Amsterdam, 23 April 2026
EMA/112901/2026
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Rexatilux

International non-proprietary name: Ranibizumab

Procedure No. EMEA/H/C/006634/0000

## Note

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

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# Table of contents

# List of abbreviations

| | |
|---|---|
| ADA | Antidrug antibody |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| AMD | Age-related macular degeneration |
| ATC | Anatomical Therapeutic Chemical |
| BCVA | Best-corrected visual acuity |
| CAT | Committee for Advanced Therapies |
| CD | Circular dichroism |
| CDSCO | Central Drugs Standard Control Organization |
| CE-SDS | Capillary electrophoresis sodium dodecyl sulphate |
| CEX-HPLC | Cation exchange high pressure liquid chromatography |
| CEX-MS | Cation exchange mass spectrometry |
| CFP | Colour fundus photography |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| Cmax | Maximum measured concentration |
| CNV | Choroidal neovascularisation |
| CRC | Central reading centre |
| CRF | Case report form |
| CRO | Contract research organization |
| CRT | Central retinal thickness |
| CSR | Clinical study report |
| DME | Diabetic macular edema |
| DP | Drug product |
| DR | Diabetic retinopathy |
| DS | Drug substance |
| DTT | Dithiothreitol |
| EC50 | Half maximal effective concentration |
| EDMC | External Data Monitoring Committee |
| ELISA | Enzyme-linked immunosorbent assay |
| EMA | European Medicines Agency |
| ETDRS | Early treatment diabetic retinopathy study |
| EU | European Union |
| FA | Fluorescein angiography |
| Fab | Fragment antigen-binding |
| FCP | Foveal centre point |
| FCS | Foveal central subfield |
| FDA | Food and Drug Administration |
| FFA | Fundus fluorescein angiography |

| | |
|---|---|
| GCP | Good clinical practice |
| GLP | Good laboratory practise |
| HC | Heavy chain |
| HCl | Hydrochloride |
| HMW | High molecular weight |
| HRP | Horse radish peroxidase |
| HUVEC | Human umbilical vein endothelial cells |
| IB | Inclusion body |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent ethics committee |
| IgG1 | Immunoglobulin G1 |
| IMP | Investigation medicinal product |
| IMPD | Investigation medicinal product dossier |
| IP | Investigational product |
| IRB | Institutional review board |
| IVT | Intravitreal |
| IWRS | Interactive web response system |
| LC | Light chain |
| LC-MS | Liquid chromatography mass spectrometry |
| MAA | Market authorisation application |
| mab | Monoclonal antibody |
| mITT | Modified intent-to-treat |
| NOAEL | No observed adverse effect level |
| NZW | New zealand white rabbits |
| OCD | Optical coherence tomography |
| OECD | Organisation For Economic Co-Operation And Development |
| PD | Pharmacodynamic(s) |
| PDR | Proliferative diabetic retinopathy |
| PFS | Prefilled syringe |
| PK | Pharmacokinetic(s) |
| PP | Per-protocol |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PT | Preferred term |
| Q-TOF | Quadrupole time of flight |
| rhuMAb | Recombinant humanised monoclonal antibody |
| RMP | Reference medicinal product |
| RMP | Risk management plan |
| ROA | Route of administration |
| ROP | Retinopathy of prematurity |
| RP-HPLC | Reverse phase high pressure liquid chromatography |

| | |
|---|---|
| RSD | Relative standard deviation |
| RVO | Retinal vein occlusion |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SD-OCT | Spectral domain optical coherence tomography |
| SE-HPLC | Size exclusion high performance liquid chromatography |
| SmPC | Summary of product characteristics |
| SOC | System organ class |
| SPR | Surface plasmon resonance |
| TEAE | Treatment-emergent adverse event |
| TESAE | Treatment-emergent serious adverse event |
| TMB | Tetramethylbenzidine |
| UPLC | Ultra performance liquid chromatography |
| USP | United states pharmacopeia |
| VA | Visual acuity |
| VEGF | Vascular endothelial growth factor |
| VEGFR | Vascular endothelial gowth factor receptor |
| WHODD | WHO drug dictionary |

# 1. Administrative/regulatory information and recommendations on the procedure

## *1.1. Scientific advice*

*Table 1: Scientific advice and protocol assistance*

| ***Date*** | ***Topic (quality/ non-clinical/ clinical)*** | ***Reference number / Coordinator(s)*** | ***Brief summary of the advice*** |
|---|---|---|---|
| 12 December 2019 | Quality, non-clinical, and clinical | EMEA/H/SA/4312/1/2019/III | The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:<br>• Analytical and functional tests at quality level to show comparability;<br>• Impact of difference in charge variants;<br>• Specification test parameters;<br>• Use of US sourced reference medicinal product in the comparative clinical study;<br>• Requirement for animal studies;<br>• Comparative clinical study design including Indian study population;<br>• Extrapolation of indications. |
| 19 May 2022 | Quality, and clinical | EMA/SA/0000086319 | The Scientific advice pertained to the following quality, and clinical aspects:<br>• strategy for marketing authorisation application submission;<br>• strategy of switching patients from US sourced vials to EU sourced vials and from vials to pre-filled syringes in ongoing clinical trials. |
| 22 February 2024 | Quality, and clinical | EMA/SA/0000161827 | The Scientific advice pertained to the following quality, and clinical |

| | | | |
|---|---|---|---|
| | | