranibizumab treatment arms (PIER dosing with less frequent administration of ranibizumab vs monthly bevacizumab). Based on the evaluation of the results from CATT, IVAN, BRAMD, the selected ranibizumab dosing scheme was questioned during the assessment.

The applicant stated that the provided studies were selected due to the comparable dosing regimen used in the E/S studies for Lytenava. This is understood, but it is pointed out that data derived from studies with differing dosing regimens (or other study design differences) could also be informative for this MAA (e.g. regarding safety, dose-response relationship etc.). The body of historical evidence for bevacizumab in nAMD is rather large, and other studies comparing bevacizumab and ranibizumab are included for example in the 2019 Cochrane review by Solomon et al.. In that regard, the selection of the studies submitted should be better argued and the selection process should be made transparent.

In order to manage bias, the applied literature search strategy for the bibliographic part of a full-mixed application should be pre-specified and should aim to depict a complete picture of the published data available. A qualitative synthesis and a systematic approach would be expected so that selection bias can be excluded. Search criteria, selection criteria and the respective selection process should be outlined and transparent. This information was submitted by the applicant as part of the responses to questions and found acceptable.

In 2019, a systematic meta-analysis was performed by Pham B et al. to evaluate the comparative effectiveness and safety of intravitreal bevacizumab, ranibizumab and aflibercept for patients with choroidal neovascular age-related macular degeneration (cn-AMD) and other indications (Pham B, Thomas SM, Lillie E, Lee T, Hamid J, Richter T, Janoudi G, Agarwal A, Sharpe JP, Scott A, Warren R, Brahmbhatt R, Macdonald E, Straus SE, Tricco AC. Anti-vascular endothelial growth factor treatment for retinal conditions: a systematic review and meta-analysis. BMJ Open. 2019 May 28;9(5):e022031. doi: 10.1136/bmjopen-2018-022031.). The treatment regimens are also summarised (e.g., three initial monthly intravitreal injections and as-needed monthly retreatment, treat and extend), as-needed retreatment criteria and the reconstitution of bevacizumab, and examined the influence of the choice of treatment regimens on the benefits and harms of the anti vascular endothelial growth factor (anti-VEGF) drugs for specific retinal conditions. Meta-analysis concluded, that over an average treatment duration of 16 months, approximately 94% of patients maintained their vision, with no statistical difference between patients treated with bevacizumab or ranibizumab (RR of vision loss: 0.91 [95% CI, 0.70 to 1.19]). Patients treated with bevacizumab or ranibizumab gained an average of seven letters in terms of mean BCVA with no statistical difference between the drugs (mean difference (MD) 0.03 letters [95% CI, −1.02 to 1.08]). Approximately 2%–4% patients treated with bevacizumab or ranibizumab became legally blind (RR: 2.04 [95% CI, 0.32 to 12.50], 3 trials, 1823 patients). Overall, the results were consistent across the 10 trials.

Emphasising the results in the meta-analysis: the number of patients becoming legally blind remained low, approximately 2%–4% patients treated with bevacizumab or ranibizumab throughout the Avastin randomised controlled studies included in the meta-analysis. Note, that visual acuity of Snellen equivalent 20/200 corresponds to the visual performance of a legally blind person.

In order to claim the literature data generated with Avastin in the course of the procedure the applicant provided quality data to establish a more robust bridge between Lytenava and Avastin (see section 2.3.). Literature data hence can be seen as additional important data benchmark, providing a certain degree of reassurance regarding Lytenava's effect size (see 3.7.1)

Literature reports on the efficacy of ophthalmic anti-VEGF products

The applicant included the following studies on ophthalmic anti-VEGF products to support the dossier. Studies supplied:

Brown 2006: Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration

Dugel 2020: HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration

Heier 2012: Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration

Heier 2022: Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials

Regillo 2008: Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1

Rosenfeld 2006: Ranibizumab for Neovascular Age-Related Macular Degeneration

The products which were investigated in these studies (Lucentis, Beovu, Eylea, Vabysmo) are approved for treatment of neovascular (wet) age-related macular degeneration throughout the European Union. The applicant furthermore submitted some additional literature reports and expert statements to support the established use of anti-VEGF therapy in clinical practice, which are acknowledged. The general mechanism of action of anti-VEGF therapy in wet AMD can be considered supported by the cited literature.

2.5.4. Discussion on clinical efficacy

Context and sources of evidence

The applicant applied for a full-mixed marketing authorisation according to Article 8(3) of Directive 2001/83/EC, composed of a combination of own data and bibliographic literature, the latter mostly based on data generated with (off-label) Avastin.

While the efficacy evaluation is primarily based on the two pivotal studies described above (NORSE ONE and NORSE TWO), the studies have methodological shortcomings (see below). Therefore, the literature data generated with Avastin was considered as additional supportive evidence for Lytenava.

In order to claim the literature data generated with Avastin, in the context of a biological drug development, it is considered necessary to establish a firm bridge between Lytenava and Avastin. Lytenava needed to be shown to be comparable to Avastin the product used in the historical studies in physicochemical, biological and functional terms. The approach to demonstrate comparability had to take into account the complexity of the biological. The pivotal step for the required bridge between Avastin and Lytenava is the similarity on a quality level, which was considered insufficiently characterised at the time of submission, and a multidisciplinary major objection was raised in this regard. Uncertainties regarding the quality comparability exercise were resolved by the applicant with the responses provided during assessment (see above). Hence, data from Avastin studies (CATT, IVAN, BRAMD) can be considered additional evidence for Lytenava.

Design and conduct of clinical studies

NORSE TWO and NORSE ONE were similarly designed multicentre, randomised, double-masked, controlled Phase 3 studies that evaluated the efficacy and safety of intravitreally administered ONS-5010. Following a screening period of up to 28 days in both studies, eligible subjects were randomised in a 1:1 ratio to receive ONS-5010 or ranibizumab in the study eye. Note that only 1 eye was designated as the study eye and the injection was performed by an unmasked physician. Prior to randomisation, the investigator was to receive and review clinical laboratory tests for eligibility and to receive confirmation of subject eligibility from the medical image reviewer. ONS-5010 was given in the same posology and dose as has been used for the off-

label IV preparations of Avastin. Subjects randomised to receive ONS-5010 were administered a monthly intravitreal injection of 1.25 mg of ONS-5010 in the study eye for up to 12 months. Subjects randomised to ranibizumab received 0.5 mg of ranibizumab by intravitreal injection in the study eye every month for 3 months (i.e., on Days 0, 30, and 60) followed by 2 additional injections, 90-days apart, on Days 150 and 240. Subjects in the ranibizumab group underwent sham procedures at visits when they did not receive an active (ranibizumab) injection. The key differences between the NORSE ONE and NORSE TWO patient populations were: (1) both treatment-naïve and previously treated subjects were included in NORSE ONE, but only treatment-naïve in NORSE TWO; and (2) baseline visual acuity was 20/40 to 20/320 in NORSE ONE, but 20/50 to 20/320 in NORSE TWO.

Changes made to the protocol of NORSE ONE seem understandable. The original protocol of NORSE TWO was approved on 19 November 2018 and was amended 6 times over the course of the study. The final approved protocol is Version 6.0, dated 20 December 2019. The applicant claims that due to results of NORSE ONE the study population of NORSE TWO was adapted. Resulting concerns on the study integrity of NORSE ONE were resolved following additional clarifications on timelines by the applicant.

Of note, the applicant considers only the NORSE TWO study as pivotal. However, also NORSE ONE had been predefined as a phase III trial, and while admittedly sample size was much smaller, the failure to show a trend for superiority of Lytenava over the control group represents a source of uncertainty on the efficacy of Lytenava.

Overall, both pivotal trials include patients who are considered relevant for the desired indication "treatment of wet AMD".

The comparator product in both studies, ranibizumab (Lucentis), is registered for use in the treatment of nAMD, macular oedema following retinal vein occlusion, diabetic macular oedema, diabetic retinopathy, and myopic CNV. The ranibizumab dosing regimen used in the PIER study was the same dosing regimen selected for use in the two Phase 3 studies, as according to the applicant it provided a regulatory approved, fixed dosing regimen that was agreed to be an acceptable control in investigational AMD clinical studies designed to support registration for the nAMD treatment indication. While it is true that this regimen has been used e.g. in the PIER study in the LUCENTIS development, it does not correspond to the most optimal treatment regimen in the label of Lucentis. As opposed to only three consecutive monthly injections, the label suggests to treat monthly until a treatment plateau is reached and then change to an "as needed" treatment scheme, where treatment is administered as needed, as soon as the efficacy of treatment is showing signs of wearing off. Provided Literature references comparing efficacy of Avastin and ranibizumab indicate that ranibizumab efficacy trends worse when applied as needed versus if ranibizumab is administered monthly. With this respect it needs to be emphasised that in the comparator arm in the NORSE ONE and NORSE TWO trials, no examination regarding reaching of a treatment plateau was performed, and it is possible that more frequent ranibizumab administrations might have resulted in a better efficacy. This is also reflected in the higher study discontinuations rate due to lack of efficacy in the ranibizumab arms of both trials (see clinical safety) as compared to the test treatment. For a comparative trial, the clear preference of CHMP would have been a comparator arm with monthly intravitreal injections of 0.5 mg ranibizumab. However, superiority over the best possible posology of ranibizumab is not a requirement for approval, and as the PIER study did demonstrate efficacy of the sub-optimal posology of ranibizumab over Sham, an indirect demonstration of superiority over sham is concluded on, in a conservative way. Nonetheless, the design poses an uncertainty on the magnitude of the absolute effect over Sham.

With responses to questions, the applicant provided comparative literature data in order to estimate the effect size of Lytenava in NORSE TWO, including data on the effect size of the used comparator dosing

scheme (PIER dosing). The data presented were generated in a single study from the Lucentis registrational PIER study, in which the ranibizumab PIER dosing was compared against sham injections, leading to a delta of 16.1 letters in the primary endpoint (mean changes from baseline in VA at 12 months). When accepting superiority of Lytenava (NORSE TWO dosing) over Ranibizumab (PIER dosing) one can assume, that under similar study conditions as in PIER, Lytenava may exhibit a similar or larger effect size, when compared to sham. Nevertheless, the reported effect size estimate from PIER was obtained at Month 12, whereas NORSE TWO did show superiority of Lytenava at Month 11. The latter is however not ensured for later timepoints with equal temporal distance from treatment (days since last treatment at Month 11: 30 days for Lytenava, 90 days for Lucentis). The differing treatment frequencies and noticeable monthly outcome dynamics related to dosing intervals, complicate a direct extrapolation of treatment effects from PIER to NORSE TWO. Moreover, the point estimate of 16.1 observed in the PIER study does not consider variability, and a confidence interval providing a lower bound for the estimated treatment effect is unfortunately not reported. Therefore, while an effect in the vicinity of the 16 points appeared plausible, considerable residual uncertainty persisted owing to study-specific conditions, variability of the estimate, and differences in timing. These elements impeded a reliable quantification of the effect size.

Subsequently in the procedure the applicant presented analyses that made the assumption of an effect size of Lytenava, that might be comparable to the effects of ranibizumab in the PIER study somewhat more plausible. The applicant argued with a direct comparison of the first three treatment months where Lytenava and ranibizumab were still administered in equal frequency in the larger NORSE TWO study. This comparison was presented as subjects gaining ≥15 letters from baseline with 95% CI. Trends between treatments shown to be very similar with a slight numerical advantage for ranibizumab at month 3, but a slight numerical advantage for Lytenava in mean letters gained at the same timepoint. This analysis is considered of particular interest, since in intravitreal anti-VEGF treatment in the target indication, the largest part of the treatment effect is reached within the first three months. Unfortunately, mean change in BCVA was not included in the discussion, which would have further strengthened this analysis. However, comparable behaviour of the two NORSE TWO treatment arms in this initial time-frame, supports comparable efficacy of Lytenava compared to the PIER study ranibizumab arm.

Importantly, a support to this efficacy claim can be derived from the supportive data from the literature generated with Avastin. The Avastin studies IVAN, CATT, and BRAMD serve as a supportive external benchmark, acknowledging that Avastin has been reported to exert meaningful efficacy in the treatment of nAMD patients, although a consistent trend for numerical outperformance of ranibizumab is noted in Avastin trials. Avastin trials: Mean (SD) letter change from baseline at 1 year: BRAMD: (bevacizumab: 5.1(14.1)/ranibizumab: 6.4(12.2)), CATT: (bevacizumab: 8.0(15.8)/ranibizumab: 8.5(14.1)), IVAN: (bevacizumab: 5.0(15.6)/ranibizumab: 5.2 (15.0)).

It is agreed that the choice of the primary and secondary endpoints is relevant. Visual acuity might be the preferred clinical outcome measure, however PD endpoints such as central retinal thickness would have been helpful to provide further support.

A Trimmed Mean approach was used to analyse the mean change in BCVA from Baseline at 11 months, using a fixed approach comparing only the best 50% of both treatment arms, and an adaptive approach, where the percentile floor for trimming was determined by the greater proportion of dropouts. Such an analysis for the overall patient population, where only the best remaining % after trimming of patients are used in the analysis, is not considered relevant for the interpretation of the trial. Consequently, the corresponding results are not considered informative to the benefit-risk assessment and are not used for B/R assessment. Also, the statistical properties of the trimmed mean analysis are not well understood. In addition, a set of further

analyses that were based on the full ITT set was performed to support the conclusions and to assess the impact of missing data. These were considered of more relevance in principle. However, most of the analyses were either anti-conservative in their imputation approaches or have not provided any missing data strategy at all. Among the set of further analyses made the results of the sensitivity analyses using reference-based imputation are considered the most meaningful approaches, although also there the imputation based on information derived from an active treatment arm (i.e. ranibizumab treated subjects) is considered as optimistic replacement for the missing data in the ONS-5010 arm. The results retrieved from the reference-based analyses (ANCOVA with MI by washout and Jump-to-Reference imputation method) are focussed on in the assessment. NORSE TWO. On request, the applicant presented a number of sensitivity analyses evaluating the potential impact of different ways to reflect missing data in the primary and secondary analysis. Corresponding results largely agree with the original analysis and results only differ for extreme assumptions about the missing data process that are not considered very realistic. Therefore, the initial results can be accepted. On request the applicant clarified that for some of the subjects that withdrew for unspecified reasons, Month 11 data were not obtained and those subjects were not taken into account for the primary analysis. Requested sensitivity analyses with a non-responder imputation for these subjects provide reassurance that no major impact on the efficacy conclusion exists.

Efficacy data and additional analyses

Study ONS-5010-001

Overall, the study did not meet its primary efficacy endpoint, the proportion of subjects achieving an increase of ≥ 15 letters in BCVA from baseline to 11 months (7.7% vs 20.8%, respectively, in the ONS-5010 and ranibizumab groups, with a risk difference of −0.1314 [95% CI = −0.3550, 0.0765]; p = 0.2387). The primary efficacy results obtained using the PP population were consistent with those observed in the ITT population, with 2 subjects (11.1%) in the ONS-5010 group and 5 subjects (25.0%) in the ranibizumab group gaining ≥ 15 letters in BCVA from baseline to 11 months (risk difference = −0.1389; 95% CI = −0.3948, 0.1366; p = 0.4103 NORSE ONE must hence be considered a failed trial. Because the difference between study drug groups in the analysis of the primary efficacy endpoint was not significant, the fixed-sequence testing stopped. No inferential conclusions could be drawn regarding the secondary efficacy endpoints. As described in the first secondary efficacy endpoint (change from baseline in BCVA to 11 months) was analysed using both fixed and adaptive approaches.

Secondary measures generally confirm, what was observed for the primary outcome measure. No trends for superiority of monthly Lytenava treatment was observed in change from baseline in BCVA. As in the primary objective the trend favoured the much less frequent ranibizumab treatment. No significant difference was observed in exploratory measure CFT from baseline to month 11.

While initially allowing both groups into the trial the applicant attributes its failure to the high and uneven proportion of previously treated patients in treatment arms.

Parameter	Ranibizumab (N = 30)	ONS-5010 (N = 31)
Prior anti-VEGF treatment, n (%)		
Yes	15 (50.0)	25 (80.6)
No	15 (50.0)	6 (19.4)

Subgroup analysis in treatment naïve patients also reveal no significant outcome in the primary measure. A slight trend in favour of ONS-5010 cannot be considered indicative of superiority. On the contrary, in pretreated patients, the trend seems to favour ranibizumab. In general numbers in subgroups are too small to derive any meaningful comparison.

While a general trend for higher efficacy in treatment naïve patients is in fact notable, efficacy on individual level seem not to be predictable. The applicant claims, that the study was "underpowered" and its failure "expected". However, it rather seems that a larger trial could have gone "both directions" with a possibility for superiority of ranibizumab over Lytenava. This possibility was disproven with the larger ONS-5010-002 study.

Study ONS-5010-002

Study ONS-5010-002 provided evidence of clinical efficacy and met its primary efficacy endpoint, demonstrating that ONS-5010 was superior to ranibizumab, when ranibizumab was administered in a manner consistent with the PIER study dosing regimen, for the proportion of subjects achieving an increase of ≥ 15 letters in BCVA from baseline to 11 months. Specifically, in the ITT population, 45 subjects (41.7%) in the ONS-5010 group compared with 24 subjects (23.1%) in the ranibizumab group gained ≥ 15 letters from baseline to 11 months. The difference observed between the study drug groups was significant, with a risk difference of 0.1859 (95% CI = 0.0442, 0.3086; p = 0.0052)

The primary efficacy results obtained using the PP population were consistent with those observed in the ITT population, with 34 subjects (41.0%) in the ONS-5010 group and 18 subjects (24.7%) in the ranibizumab group gaining ≥ 15 letters in BCVA from baseline to 11 months; the difference between study drug groups strongly favoured ONS-5010, with a risk difference of 0.1631 (95% CI = 0.0120, 0.3083; p = 0.0409).

While superiority could be shown in the primary measure of this trial it was unclear how those findings should be interpreted regarding a potential effect over placebo, after the study population was widely limited to treatment naïve patients, the smaller NORSE ONE in a broader AMD population failed, and a particularly weak ranibizumab regimen was selected. In this context the applicant submitted relevant data together with the responses to questions making it plausible that a sufficiently well characterised effect could be extrapolated from treatment naïve to pretreated patients.

The primary endpoint is measured after 11 months of treatment instead of 12 months. Due to the differences in the treatment regimens and therefore the temporal distance to the previous treatment application, the impact of the selection of this timepoint on the difference between the treatment arms is estimated as high.

The applicant presented a number of the sensitivity analyses to evaluate the robustness of the primary and secondary analysis with respect to missing data assumptions. Specifically, for the primary endpoint a worst-case, a non-responder and a tipping point analysis were provided on request. The results of the worst-case analysis and the tipping point analysis show that the treatment effect demonstrated by the primary analysis does not remain statistically significant across all possible missing data assumptions. However, corresponding scenarios – where significance is lost – would imply substantially different response rates within subjects that discontinued treatment (60% vs. 0%) between arms. Consequently, the results of the requested sensitivity analyses indicate that the primary analysis can be considered sufficiently robust with respect to deviations from the underlying missing data assumptions. Overall, these sensitivity analyses support that the effect of ONS-5010, as demonstrated by primary and secondary analyses, can be considered robust across a wide range of missing data assumptions.

Concerning the secondary endpoint - mean change from baseline to Month 11 in BCVA - the applicant presented results from a trimmed mean analysis. Corresponding results are, however, not considered to allow relevant interpretation. Consequently, sensitivity analyses based on using multiple imputation by washout, and jump to reference imputation are considered more relevant to inform the benefit-risk assessment. In study NORSE TWO the LS mean change in BCVA from baseline to 11 months using an ANCOVA with MI by washout was 9.156 in the ONS-5010 group and 5.351 letters in the ranibizumab group (LS mean difference of 3.805 [95% CI = -0.016, 7.626]; p = 0.0510). Similarly, the LS mean change in BCVA from baseline to 11 months using Jump-to-reference was 11.205 letters in the ONS-5010 group and 6.904 letters in the ranibizumab group (LS mean difference = 4.301 [95% CI = 0.934, 7.668]; p = 0.0125). While some residual uncertainties with respect to the plausibility of the underlying missing data assumptions remained, these analyses do indicate a superior treatment effect of ONS-5010 on the mean change from baseline to Month 11 in BCVA when compared to ranibizumab.

There was a significant difference favouring ONS-5010 when compared with ranibizumab in the sequential testing of the first 3 remaining secondary efficacy endpoints (i.e., the proportions of subjects who gained ≥ 5 letters and ≥ 10 letters in BCVA from baseline to 11 months, and the proportion of subjects who lost < 15 letters in BCVA from baseline to 11 months). In the ONS-5010 group, 74 subjects (68.5%) gained ≥ 5 letters in BCVA, 61 subjects (56.5%) gained ≥ 10 letters in BCVA, and 101 subjects (93.5%) lost < 15 letters in BCVA from baseline to 11 months. In the ranibizumab group, 53 subjects (51.0%), 36 subjects (34.6%), and 86 subjects (82.7%) were included in the same respective BCVA responder categories. For each of these fixed-sequence secondary endpoints, the difference between study drug groups was significant (p ≤ 0.0185). Of note, the above mentioned analyses cannot be considered independent metrics but rather as sequential analyses on the primary measure. All 3 secondary endpoints and the corresponding statistical analysis are performed using the same information retrieved from the patient. Hence, there is a strong correlation in the outcomes and the endpoints do not cover sufficiently independent aspects of the efficacy evaluation.

2.5.5. Conclusions on the clinical efficacy

Considering in isolation the NORSE ONE and NORSE TWO studies, only the existence of a treatment effect can be concluded, and not its magnitude (due to limitations in the study design). However, considering the knowledge on the effect of the comparator, even with an (over) conservative estimation, superiority of Lytenava over a putative sham in terms of ≥15 letters gained from baseline to 1 year would be preserved. Moreover, and relevantly, supportive evidence from Avastin literature data, which is possible to extrapolate to Lytenava based on the established scientific bridge, support existence of an effect size of >5 letters mean change from baseline, that is considered clinically relevant.

Of note, no claim regarding non-inferiority or comparability of Lytenava in efficacy to other anti-VEGFs (if administered according to label) is considered acceptable based on available data.

2.5.6. Clinical safety

Similarly to the discussions under clinical efficacy, literature references regarding Avastin are considered supportive data. An assessment of literature studies can be found under clinical efficacy/supportive studies.

2.5.6.1. Patient exposure

Table 1. Tabular Listing of All Clinical Studies Relevant to the Evaluation of Safety

Study Type, Identifier, Study Centers, Location	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	Number of Subjects	Diagnosis	Safety Variables
Phase 3 Controlled							
Efficacy/Safety ONS-5010-001 (NORSE ONE) 10 study centers in Australia	• To evaluate the efficacy of intravitreal injections of ONS-5010 as compared with ranibizumab in preventing vision loss, as measured by the difference in proportion of subjects who gain ≥ 15 letters from baseline in BCVA at 11 months • To evaluate the safety and tolerability of intravitreal injections of ONS-5010 administered monthly from baseline to 12 months	Multicenter, randomized, double masked, active controlled	**ONS-5010**: 1.25 mg by intravitreal injection monthly in the study eye **Ranibizumab**: 0.5 mg by intravitreal injection in the study eye every month for 3 months (ie, on Days 0, 30, and 60) followed by 2 additional injections on Days 150 and 240[a]	**ONS-5010**: 12 months **Ranibizumab**: 11 months	**ONS-5010**: 31 **Ranibizumab**:30	Active primary or recurrent subfoveal CNV lesions, with or without a classic CNV component, secondary to AMD	• AEs • Postinjection assessments • IOP • Slit-lamp biomicroscopy • Dilated ophthalmoscopy • Fundus autofluorescence • Fluorescein angiography • Physical examination • Vital signs • Clinical laboratory tests • Immunogenicity

Study Type, Identifier, Study Centers, Location	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	Number of Subjects	Diagnosis	Safety Variables
Efficacy/Safety (Pivotal) ONS-5010-002 (NORSE TWO) 39 study centers in the US	• To evaluate the efficacy of intravitreal injections of ONS-5010 as compared with ranibizumab in preventing vision loss, as measured by the difference in proportion of subjects who gain ≥ 15 letters from baseline in BCVA at 11 months • To evaluate the safety and tolerability of intravitreal injections of ONS-5010 administered monthly from baseline to 12 months	Multicenter, randomized, double masked, active controlled	**ONS-5010**: 1.25 mg by intravitreal injection monthly in the study eye **Ranibizumab**: 0.5 mg by intravitreal injection in the study eye every month for 3 months (ie, on Days 0, 30, and 60) followed by 2 additional injections on Days 150 and 240[a]	**ONS-5010**: 12 months **Ranibizumab**: 11 months	**ONS-5010**: 113 **Ranibizumab**:115	Active primary subfoveal CNV lesions, with or without a classic CNV component, secondary to AMD	• AEs • Postinjection assessments • IOP • Slit-lamp biomicroscopy • Dilated ophthalmoscopy • Fundus autofluorescence • Fluorescein angiography • Physical examination • Vital signs • Clinical laboratory tests • Immunogenicity
Phase 3 Open Label							
Safety ONS-5010-003 (NORSE THREE) 18 study centers in the US[b]	• To conduct a descriptive statistical analysis of the frequency and incidence of TEAEs following 3 IVT injections of ONS-5010	Prospective, multicenter, open label, nonrandomized	**ONS-5010**: 1.25 mg by intravitreal injection monthly in the study eye	3 months	197	65 subjects with AMD 24 subjects with BRVO 108 subjects with DME	• AEs • Postinjection assessments • IOP • Slit-lamp biomicroscopy • Dilated ophthalmoscopy • SD-OCT • BCVA • Clinical laboratory tests • Vital signs

Study Type, Identifier, Study Centers, Location	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	Number of Subjects	Diagnosis	Safety Variables
Safety (ongoing) ONS-5010-007 (NORSE SEVEN) 3 study centers in the US	• To conduct a descriptive statistical analysis of the frequency and incidence of AEs following administration of ONS-5010 when packaged in glass vials or in prefilled syringes	Prospective, multicenter, open label, nonrandomized	ONS-5010: 1.25 mg by intravitreal injection monthly in the study eye	3 months	120 planned; 60 enrolled as of 11 Feb 2022	23 subjects with AMD 9 subjects with BRVO 28 subjects with DME	• AEs • Postinjection assessments • IOP • Slit-lamp biomicroscopy • Dilated ophthalmoscopy • SD-OCT • BCVA • Clinical laboratory tests • Vital signs
Phase 1							
Pharmacokinetics ONS-1045-001 1 study center in the Netherlands	• To demonstrate systemic safety and bioequivalence of ONS-1045 to the EU- and US-licensed product of Avastin following a single 2.0 mg/kg IV infusion, in healthy male adult subjects	Single center, double blind, randomized, single dose, parallel group	ONS-1045 2 mg/kg; single IV infusion	Single dose	135	Healthy adult males	• AEs • Physical examination • Vital signs • ECG • Clinical laboratory tests • Immunogenicity

AE = adverse event; AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; BRVO = branched retinal vein occlusion; CNV = choroidal neovascularization; DME = diabetic macular edema; ECG = electrocardiogram; EU = European Union; IOP = intraocular pressure; IV = intravenous; IVT = intravitreal; SD-OCT = spectral domain-optical coherence tomography; TEAE = treatment-emergent adverse event; US = United States

a Subjects in the ranibizumab group underwent sham procedures at visits when they did not receive an active (ranibizumab) injection.

b A total of 20 study centers were recruited; 18 of those study centers enrolled at least 1 subject in the study.

The safety database of Lytenava mainly consists of two controlled Phase III studies in wet AMD patients (NORSE ONE and NORSE TWO) as well as open label studies. In addition, data from an IV single dose PK study with ONS-5010 are available however not considered pivotal.

Comparative evaluation of safety is hampered by the fact, that ONS-5010 is much more frequently administered than ranibizumab.

For the overall safety database, the safety data from the 3 completed Phase 3 studies including the controlled studies (ONS-5010-001 and ONS-5010-002) and the open-label study (ONS-5010-003) were pooled and discussed. ONS-5010-003 (NORSE THREE) was a Phase 3 safety study of intravitreally administered ONS-5010 for 3 months included subjects with nAMD, diabetic macular oedema (DME) and branched retinal vein occlusion (BRVO).

2.5.6.2. Adverse events

Table 4. Pooled Phase 3 Studies ONS-5010-001, ONS-5010-002, and ONS-5010-003: Summary of Treatment-Emergent Adverse Events (Safety Population)

Characteristic	Ranibizumab (N = 145) n (%)/m	ONS-5010 (N = 341) n (%)/m	Overall (N = 486) n (%)/m
At least 1 TEAE	103 (71.0)/315	168 (49.3)/465	271 (55.8)/780
At least 1 TEAE related to study drug/study procedure	16 (11.0)/22	41 (12.0)/59	57 (11.7)/81
Maximum severity			
CTCAE Grade 1	49 (33.8)/210	92 (27.0)/320	141 (29.0)/530
CTCAE Grade 2	40 (27.6)/85	46 (13.5)/102	86 (17.7)/187
CTCAE Grade 3	10 (6.9)/16	22 (6.5)/34	32 (6.6)/50
CTCAE Grade 4	2 (1.4)/2	4 (1.2)/5	6 (1.2)/7
CTCAE Grade 5	2 (1.4)/2	4 (1.2)/4	6 (1.2)/6
At least 1 ocular TEAE	70 (48.3)/146	98 (28.7)/186	168 (34.6)/332
At least 1 ocular TEAE in study eye	52 (35.9)/87	73 (21.4)/115	125 (25.7)/202
At least 1 ocular TEAE in fellow eye	39 (26.9)/59	48 (14.1)/71	87 (17.9)/130
At least 1 ocular TEAE related to study drug/study procedure	15 (10.3)/21	41 (12.0)/57	56 (11.5)/78
At least 1 ocular TEAE in study eye related to study drug/study procedure	15 (10.3)/20	41 (12.0)/57	56 (11.5)/77
At least 1 ocular TEAE in fellow eye related to study drug/study procedure	1 (0.7)/1	0	1 (0.2)/1
At least 1 ≥ Grade 3 TEAE	14 (9.7)/20	30 (8.8)/43	44 (9.1)/63
At least 1 ≥ Grade 3 TEAE related to study drug/study procedure	1 (0.7)/1	4 (1.2)/5	5 (1.0)/6
At least 1 serious TEAE	18 (12.4)/24	29 (8.5)/39	47 (9.7)/63
At least 1 serious TEAE related to study drug/study procedure	1 (0.7)/1	4 (1.2)/5	5 (1.0)/6
At least 1 TEAE leading to discontinuation	6 (4.1)/7	6 (1.8)/6	12 (2.5)/13
At least 1 TEAE leading to discontinuation related to study drug/study procedure	1 (0.7)/1	1 (0.3)/1	2 (0.4)/2

CTCAE = Common Terminology Criteria for Adverse Events (version 4.03); m = number of events; n = number of subjects; TEAE = treatment-emergent adverse event
Related events were those identified as definitely, probably, or possibly related per the investigator. For maximum relationship and maximum severity, subject incidence rates were reported; therefore, a subject contributes only once to each summary for their highest severity and relationship.
Source: ISS Table 2.1.1

Overall, 168 of the 486 subjects (34.6%) with TEAEs experienced at least 1 ocular event each; of those subjects, 125 (74.4%) had at least 1 ocular event in the study eye and 87 (51.8%) had at least 1 ocular event in the fellow eye (Table 4). In the ONS-5010 group, a smaller proportion of subjects than subjects in the ranibizumab group had at least 1 ocular event (28.7% vs 48.3%, respectively), at least 1 ocular TEAE in the study eye (21.4% vs 35.9%, respectively), or at least 1 ocular TEAE in the fellow eye (14.1% vs 26.9%, respectively).

Of the 168 subjects with ocular TEAEs, 56 (11.5%) had events that were considered by the investigator to be study drug/study procedure related. All but 1 of the related ocular TEAEs occurred in the study eye in the ONS-5010 and ranibizumab groups (12.0% vs 10.3%).

Overall treatment related ocular events seem to be slightly more frequent in ONS-5010 treated patients.

Table 5. **Pooled Phase 3 Studies ONS-5010-001, ONS-5010-002, and ONS-5010-003: Treatment-Emergent Ocular Adverse Events Occurring in the Study Eye of > 2 Subjects in Either Study Drug Group (Safety Population)**

System Organ Class Preferred Term	Ranibizumab (N = 145) n (%)	ONS-5010 (N = 341) n (%)
At Least 1 Ocular TEAE in Study Eye	52 (35.9)	73 (21.4)
Eye disorders	49 (33.8)	67 (19.6)
Conjunctival hyperaemia	2 (1.4)	0
Detachment of retinal pigment epithelium	1 (0.7)	1 (0.3)
Eye irritation	0	2 (0.6)
Eye pruritus	0	2 (0.6)
Hordeolum	2 (1.4)	0
Macular scar	1 (0.7)	1 (0.3)
Neovascular age-related macular degeneration	2 (1.4)	0
Ocular discomfort	0	2 (0.6)
Vision blurred	0	2 (0.6)
Blepharitis	2 (1.4)	1 (0.3)
Lacrimation increased	3 (2.1)	0
Metamorphopsia	3 (2.1)	0
Posterior capsule opacification	1 (0.7)	2 (0.6)
Retinal degeneration	2 (1.4)	1 (0.3)
Cataract	2 (1.4)	2 (0.6)

Table 7. **Pooled Phase 3 Studies ONS-5010-001, ONS-5010-002, and ONS-5010-003: Treatment-Emergent Nonocular Adverse Events Occurring in at > 2 Subjects in Either Study Drug Group (Safety Population)**

System Organ Class Preferred Term	Ranibizumab (N = 145) n (%)	ONS-5010 (N = 341) n (%)
Blood and lymphatic system disorders	2 (1.4)	6 (1.8)
Anaemia	0	3 (0.9)
General disorders and administration site conditions	6 (4.1)	6 (1.8)
Fatigue	0	3 (0.9)
Immune system disorders	1 (0.7)	6 (1.8)
Seasonal allergy	0	4 (1.2)
Infections and infestations	16 (11.0)	45 (13.2)
Urinary tract infection	5 (3.4)	19 (5.6)
COVID-19	3 (2.1)	9 (2.6)
Bronchitis	2 (1.4)	3 (0.9)
Influenza	2 (1.4)	2 (0.6)
Sinusitis	1 (0.7)	3 (0.9)
Injury, poisoning and procedural complications	10 (6.9)	20 (5.9)
Fall	4 (2.8)	7 (2.1)
Investigations	19 (13.1)	32 (9.4)
White blood cells urine positive	5 (3.4)	3 (0.9)
Blood pressure increased	2 (1.4)	3 (0.9)
Urine analysis abnormal	2 (1.4)	3 (0.9)

System Organ Class Preferred Term	Ranibizumab (N = 145) n (%)	ONS-5010 (N = 341) n (%)
Blood urea increased	3 (2.1)	1 (0.3)
Blood creatinine increased	1 (0.7)	3 (0.9)
Blood pressure diastolic decreased	0	4 (1.2)
Musculoskeletal and connective tissue disorders	6 (4.1)	10 (2.9)
Back pain	3 (2.1)	3 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (4.8)	9 (2.6)
Squamous cell carcinoma of skin	0	3 (0.9)
Nervous system disorders	10 (6.9)	9 (2.6)
Dizziness	0	3 (0.9)
Renal and urinary disorders	6 (4.1)	12 (3.5)
Haematuria	3 (2.1)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	7 (4.8)	11 (3.2)
Cough	1 (0.7)	3 (0.9)
Respiratory failure	0	3 (0.9)
Vascular disorders	12 (8.3)	11 (3.2)
Hypertension	2 (1.4)	4 (1.2)

COVID-19 = coronavirus disease 2019
Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 23.0.
Table only includes nonocular events experienced by > 2 subjects in either study drug group. System organ classes are presented only if at least 1 preferred term within that class was reported for > 2 subjects in either study drug group.
Source: ISS Table 2.2.1

Over the course of the 3 Phase 3 studies (ONS-5010-001, ONS-5010-002, and ONS-5010-003), a smaller proportion of subjects in the ONS-5010 group than subjects in the ranibizumab group experienced events (49.3% [168 of 341 subjects] vs 71.0% [103 of 145 subjects]), whereas the number of events reported was greater in the ONS-5010 group than in the ranibizumab group (465 and 315 events, respectively).

Overall, the system organ classes (SOCs) in which events occurred at the 3 highest frequencies (inclusive of all ocular [regardless of eye] and non-ocular events) over the course of the studies were eye disorders (32.3% [157 subjects]), infections and infestations (12.6% [61 subjects]), and investigations (10.5% [51 subjects]). With the exception of the SOC of eye disorders, wherein the frequency of events was lower in the ONS-5010 group versus the ranibizumab group (26.1% vs 46.9%, respectively), the frequency of events was broadly similar between the ONS-5010 and ranibizumab groups for the aforementioned SOCs (infections and infestations = 13.2% vs 11.0%, respectively, and investigations = 9.4% vs 13.1%, respectively).

Ocular Events

Within the ONS-5010 group, the ocular events occurring in the study eye reported at the 3 highest frequencies were conjunctival haemorrhage (5.3% [18 subjects]), IOP increased (2.3% [8 subjects]), and eye pain and vitreous floaters (1.8% [6 subjects] each)

The ocular events occurring within 90 days of study drug administration that were reported at the 3 highest frequencies in the study eye for subjects treated with ONS-5010 were conjunctival haemorrhage (2.6% [9 subjects]), eye pain and IOP increased (1.8% [6 subjects] each), and vitreous floaters (1.5% [5 subjects]) (Table 6).

Within the ranibizumab group, the ocular events occurring in the study eye reported at the 3 highest frequencies were visual acuity reduced (11.0% [16 subjects]), retinal haemorrhage (4.1% [6 subjects]), and conjunctival haemorrhage and subretinal fluid (2.8% [4 subjects] each) (Table 5).

Non-ocular Events

The non-ocular events reported at the 3 highest frequencies in the ONS-5010 group were urinary tract infection (5.6% [19 subjects]), COVID-19 (2.6% [9 subjects]), and fall (2.1% [7 subjects] each) (Table 7). Note that, for the event of urinary tract infection, 19 subjects had events that were coded to the SOC of infections and infestations, while 2 subjects had events that were coded to the SOC of renal and urinary disorders.

Treatment emergent Adverse Events by Relationship

Over the course of the pooled Phase 3 studies (ONS-5010-001, ONS-5010-002, and ONS-5010-003), 57 subjects (11.7%), including 41 (12.0%) in the ONS-5010 group and 16 (11.0%) in the ranibizumab group, experienced at least 1 TEAE (ocular [regardless of eye] and nonocular combined) that was considered related to the study drug/study procedure (ISS Table 2.1.1).

Of the related ocular TEAEs occurring in the study eye, the individual events reported for more than 2 subjects each in the ONS-5010 group were conjunctival haemorrhage (17 subjects [5.0%]), vitreous floaters (5 subjects [1.5%]), IOP increased and eye pain (4 subjects [1.2%] each), and dry eye (3 subjects [0.9%]) (Table 8). The individual study drug/study procedure related events in the study eye that occurred within 90 days after the first injection of ONS-5010 were similar, with the same events, except for dry eye (ie, the events of conjunctival haemorrhage, vitreous floaters, IOP increased, and eye pain), being the most frequently reported (ISS Table 2.8.2).

In the ranibizumab group, the only individual related ocular TEAE occurring in the study eye reported for more than 2 subjects was conjunctival haemorrhage (4 subjects [2.8%]).

One related ocular TEAE of cataract in the fellow eye was reported in 1 subject from the ONS-5010 group. While cataract has been associated with intravitreal administration due to trauma from the injection, there is no mechanism of action linking a fellow eye cataract to anti-VEGF treatment or procedure. As such, this event is considered to be not related.

Regarding related nonocular TEAEs, acute myocardial infarction and blood pressure increased were the only events reported in the ONS-5010 group (Table 9). While these events were considered to be possibly related, both subjects had cardiovascular disease and risk factors in their medical history. The subject reporting the event of acute myocardial infarction required hospitalisation, and following treatment, the event was considered to be resolved. Considering the hypothetical risk of thrombotic events following anti-VEGF treatment, this event of myocardial infarction was regarded as possibly related to study drug. However, in view of the subject’s cardiovascular medical history, the most probable cause for this event was deemed to be the subject’s underlying reported coronary artery disease and vascular risk factors . Prior to starting study drug, the subject reporting increased blood pressure had a history of hypertension, which was being medically managed. One week before event onset, the subject had changed his antihypertensive medication. Due to the known low systemic exposure of intravitreal ONS-5010 and the subject’s known medical history, there is an unlikely relationship to the study drug.

Cerebral infarction was the only related nonocular TEAE reported in one subject in the ranibizumab group.

The types and frequencies of events (ocular [regardless of eye] and nonocular combined, ocular in the study eye, or nonocular) that occurred during the first 90 days after the first administration of ONS-5010 that were considered related to the study drug/study procedure were generally similar to those observed over the course of the longer duration Phase 3 studies (ie, up to 12 months).

Based on a review of ocular (study eye) and nonocular events considered by the investigator to be related to the study drug/study procedures, no meaningful differences between study drug groups were observed. Due to the small number of subjects with related ocular events in the study eye, there were no safety signals or trends; the few related, individual events occurring in 2 or more subjects each were generally expected for ONS-5010 and ranibizumab.

Table 8. Pooled Phase 3 Studies ONS-5010-001, ONS-5010-002, and ONS-5010-003: Study Drug or Study Procedure Related Treatment-Emergent Ocular Adverse Events Occurring in the Study Eye (Safety Population)

System Organ Class Preferred Term	Ranibizumab (N = 145)	ONS-5010 (N = 341)
Eye disorders	11 (7.6)	37 (10.9)
Abnormal sensation in eye	1 (0.7)	0
Blindness transient	0	1 (0.3)
Cataract	1 (0.7)	0
Conjunctival haemorrhage	4 (2.8)	17 (5.0)
Conjunctival hyperaemia	1 (0.7)	0
Corneal abrasion	1 (0.7)	2 (0.6)
Corneal scar	0	1 (0.3)
Dry age-related macular degeneration	1 (0.7)	0
Dry eye	1 (0.7)	3 (0.9)
Eye irritation	0	2 (0.6)
Eye pain	1 (0.7)	4 (1.2)
Eye pruritus	0	1 (0.3)
Iritis	0	1 (0.3)
Keratopathy	0	1 (0.3)
Lacrimation increased	2 (1.4)	0
Ocular discomfort	0	2 (0.6)
Ocular hyperaemia	0	1 (0.3)
Photopsia	0	1 (0.3)
Punctate keratitis	1 (0.7)	2 (0.6)
Retinal pigment epithelial tear	0	1 (0.3)
Subretinal fluid	1 (0.7)	0
Vitreous detachment	0	1 (0.3)
Vitreous floaters	0	5 (1.5)
Vitreous haemorrhage	0	2 (0.6)
General disorders and administration site conditions	2 (1.4)	0
Injection site pain	2 (1.4)	0
Immune system disorders	0	1 (0.3)
Iodine allergy	0	1 (0.3)

System Organ Class Preferred Term	Ranibizumab (N = 145)	ONS-5010 (N = 341)
Infections and infestations	0	1 (0.3)
Endophthalmitis	0	1 (0.3)
Injury, poisoning and procedural complications	2 (1.4)	0
Procedural pain	2 (1.4)	0
Investigations	1 (0.7)	4 (1.2)
Intraocular pressure increased	1 (0.7)	4 (1.2)

Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 23.0.
Source: ISS Table 2.8.1

Table 9. Pooled Phase 3 Studies ONS-5010-001, ONS-5010-002, and ONS-5010-003: Study Drug or Study Procedure Related Treatment-Emergent Nonocular Adverse Events (Safety Population)

System Organ Class Preferred Term	Ranibizumab (N = 145) n (%)	ONS-5010 (N = 341) n (%)
Cardiac disorders	0	1 (0.3)
Acute myocardial infarction	0	1 (0.3)
Investigations	0	1 (0.3)
Blood pressure increased	0	1 (0.3)
Nervous system disorders	1 (0.7)	0
Cerebral infarction	1 (0.7)	0

Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 23.0.
Source: ISS Table 2.3.1

*

2.5.6.1. Serious adverse events, deaths, other significant events

Table 11. Pooled Phase 3 Studies ONS-5010-001, ONS-5010-002, and ONS-5010-003: All Treatment-Emergent Serious Adverse Events (Safety Population)

System Organ Class Preferred Term	Ranibizumab (N = 145) n (%)	ONS-5010 (N = 341) n (%)
Blood and lymphatic system disorders	0	1 (0.3)
Anaemia	0	1 (0.3)
Cardiac disorders	3 (2.1)	7 (2.1)
Acute myocardial infarction	0	2 (0.6)
Aortic valve stenosis	0	1 (0.3)
Atrioventricular block complete	0	1 (0.3)
Bundle branch block	0	1 (0.3)
Bundle branch block right	1 (0.7)	0
Cardiac arrest	1 (0.7)	0
Cardiac failure acute	0	1 (0.3)
Cardiac failure congestive	0	1 (0.3)
Cardiogenic shock	0	1 (0.3)
Ischaemic cardiomyopathy	0	1 (0.3)
Myocardial infarction	0	2 (0.6)
Pericardial effusion	1 (0.7)	0
Eye disorders	0	3 (0.9)
Blindness transient	0	1 (0.3)
Retinal haemorrhage	0	1 (0.3)
Visual impairment	0	1 (0.3)
General disorders and administration site conditions	1 (0.7)	1 (0.3)
Cardiac death	1 (0.7)	0
Death[a]	0	1 (0.3)
Infections and infestations	3 (2.1)	10 (2.9)
COVID-19	1 (0.7)	1 (0.3)
COVID-19 pneumonia	1 (0.7)	1 (0.3)
Cellulitis	0	1 (0.3)
Clostridium difficile infection	0	1 (0.3)
Endophthalmitis	0	1 (0.3)
Lower respiratory tract infection	0	1 (0.3)
Pneumonia	0	1 (0.3)

System Organ Class Preferred Term	Ranibizumab (N = 145) n (%)	ONS-5010 (N = 341) n (%)
Pyelonephritis	1 (0.7)	0
Sepsis	0	1 (0.3)
Staphylococcal bacteraemia	0	1 (0.3)
Urinary tract infection	0	1 (0.3)
Injury, poisoning and procedural complications	1 (0.7)	1 (0.3)
Hip fracture	1 (0.7)	0
Rib fracture	0	1 (0.3)
Investigations	0	2 (0.6)
Intraocular pressure increased	0	2 (0.6)
Metabolism and nutrition disorders	1 (0.7)	1 (0.3)
Hypokalaemia	1 (0.7)	0
Hyponatraemia	0	1 (0.3)
Musculoskeletal and connective tissue disorders	2 (1.4)	1 (0.3)
Ankle pain	1 (0.7)	0
Back pain	1 (0.7)	0
Bursitis	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.4)	1 (0.3)
Acute leukaemia	0	1 (0.3)
Bladder neoplasm	1 (0.7)	0
Squamous cell carcinoma of the tongue	1 (0.7)	0
Nervous system disorders	5 (3.4)	0
Cerebral infarction	1 (0.7)	0
Cerebrovascular accident	1 (0.7)	0
Confusional state	1 (0.7)	0
Embolic stroke	1 (0.7)	0
Seizure	1 (0.7)	0
Renal and urinary disorders	2 (1.4)	1 (0.3)
Chronic kidney disease	0	1 (0.3)
Haemorrhage urinary tract	1 (0.7)	0
Nephrolithiasis	1 (0.7)	0
Respiratory, thoracic and mediastinal disorders	2 (1.4)	4 (1.2)
Asthma	1 (0.7)	0
Chronic obstructive pulmonary disease	0	1 (0.3)
Pleural effusion	1 (0.7)	0
Pulmonary embolism	0	1 (0.3)

System Organ Class Preferred Term	Ranibizumab (N = 145) n (%)	ONS-5010 (N = 341) n (%)
Respiratory failure	0	2 (0.6)
Vascular disorders	2 (1.4)	1 (0.3)
Epistaxis	1 (0.7)	0
Hypotension	1 (0.7)	0
Transient ischaemic attack	0	1 (0.3)

COVID-19 = coronavirus disease 2019
Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 23.0.
a Death was related to coronavirus disease 2019.
Source: ISS Table 2.12.1

Table 10. Pooled Phase 3 Studies ONS-5010-001, ONS-5010-002, and ONS-5010-003: Treatment-Emergent Adverse Events Leading to Death by Preferred Term (Safety Population)

Preferred Term	Ranibizumab (N = 145) n (%)	ONS-5010 (N = 341) n (%)
Cardiac arrest	1 (0.7)	0
Cardiac death	1 (0.7)	0
COVID-19	0	1 (0.3)
COVID-19 pneumonia	0	1 (0.3)
Death[a]	0	1 (0.3)
Myocardial infarction	0	1 (0.3)
Respiratory failure	0	1 (0.3)

COVID-19 = coronavirus disease 2019
Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 23.0.
a Death was related to coronavirus disease 2019.
Source: ISS Table 2.18.1; ONS-5010-002 Table 14.3.1.13B; ONS-5010-003 Section 12.3.1.1

Overall, 44 subjects (9.1%), including 30 (8.8%) in the ONS-5010 group and 14 (9.7%) in the ranibizumab group, experienced at least 1 TEAE (ocular [regardless of study eye] and nonocular combined) that was ≥ Grade 3 in severity. Over the course of the pooled Phase 3 studies, most of the individual TEAEs with severities of Grade 3 or higher were experienced by only 1 subject each in either study drug group. The ocular events with a severity of Grade 3 or higher in the ONS-5010 group were blindness transient, retinal haemorrhage, visual impairment, endophthalmitis, iritis, and IOP increased (occurring in 1 subject each); in the ranibizumab group, the events were retinal detachment and retinal tear (both occurring in the same subject;.

Over the course of the 3 pooled Phase 3 studies (ONS-5010-001, ONS-5010-002, and ONS-5010-003), 5 subjects experienced TEAEs with severities of Grade 3 or higher that were considered by the investigator to be related to the study drug/study procedure. The events experienced by these subjects in the ONS-5010 group were acute myocardial infarction, blindness transient, iritis, endophthalmitis, and IOP increased (reported in 1 subject each); in the ranibizumab group, the only Grade 3 or higher study drug/study procedure related TEAE was cerebral infarction (reported in 1 subject).

No safety signals or trends were observed based on a review of the severity of ocular and nonocular TEAEs reported in the study, including based on their relationship to study drug/study procedures. Numbers and percentages of subjects with events ≥ Grade 3 in severity were rather similar between ONS-5010 and a less frequent regimen of ranibizumab. However the limited size of the Phase 3 program in terms of safety is noted (N=341 ONS-5010 patients). Rarer events might not have been detected. Deaths were rare, equally distributed and potentially not treatment related.

Phase 1 Pharmacokinetics Study

Of the 135 subjects in the safety population administered IV ONS-1045, a total of 116 (85.9%) subjects experienced at least 1 TEAE each during the study, with a similar proportion of subjects experiencing events in the ONS-1045 (86.7% [39 of 45 subjects]), Avastin US (88.9% [40 of 45 subjects]), and Avastin EU (82.2% [37 of 45 subjects]) groups (CHDR1427_ONS-1045-001 CSR, Section 9.2).

No deaths or other nonfatal SAEs occurred, and no subject discontinued from the study due to TEAEs (CHDR1427_ONS-1045-001 CSR, Section 9.3). Most reported TEAEs were mild in intensity and no severe events were reported. Summaries of TEAEs by severity and by relationship to study drug are presented in the CSR (CHDR1427_ONS-1045-001 CSR, Appendix G and Appendix H, respectively).
Among healthy subjects who had a single IV administration of ONS-1045, the SOCs in which events occurred at the 3 highest frequencies were infections and infestations (45.9% [62 subjects]), nervous system disorders (37.8% [51 subjects]), and gastrointestinal disorders (21.5% [29 subjects]).
The TEAEs reported at the 3 highest frequencies across study drug groups were nasopharyngitis (37.8% [17 subjects] in the ONS-1045 group, 24.4% [11 subjects] in the Avastin US group, and 26.7% [12 subjects] in the Avastin EU group), headache (28.9% [13 subjects] in the ONS-1045 group, 37.8% [17 subjects] in the Avastin US group, and 26.7% [12 subjects] in the Avastin EU group), and musculoskeletal pain (6.7% [3 subjects] in the ONS-1045 group, 13.3% [6 subjects] in the Avastin US group, and 13.3% [6 subjects] in the Avastin EU group).
Results derived from this trial are considered supportive only, due to ONS-1045 use (intravenous formulation) and intravenous and not intravitreal administration.

Ongoing Open-Label Safety Study ONS-5010-007

As of the data cutoff date (18 May 2022), 25 of the 60 treated subjects (41.7%) had experienced at least 1 TEAE each. Of the 25 subjects with TEAEs, 5 had ocular events in the study eye; no individual ocular event occurring in the study eye was reported by more than 1 subject each, except for lacrimation increased which occurred in 2 subjects (ONS-5010-007 CSR Table 14.3.1.4). Of the 5 subjects with ocular TEAEs in the study eye, 3 had events that were considered by the investigator to be study drug/study procedure related (conjunctival haemorrhage, eye pain, and lacrimation increased) (ONS-5010-007 CSR Table 14.3.1.3). No subject had a Grade 4 or 5 event, but 4 subjects had 5 SAEs (diabetes mellitus inadequate control and acute kidney injury in 1 subject; prostate cancer, seizure like phenomena, and pleural effusion in 1 subject each [ONS-5010-007 Table 14.3.1.12]).
Although ONS-5010-007 evaluated ONS-5010 manufactured using the proposed commercial process, no new or adverse safety signals were observed as of the data cutoff date that would alter the established safety profile for ONS-5010 derived from the completed studies.
No relevant strong signal was to date identified in the OLS Study ONS-5010-007

2.5.6.2. Laboratory findings

All in all laboratory parameters under ONS-5010 treatment seem to be comparable to ranibizumab treatment, small differences are noted for Intraocular pressure where 2.6. vs 1.4 % of patients are affected. This might however be either chance or due to a more frequent drug administration of ONS-5010.

No unexpected findings were observed for vital signs or special investigations.

Notable in terms of efficacy are however CFT measurements:

The results of CFT measurements are presented by visit for the study eyes and fellow eyes in ISS Table 3.6.1. In the study eyes, the mean CFT decreased from 352.8 µm at baseline to 312.5 µm at Day 330 in the ONS-5010 group and from 407.1 µm to 312.8 µm at the same respective time points in the ranibizumab group. In the fellow eyes, the mean CFT remained relatively stable in the ONS-5010 group (281.8 µm at baseline and 282.0 µm at Day 330), and the ranibizumab group (287.0 µm to 275.9 µm at the same respective assessments).

It seems that despite less frequent treatment, ranibizumab showed a stronger improvement in CFT than ONS-5010 which is in line with data from Avastin studies where bevacizumab widely trends worse compared to ranibizumab in anatomical/functional PD markers.

Withdrawal and Rebound

ONS-5010 is physician administered monthly by intravitreal injection. With no clinical or nonclinical data suggesting physical dependency attributable to the components of ONS-5010, the potential for withdrawal or rebound effects is negligible.

Pertaining to when and how patients should change their monthly treatment regimen to an "as needed" schedule, available Lytenava data enables effect size estimation after one year with a monthly dosing schedule, which is already hampered owing to the Phase 3 study design and thus, linked to uncertainties. Therefore, the most plausible time point to switch to an as needed regimen seems after one year of a monthly treatment schedule, based on Lytenava data. Based on Avastin data, the applicant suggested, three monthly injections followed by an as needed regiment, which can be accepted.

2.5.6.3. Safety in special populations

Upon request, the applicant submitted the below table. The results displayed do not raise specific concerns.

Table 1: Treatment-Emergent Adverse Events Summary by Age Subgroup in the Pooled NORSE ONE, NORSE TWO and NORSE THREE Trials (Safety Population)

Characteristic	Ranibizumab N=145 n (%)/m				ONS-5010 N=341 n (%)/m				Overall N=486 n (%)/m			
	<65 (N=6)	65-74 (N=35)	75-84 (N=65)	85+ (N=39)	<65 (N=103)	65-74 (N=78)	75-84 (N=100)	85+ (N=60)	<65 (N=109)	65-74 (N=113)	75-84 (N=165)	85+ (N=99)
At least 1 TEAE	3 (50.0)/11	27 (77.1)/73	45 (69.2)/150	28 (71.8)/81	35 (34.0)/92	38 (48.7)/94	52 (52.0)/154	43 (71.7)/125	38 (34.9)/103	65 (57.5)/167	97 (58.8)/304	71 (71.7)/206
At least 1 TEAE related to study drug/study procedure	1 (16.7)/1	4 (11.4)/9	9 (13.8)/10	2 (5.1)/2	8 (7.8)/12	9 (11.5)/15	17 (17.0)/24	7 (11.7)/8	9 (8.3)/13	13 (11.5)/24	26 (15.8)/34	9 (9.1)/10
At least 1 ocular TEAE	3 (50.0)/6	16 (45.7)/41	32 (49.2)/57	19 (48.7)/42	16 (15.5)/27	22 (28.2)/44	40 (40.0)/85	20 (33.3)/30	19 (17.4)/33	38 (33.6)/85	72 (43.6)/142	39 (39.4)/72

At least 1 ocular TEAE in study eye	2 (33.3)/3	11 (31.4)/26	23 (35.4)/37	16 (41.0)/21	13 (12.6)/23	15 (19.2)/29	28 (28.0)/46	17 (28.3)/17	15 (13.8)/26	26 (23.0)/55	51 (30.9)/83	33 (33.3)/38
At least 1 ocular TEAE in fellow eye	3 (50.0)/3	9 (25.7)/15	16 (24.6)/20	11 (28.2)/21	4 (3.9)/4	11 (14.1)/15	24 (24.0)/39	9 (15.0)/13	7 (6.4)/7	20 (17.7)/30	40 (24.2)/59	20 (20.2)/34
At least 1 ocular TEAE related to study drug/study procedure	1 (16.7)/1	4 (11.4)/9	8 (12.3)/9	2 (5.1)/2	8 (7.8)/12	9 (11.5)/15	17 (17.0)/23	7 (11.7)/7	9 (8.3)/13	13 (11.5)/24	25 (15.2)/32	9 (9.1)/9
At least 1 ocular TEAE in study eye related to study drug/study procedure	1 (16.7)/1	4 (11.4)/9	8 (12.3)/8	2 (5.1)/2	8 (7.8)/12	9 (11.5)/15	17 (17.0)/23	7 (11.7)/7	9 (8.3)/13	13 (11.5)/24	25 (15.2)/31	9 (9.1)/9
At least 1 ocular TEAE in fellow eye related to study drug/study procedure	0	0	1 (1.5)/1	0	0	0	0	0	0	0	1 (0.6)/1	0
At least 1 ≥ Grade 3 TEAE	0	3 (8.6)/3	7 (10.8)/11	4 (10.3)/6	7 (6.8)/16	4 (5.1)/4	9 (9.0)/10	10 (16.7)/13	7 (6.4)/16	7 (6.2)/7	16 (9.7)/21	14 (14.1)/19
At least 1 ≥ Grade 3 TEAE related to study drug/study procedure	0	0	1 (1.5)/1	0	0	1 (1.3)/1	2 (2.0)/3	1 (1.7)/1	0	1 (0.9)/1	3 (1.8)/4	1 (1.0)/1
At least 1 serious TEAE	1 (16.7)/1	4 (11.4)/4	8 (12.3)/13	5 (12.8)/6	6 (5.8)/11	3 (3.8)/3	9 (9.0)/10	11 (18.3)/15	7 (6.4)/12	7 (6.2)/7	17 (10.3)/23	16 (16.2)/21
At least 1 serious TEAE related to study drug/study procedure	0	0	1 (1.5)/1	0	0	1 (1.3)/1	2 (2.0)/3	1 (1.7)/1	0	1 (0.9)/1	3 (1.8)/4	1 (1.0)/1
At least 1 TEAE leading to discontinuation	0	2 (5.7)/3	2 (3.1)/2	2 (5.1)/2	2 (1.9)/2	2 (2.6)/2	0	2 (3.3)/2	2 (1.8)/2	4 (3.5)/5	2 (1.2)/2	4 (4.0)/4
At Least 1 TEAE Leading to Treatment or Study Discontinuation Related to Either Study Drug or to Study Procedure	0	0	1 (1.5)/1	0	0	0	0	1 (1.7)/1	0	0	1 (0.6)/1	1 (1.0)/1

CTCAE = Common Terminology Criteria for Adverse Events; m = number of events; n = number of subjects; SAE = Serious Adverse Event. TEAE = Treatment-Emergent Adverse Event.
Note: Adverse events are coded using MedDRA version 23.0. Toxicity is graded using NCI CTCAE version 4.03. For maximum severity, subject incidence rates are reported; therefore a subject contributes only once to each summary for their highest severity.
Source: Appendix 1-Q102 Adhoc Table 2.1.3

2.5.6.4. Immunological events

The applicant has developed a three tiered approach to assess immunogenicity of ONS-5010. In brief, anti-drug antibodies form a bridge between Biotin-ONS-5010 and Sulfo-Tag-ONS-5010 molecules. This complex is bound to Streptavidin and detected by a chemiluminescent signal, directly proportional to the amount of ADA present in the human serum. Samples analysed in the screening assay (tier 1) having responses equal to or above the plate specific cut point are re-analysed in the presence of anti-VEGF antibody (tier 2B) to identify samples that screened positive due to target interference. Sample with responses equal to or above the plate

specific cut point are then analysed in the confirmatory assay (tier 2). Confirmed positive samples are analysed in the titre assay (tier 3) in which samples are diluted until a negative response is obtained. The sample titre is reported as the reciprocal of the greatest dilution that has a response above the cut point. Validity of results and of the method for its intended use was confirmed in the range of 81-2000 ng/ml in serum matrix. Positive and negative controls were well selected, and sample receipt, analysis results and data reduction were well documented. Presented approach is considered state of the art, and seems acceptable.

Clinical

It is unclear why Immunogenicity assessment has not been implemented as an objective in both of the applicant's pivotal trials. Immunogenicity testing has been performed only in a subset of patients in Phase 3 trials, 95 samples were analysed in the NORSE ONE study, 33 samples in the NORSE TWO trial. No ADA were identified in that subset. In the applicant's Phase 1 PK with ONS-1045 (iv administration), immunogenicity was addressed as well. Only one subject (#28, Avastin EU) tested confirmed positive for anti-drug antibodies, with a titre of 1:10. The antibodies were first detected on study day 99, and were not neutralizing.

2.5.6.5. Discontinuation due to adverse events

Table 2. Pooled Phase 3 Studies ONS-5010-001, ONS-5010-002, and ONS-5010-003: Disposition of Subjects

	Ranibizumab n (%)	ONS-5010 n (%)	Total n (%)
Screened			696
Received at least 1 dose of study drug	145	341	486
Safety population	145 (100.0)	341 (100.0)	486 (100.0)
Completed study	116 (80.0)	320 (93.8)	436 (89.7)
Discontinued study	26 (17.9)	21 (6.2)	47 (9.7)
Primary reason for study discontinuation			
Consent withdrawn/subject withdrew consent	16 (11.0)	3 (0.9)	19 (3.9)
Adverse event	3 (2.1)	7 (2.1)	10 (2.1)
Lost to follow-up	0	6 (1.8)	6 (1.2)
Sponsor decision	1 (0.7)	3 (0.9)	4 (0.8)
Other	3 (2.1)	1 (0.3)	4 (0.8)
Lack of efficacy	2 (1.4)	1 (0.3)	3 (0.6)
Noncompliance/protocol violation	1 (0.7)	0	1 (0.2)
Discontinued treatment	17 (11.7)	9 (2.6)	26 (5.3)
Primary reason for treatment discontinuation			
Lack of efficacy	7 (4.8)	2 (0.6)	9 (1.9)
Subject withdrew consent	6 (4.1)	2 (0.6)	8 (1.6)
Sponsor decision	1 (0.7)	3 (0.9)	4 (0.8)
Adverse event	2 (1.4)	1 (0.3)	3 (0.6)
Noncompliance/protocol violation	1 (0.7)	0	1 (0.2)
Other	0	1 (0.3)	1 (0.2)

Percentages are based on the number who received at least 1 dose of study drug. The table excludes reasons for discontinuation if no subject in either treatment group discontinued for the specific reason.
Source: ISS Table 1.1.1

The rate of Study Discontinuation in the applicant's Phase 3 trial was higher in the ranibizumab treated patients than in ONS-5010 treated patients (26(17.9%) vs. 21(6.2%).

Most patients in the ranibizumab arms discontinued treatment due to "Consent" withdrawn and "lack of efficacy". Both indicate, that the ranibizumab regimen was not designed to reach the optimal treatment effect. No signal regarding discontinuations due to particular safety reasons are noted.

2.5.7. Discussion on clinical safety

The main source of evidence for the safety of Lytenava come from the 341 patients treated in the Phase 3 NORSE ONE, NORSE TWO and NORSE THREE, while supporting evidence comes from the literature data generated with Avastin.

Safety data from the single dose PK bridging trial to EU and US Avastin is of limited value regarding safety evaluation since intravenous administration of Lytenava was evaluated.

In the Phase 3 population, the evaluable safety database is quite limited for a standalone application.

It is notable that the comparison between treatment arms regarding safety was also conducted "unevenly" meaning that 12 months Lytenava data was compared to 11 months of ranibizumab data. While this is in principle not desirable, it is considered the more conservative analysis.

The overall safety profile seems comparable to the less frequently administered comparator, which is reassuring.

Immunogenicity has been investigated in a subgroup of patients however, without clear strategy and a predefined objective in both studies. However, data from Phase I together with data presented from a subset of IVT treated patients suggest that the immunogenic potential of ONS-5010 after IVT administration remains low.

The rate of Study Discontinuation in the applicant's Phase 3 trials was higher in the ranibizumab treated patients than in ONS-5010 treated patients (26(17.9%) vs. 21(6.2%)).

Most patients in the ranibizumab arms discontinued treatment due to "Consent" withdrawn and "lack of efficacy". Both indicate, that the ranibizumab regimen was not designed to reach the optimal treatment effect. One could also interpret this imbalance as a signal of efficacy of ONS-5010. However, it is unclear how to quantify this assumption. No signal regarding discontinuations due to particular safety reasons are noted.

Over the course of the 3 Phase 3 studies (ONS-5010-001, ONS-5010-002, and ONS-5010-003), a smaller proportion of subjects in the ONS-5010 group than subjects in the ranibizumab group experienced events (49.3% [168 of 341 subjects] vs 71.0% [103 of 145 subjects]), whereas the number of events reported was greater in the ONS-5010 group than in the ranibizumab group (465 and 315 events, respectively).

Overall, the system organ classes (SOCs) in which events occurred at the 3 highest frequencies (inclusive of all ocular [regardless of eye] and non-ocular events) over the course of the studies were eye disorders (32.3% [157 subjects]), infections and infestations (12.6% [61 subjects]), and investigations (10.5% [51 subjects]). With the exception of the SOC of eye disorders, wherein the frequency of events was lower in the ONS-5010 group versus the ranibizumab group (26.1% vs 46.9%, respectively), the frequency of events was broadly similar between the ONS-5010 and ranibizumab groups for the aforementioned SOCs (infections and infestations = 13.2% vs 11.0%, respectively, and investigations = 9.4% vs 13.1%, respectively).

Ocular Events

Within the ONS-5010 group, the ocular events occurring in the study eye reported at the 3 highest frequencies were conjunctival haemorrhage (5.3% [18 subjects]), IOP increased (2.3% [8 subjects]), and eye pain and vitreous floaters (1.8% [6 subjects] each)

The ocular events occurring within 90 days of study drug administration that were reported at the 3 highest frequencies in the study eye for subjects treated with ONS-5010 were conjunctival haemorrhage (2.6% [9 subjects]), eye pain and IOP increased (1.8% [6 subjects] each), and vitreous floaters (1.5% [5 subjects]) (Table 6).

Within the ranibizumab group, the ocular events occurring in the study eye reported at the 3 highest frequencies were visual acuity reduced (11.0% [16 subjects]), retinal haemorrhage (4.1% [6 subjects]), and conjunctival haemorrhage and subretinal fluid (2.8% [4 subjects] each) (Table 5).

Non-ocular Events

The non-ocular events reported at the 3 highest frequencies in the ONS-5010 group were urinary tract infection (5.6% [19 subjects]), COVID-19 (2.6% [9 subjects]), and fall (2.1% [7 subjects] each) (Table 7). Note that, for the event of urinary tract infection, 19 subjects had events that were coded to the SOC of infections and infestations, while 2 subjects had events that were coded to the SOC of renal and urinary disorders (ISS Table 2.2.1).

All in all, the frequencies of observed ocular and non-ocular events do not give rise to concern. It is however hard to comparatively assess especially ocular AEs which might be caused or affected by intravitreal injection, due to different dosing regimens (monthly vs q3months plus interim sham injections). The relevant safety comparison would have been monthly ONS-5010 vs monthly ranibizumab treatment. In both pivotal trials we are dealing with a artificial comparator that is administered less frequent than the test product. . However, this provides a conservative view of the safety of Lytenava, which is acceptable.

Overall, 44 subjects (9.1%), including 30 (8.8%) in the ONS-5010 group and 14 (9.7%) in the ranibizumab group, experienced at least 1 TEAE (ocular [regardless of study eye] and nonocular combined) that was ≥ Grade 3 in severity. Over the course of the pooled Phase 3 studies, most of the individual TEAEs with severities of Grade 3 or higher were experienced by only 1 subject each in either study drug group. The ocular events with a severity of Grade 3 or higher in the ONS-5010 group were blindness transient, retinal haemorrhage, visual impairment, endophthalmitis, iritis, and IOP increased (occurring in 1 subject each); in the ranibizumab group, the events were retinal detachment and retinal tear (both occurring in the same subject.

Over the course of the 3 pooled Phase 3 studies (ONS-5010-001, ONS-5010-002, and ONS-5010-003), 5 subjects experienced TEAEs with severities of Grade 3 or higher that were considered by the investigator to be related to the study drug/study procedure. The events experienced by these subjects in the ONS-5010 group were acute myocardial infarction, blindness transient, iritis, endophthalmitis, and IOP increased (reported in 1 subject each); in the ranibizumab group, the only Grade 3 or higher study drug/study procedure related TEAE was cerebral infarction (reported in 1 subject).

This imbalance is considered remarkable however it is again difficult to interpret due to much rarer verum injections of the comparator.

No safety signals or trends were observed based on a review of the severity of ocular and nonocular TEAEs reported in the study, including based on their relationship to study drug/study procedures. Numbers and percentages of subjects with events ≥ Grade 3 in severity were rather similar between ONS-5010 and a less frequent regimen of ranibizumab. However the limited size of the Phase 3 program in terms of safety is noted (N=341 ONS-5010 patients). Rarer events might not have been detected. Deaths were rare, equally distributed and potentially not treatment related.

The applicant reported that approximately 70% of the subjects (238 of 341) who received ONS-5010 were ≥ 65 years of age and approximately 47% of the subjects (160 of 341) were ≥ 75 years of age. No significant differences in safety were seen with increasing age in these studies. No other analyses in special populations were performed, which is acceptable due to the indication and the route of administration.

No unexpected findings were observed for vital signs or special investigations.

Notable in terms of efficacy are however CFT measurements:

The results of CFT measurements are presented by visit for the study eyes and fellow eyes in ISS Table 3.6.1. In the study eyes, the mean CFT decreased from 352.8 µm at baseline to 312.5 µm at Day 330 in the ONS-5010 group and from 407.1 µm to 312.8 µm at the same respective time points in the ranibizumab group. In the fellow eyes, the mean CFT remained relatively stable in the ONS-5010 group (281.8 µm at baseline and 282.0 µm at Day 330), and the ranibizumab group (287.0 µm to 275.9 µm at the same respective assessments).

It seems that despite less frequent treatment, ranibizumab showed a stronger improvement in CFT than ONS-5010.

All in all laboratory parameters under ONS-5010 treatment seem to be comparable to ranibizumab treatment, small differences are noted for Intraocular pressure where 2.6. vs 1.4 % of patients are affected. This might however be either chance or due to a more frequent drug administration.

In general, information about systemic absorption of Lytenava was insufficient and there was a lack of data linking systemic levels of ONS-5010 with risk to develop certain adverse events. This was considered to be of particular interest, as intravitreally administered bevacizumab leads to systemic accumulation when administered monthly, which has also been shown to be substantially higher compared to other IVT anti-VEGFs (Avery 2014, 2017). as part of the responses provided during assessment, data from a PK model were provided, predicting a serum steady-state to be reached after approximately 5 months and at levels far below those reached via IV administration in oncologic settings. Some uncertainties entering the B/R remain due to limitations of the PK model applied, including a very limited data set Lytenava IVT entering into the model, inadequate capturing of the last IV data point when using a linear PK, plateauing of population predictions and consequently unreliable concentration estimations. However, no relevant safety issues are anticipated based on the data provided.

Pertaining to when and how patients should change their monthly treatment regimen to an "as needed" schedule, available Lytenava data enables effect size estimation after one year with a monthly dosing schedule, which is already hampered owing to the Phase 3 study design and thus, linked to uncertainties. Therefore, the most plausible time point to switch to an as needed regimen seems after one year of a monthly treatment schedule, based on Lytenava data. However, the wording proposal in the SmPC states "that three or more consecutive monthly injections may be needed", after which the HCP may individualise treatment intervals based on disease activity. In view of the established bridging exercise to Avastin, literature data of Avastin regarding a similar regimen could be taken into account as supportive evidence and thus the proposed treatment regimen is considered acceptable.

2.5.8. Conclusions on the clinical safety

Taken together, the safety data from Lytenava trials suggest a safety profile that is considered acceptable for use in the target indication.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Endophthalmitis • Intraocular inflammation • Intraocular pression increase • Retinal detachment/tear
Important potential risks	• Thromboembolic events
Missing information	• None

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Safety concern	**Routine risk minimisation activities**
Important identified risks	
Endophthalmitis	Routine risk communication: SmPC Section 4.2 Posology and method of administration Section 4.3 Contraindication Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information Leaflet (PL) Section 2 What you need to know before you use Lytenava Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for performing intravitreal injection procedure under aseptic conditions presented in SmPC Section 4.2, 6.6 and PL

	Section 3 as well as in the Information intended for HCP only – Method of administration. Recommendation for instructing patients to report any symptoms without delay in SmPC Section 4.4. Instructions on how to detect early signs and symptoms of endophthalmitis are provided in PL Sections 2 and 4. Other routine risk minimisation measures beyond the Product Information: Pack size: one vial for single use only. Legal Status Lytenava is only available by prescription. It must be administered by a qualified ophthalmologist experienced in intravitreal injections and under aseptic conditions.
Intraocular inflammation	Routine risk communication : SmPC Section 4.3 Contraindication Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information Leaflet (PL) Section 2 What you need to know before you use Lytenava Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for performing intravitreal injection procedure under aseptic conditions presented in SmPC Section 4.2, 6.6 and PL Section 3 as well as in the Information intended for HCP only – Method of administration. Recommendation for instructing patients to report any symptoms without delay in SmPC Section 4.4 Instructions on how to detect early signs and symptoms of intraocular inflammation are provided in PL Sections 2 and 4. Other routine risk minimisation measures beyond the Product Information: Pack size: one vial for single use only. Legal Status:

	Lytenava is only available by prescription. It must be administered by a qualified ophthalmologist experienced in intravitreal injections and under aseptic conditions.
Intraocular pressure increase	Routine risk communication: SmPC Sections 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Section 4.9 Overdose Patient Information Leaflet (PL) Section 2 What you need to know before you use Lytenava Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for performing intravitreal injection procedure under aseptic conditions presented in SmPC Section 4.2, 6.6 and PL Section 3 as well as in the Information intended for HCP only – Method of administration. Recommendation for instructing patients to report any symptoms without delay in SmPC Section 4.4 Instructions on how to detect early signs and symptoms of intraocular pressure increase are provided in PL Sections 2 and 4. Other routine risk minimisation measures beyond the Product Information: Pack size: one vial for single use only. Legal Status: Lytenava is only available by prescription. It must be administered by a qualified ophthalmologist experienced in intravitreal injections and under aseptic conditions.
Retinal detachment/tear	Routine risk communication:

	SmPC Sections 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information Leaflet (PL) Section 2 What you need to know before you use Lytenava Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for performing intravitreal injection procedure under aseptic conditions presented in SmPC Section 4.2, 6.6 and PL Section 3 as well as in the Information intended for HCP only – Method of administration. Recommendation for instructing patients to report any symptoms without delay in SmPC Section 4.4 Instructions on how to detect early signs and symptoms of retinal detachment/tear are provided in PL Sections 2 and 4. Other routine risk minimisation measures beyond the Product Information: Pack size: one vial for single use only. Legal Status: Lytenava is only available by prescription. It must be administered by a qualified ophthalmologist experienced in intravitreal injections and under aseptic conditions.
Important potential risk	
Thromboembolic events	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information Leaflet Section 2 What you need to know before you use Lytenava Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable. Other routine risk minimisation measures beyond the Product Information:

	Pack size: one vial for single use only. Legal Status Lytenava is only available by prescription. It must be administered by a qualified ophthalmologist experienced in intravitreal injections and under aseptic conditions.
Missing information	
None	None

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

Based on the new indication and route of administration, the PRAC is of the opinion that a separate entry in the EURD list for Lytenava is needed, as it cannot follow the already existing entry for bevacizumab. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lytenava (bevacizumab gamma) is included in the additional monitoring list as it is a biological product approved after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Neovascular (wet) age-related macular degeneration (nAMD) is a degenerative disease of the central portion of the retina (the macula) that results primarily in loss of central vision. Wet AMD is characterised by growth of abnormal vessels into the subretinal space, usually from the choroidal circulation and less frequently from the retinal circulation. These abnormal blood vessels (choroidal neovascularisation) leak, leading to collections of subretinal fluid and/or blood beneath the retina. Wet AMD is characterised by rapid distortion and loss of central vision over a period of days to weeks. The contralateral eye is at high risk of developing neovascularisation. The aim of therapy is to slow down the progression of AMD and central vision loss.

3.1.2. Available therapies and unmet medical need

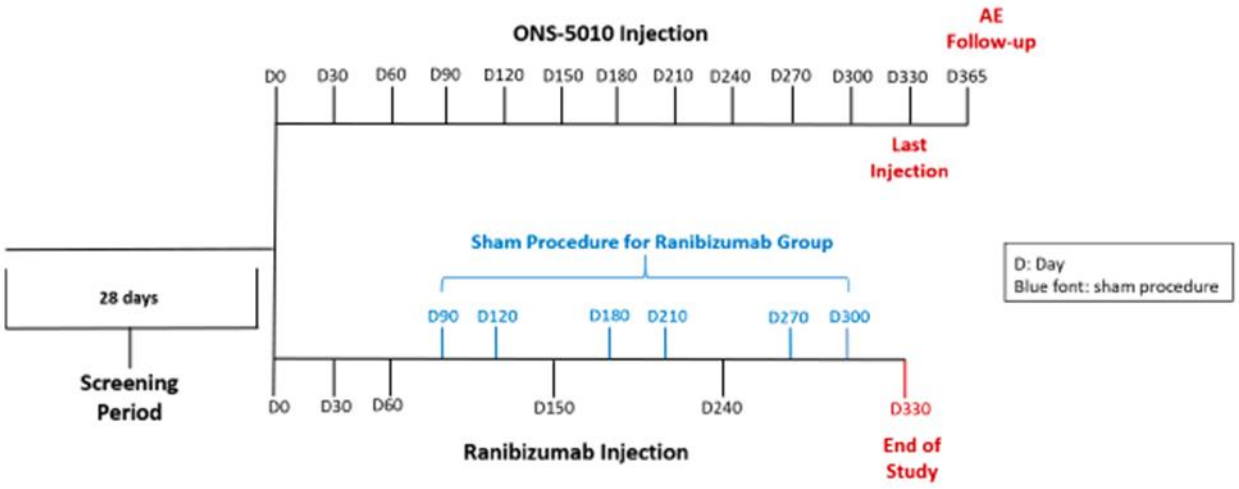
Intravitreal injection of a vascular endothelial growth factor (VEGF) inhibitor is the gold standard of therapy. Photodynamic therapy (PDT) is another option and often used in combination with anti-VEGF agents. Supplementation with zinc and antioxidant vitamins as well as visual aids are suggested.

Aflibercept (Eylea), ranibizumab (Lucentis) and brolucizumab (Beovu) are approved in AMD. All three products are available across the European Union. Bevacizumab is used off-label.

3.1.3. Main clinical studies

ONS-5010-002 (NORSE TWO) and ONS-5010-001 (NORSE ONE) were similarly designed multicentre, randomised, double-masked, controlled Phase 3 studies that evaluated the efficacy and safety of intravitreally administered ONS-5010. Both studies were conducted in accordance to Good Clinical Practice. The key differences between the NORSE ONE and NORSE TWO patient populations were: (1) the inclusion of both treatment-naïve and previously treated subjects in NORSE ONE, while only treatment-naïve patients were included in NORSE TWO; and (2) the range for baseline visual acuity was 20/40 to 20/320 in NORSE ONE, and 20/50 to 20/320 in NORSE TWO.

Figure 2. Studies NORSE TWO and NORSE ONE: Study Schematic



Following a screening period of up to 28 days in both studies, eligible subjects were randomised in a 1:1 ratio to receive ONS-5010 or ranibizumab in the study eye. Note that only 1 eye was designated as the study eye and the injection was performed by an unmasked physician. Prior to randomisation, the investigator was to receive and review clinical laboratory tests for eligibility and also to receive confirmation of subject eligibility from the medical image reviewer.

In the Phase 3 studies ONS-5010-001 and ONS-5010-002, ONS-5010 was given in the same posology and dose as has been used off-label for the off-label IV preparations of Avastin. Subjects randomised to receive ONS-5010 were administered a monthly intravitreal injection of 1.25 mg of ONS-5010 in the study eye for up to 12 months. Subjects randomised to ranibizumab received 0.5 mg of ranibizumab by intravitreal injection in the study eye every month for 3 months (i.e., on Days 0, 30, and 60) followed by 2 additional injections, 90-days apart, on Days 150 and 240. Subjects in the ranibizumab group underwent sham procedures at visits when they did not receive an active (ranibizumab) injection.

In each study, the last planned study visit differed depending on which study drug group the subject was randomised to, concluding at Day 330 for subjects in the ranibizumab group and at Day 365 for subjects in the ONS-5010 group; following the last study visit, all subjects reverted to the investigator's standard of care.

The efficacy assessments were conducted throughout the dosing and evaluation phases of each study. For subjects in both the ONS-5010 and ranibizumab groups, evaluation period for efficacy was 11 months (through Day 330); note that safety was assessed for 12 months (through Day 365) in the ONS-5010 group. In both studies, the determination of efficacy was based on best-corrected visual acuity (BCVA) (test distance of 4 m using certified lanes) assessments and measurements of central foveal thickness (CFT) by spectral domain-optical coherence tomography (SD-OCT). Measurements of BCVA were obtained for each eye separately prior to study drug injection and any assessments requiring dilation. The number of letters read correctly (for each eye) based on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart was recorded at all study visits. Imaging by SD-OCT was performed.

3.2. Favourable effects

In the NORSE TWO study (in treatment naïve patients) Lytenava has formally shown superiority over ranibizumab administered in a manner consistent with the PIER study dosing regimen, for the proportion of subjects achieving an increase of ≥ 15 letters in BCVA from baseline to 11 months. Specifically, in the ITT population, 45 subjects (41.7%) in the ONS-5010 group compared with 24 subjects (23.1%) in the ranibizumab group gained ≥ 15 letters from baseline to 11 months. The difference observed between the study drug groups was significant, with a risk difference of 0.1859 (95% CI = 0.0442, 0.3086; p = 0.0052).

In the NORSE TWO study primary efficacy results obtained using the PP population were consistent with those observed in the ITT population, with 34 subjects (41.0%) in the ONS-5010 group and 18 subjects (24.7%) in the ranibizumab group gaining ≥ 15 letters in BCVA from baseline to 11 months; the difference between study drug groups strongly favoured ONS-5010, with a risk difference of 0.1631 (95% CI = 0.0120, 0.3083; p = 0.0409).

Secondary endpoints were generally supportive of the above results. Of note, all of these analyses were based on the same clinical endpoint BCVA, thereby representing analyses from different angles on the same endpoint, rather than complementary replication of clinical efficacy from different endpoints.

Supportive efficacy data is provided with data from published literature. Another bevacizumab product, Avastin, while not approved for the treatment of nAMD, has repeatedly shown (CATT, IVAN, BRAMD studies) non-inferiority to ranibizumab when applied in the same frequency for the treatment of nAMD in literature, despite trending worse in some PD markers. Literature reports and expert statements provided support the established use of anti-VEGF therapy in nAMD in clinical practice.

3.3. Uncertainties and limitations about favourable effects

While superiority over ranibizumab is not a requirement, the failure of NORSE ONE to meet its primary objective generates some degree of uncertainty. In particular, it is observed that NORSE ONE included pretreated patients, while NORSE TWO did not. Nevertheless, extrapolation from treatment-naïve patients to the broader patient population is considered acceptable.

There are two elements of the design of the pivotal studies that make the results difficult to interpret, namely the posology of the comparator and the schedule of assessments. While Lytenava was administered monthly, the comparator (ranibizumab) was not. The comparator was administered according to the PIER study of Lucentis, which foresees a less frequent administration than is foreseen in the Lucentis label in the EU, although it is included in the US Lucentis label. This is further critical in light of the dropout pattern shown in study NORSE TWO, after which subjects seem to discontinue solely in the comparator arm due to lack-of-efficacy or because they received rescue medication. In addition, the primary endpoint was measured at the same study visit, which was approximately 30 days after the last ONS-5010 injection but 90 days after the last ranibizumab injection. When accepting superiority of Lytenava (NORSE TWO dosing) over Ranibizumab (PIER dosing), and considering the efficacy results of the PIER study for ranibizumab over sham, one can assume, that under similar study conditions as in PIER, Lytenava may exhibit a similar effect size when compared to sham. Therefore, while an effect in the vicinity of the 16 points is plausible, considerable residual uncertainty persists owing to study-specific conditions, variability of the estimate, and differences in timing.

The possibility to rely on the supportive efficacy data from the literature depends on a bridge being established between Lytenava and Avastin. At initial submission, the applicant did not provide sufficient bridging data to allow extrapolation of literature data generated with Avastin to Lytenava. No solid comparability exercise on an analytical and functional level had been performed. A PK trial bridging the i.v. formulation of ONS-5010 to Avastin was not considered sufficient without a stringent and complete quality comparability. From the additionally submitted information provided by the applicant with the responses to questions, it is sufficiently demonstrated that ONS-5010 and EU-Avastin are of comparable quality in light of representative quality attributes. Thus, it can be concluded that the bibliographic data from Avastin can serve as additional supportive evidence. In this context, results from the provided bibliographic studies (CATT, IVAN, BRAMD) comparing bevacizumab and ranibizumab in wAMD indicate in all three studies no statistical difference, but clear trends in favour of ranibizumab and across almost all parameters evaluated. A high proportion of legally blind patients at the end of Study NORSE TWO is also of note. To date, according to clinical consensus, wet AMD patients with BCVA of 20/200 in Snellen equivalent will not be treated further with VEGF-inhibitors. However, as the high proportion was observed in both treatment arms and is based on low absolute numbers, this may reflect aspects of procedures or the patients' selection in the study and/or a random finding that cannot be attributed to treatment.

3.4. Unfavourable effects

Overall, the safety profile seems comparable to the less frequently administered (and therefore in terms of safety potentially more conservative) comparator.

The rate of study discontinuation in the Aapplicant's Phase 3 trials was higher in the ranibizumab treated patients than in ONS1050 treated patients: 26(17.9%) vs. 21(6.2%).

With the exception of the SOC of eye disorders, where the frequency of events was lower in the ONS-5010 group versus the ranibizumab group (26.1% vs 46.9%, respectively), the frequency of events was broadly similar between the ONS-5010 and ranibizumab groups for the most commonly reported SOCs (infections and infestations = 13.2% vs 11.0%, respectively, and investigations = 9.4% vs 13.1%, respectively).

In the ONS-5010 group, the ocular events occurring in the study eye reported at the 3 highest frequencies were conjunctival haemorrhage (5.3% [18 subjects]), IOP increased (2.3% [8 subjects]), and eye pain and vitreous floaters (1.8% [6 subjects] each).

The non-ocular events reported at the 3 highest frequencies in the ONS-5010 group were urinary tract infection (5.6% [19 subjects]), COVID-19 (2.6% [9 subjects]), and fall (2.1% [7 subjects] each).

All in all laboratory parameters under ONS-5010 treatment seem to be comparable to ranibizumab treatment, small differences are noted for intraocular pressure where 2.6. vs 1.4 % of patients are affected.

3.5. Uncertainties and limitations about unfavourable effects

It is notable that in the phase III program, the comparison between treatment arms regarding safety was also conducted "unevenly" meaning that 12 months Lytenava data was compared to 11 months of ranibizumab data. While this is in principle not desirable, it is considered a conservative comparison.

Immunogenicity has been investigated in a subgroup of patients however, without clear strategy and a predefined objective in both studies. However, data from Phase I together with data presented from a subset

of IVT treated patients suggest that the immunogenic potential of ONS-5010 after IVT administration remains low.

The limited size of the Phase 3 program in terms of safety is noted (N=341 ONS-5010 patients, 144 treated over one year). Rarer events might not have been detected. However, the supportive literature data from the studies with Avastin is reassuring in this sense.

The clinical implications of suppression of systemic VEGF after IVT anti-VEGF therapy are not known, which in the case of Lytenava is seen as an important uncertainty, especially since only very limited data on systemic exposure following IVT administration of Lytenava was provided. The applied serum sampling scheme following one intravitreal injection of subjects from NORSE ONE and NORSE TWO was too short as no peak was reached and respective data are therefore considered inadequate to determine PK parameters. No data on systemic accumulation following repeat dosing of Lytenava were available. However, in the literature, monthly IVT bevacizumab (Avastin) was reported to lead to significantly higher systemic accumulation compared to other anti-VEGF IVT products: in a report by Avery et al. from 2017, three monthly IVT bevacizumab injections increased Cmax by 93% compared to a single administration. Given that the follow-up duration of this bibliographic study was limited to three months, the steady-state serum concentration of bevacizumab following monthly IVT administrations was unknown at the time of submission. Further, a meta-analysis conducted by Avery and Gordon in 2016 reported increased risks for death and potentially for cerebrovascular accidents in high-risk DME patients, defined as those who received 2 years of monthly anti-VEGF treatment (ranibizumab or aflibercept). Given that monthly IVT bevacizumab was shown to accumulate substantially more than aflibercept or ranibizumab, this raised concerns. Indeed, a retrospective study assessing systemic effects of IVT bevacizumab, aflibercept, and ranibizumab (Kang 2023), reported the highest incidences for the safety outcomes major bleeding, all-cause admission, and all-cause death from bevacizumab treated patients. During the procedure, the applicant provided additional analyses from a Lytenava PK model including predictions that a steady-state would be reached after around 5 monthly IVT administrations, and the predicted steady-state concentration was comparably much lower than after IV administrations in oncologic settings. While some uncertainties regarding the applied PK model remain, no relevant safety concerns are identified given the lower serum levels following IVT administration.

3.6. Effects Table

Effects Table for Lytenava for neovascular (wet) age-related macular degeneration (nAMD).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint of pivotal trial	% subjects 15 or more BCVA letters improvement	%	Lytenava, administered monthly	Ranibizumab, administered following the PIER study dosing regimen (monthly for the first 3 month followed by 2 injections 3 month apart)	The proportion of subjects achieving an increase of 15 or more letters in the Lytenava arm was 41.7% (45 of 108) and in the Ranibizumab arm 23.1% (24 of 104). To compare both arms a Fisher's exact test was performed, Risk difference = 0.19 (95% CI: 0.04; 0.31), p<.01 Ranibizumab was administered less frequent than Lytenava (instead intravitreal SHAM) and NOT in accordance to the authorised treatment regimen in the label Secondary endpoints are other ways of looking at BCVA and are consistent. NORSE ONE does not replicate the finding, but the Avastin data from the literature offer support to superiority to a hypothetical Sham.	**NORSE TWO**
Unfavourable Effects						
Eye disorders	Most prevalent SOC in Ph III	%	Lytenava 26.9	Ranibizumab vs.46.9%	Ranibizumab was administered less frequent, instead intravitreal SHAM	
Infections and Infestations	Prevalent SOC in PhIII	%	Lytenava 13.2	Ranibizumab 11.0%	Ranibizumab was administered less frequent, instead intravitreal SHAM	
IOP increased	Ocular AE	%	Lytenava 2.6	Ranibizumab 1.4	Ranibizumab was administered less frequent, instead intravitreal SHAM	PH3

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Preservation of visual function is the main aim of the treatment of nAMD and a significant outcome for patients. The effect size of Lytenava can be assumed to be comparable to the effect size of ranibizumab in the PIER study. Moreover, the strengthened bridging to Avastin literature data support existence of an effect size of >5 letters mean change from baseline which is considered clinically relevant.

The unfavourable effects appear manageable and similar to those of approved alternatives.

3.7.2. Balance of benefits and risks

A precise estimate of the efficacy of Lytenava is impeded by shortcomings in the study design of the two pivotal trials (NORSE ONE and TWO). Even though this remains associated with an uncertainty, based on the comparability of the most relevant initial time course in NORSE TWO, it is plausible that the effect size of Lytenava can be assumed to be comparable to the effect size of ranibizumab. Moreover, and relevantly, supportive evidence from Avastin literature data, which is possible to extrapolate to Lytenava based on the established scientific bridge, support existence of an effect size of >5 letters mean change from baseline, that is considered clinically relevant.

Weighing this clinically relevant effect against a safety profile that proved – in a direct comparison in the target indication - rather comparable to ranibizumab even though Lytenava was administered more frequently than ranibizumab, the benefit of monthly administered Lytenava is considered to exceed the risks.

The benefit/risk balance of Lytenava is hence considered positive.

3.8. Conclusions

The overall benefit/risk balance of Lytenava is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Lytenava is favourable in the following indication(s):

Lytenava is indicated in adults for treatment of neovascular (wet) age-related macular degeneration (nAMD).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.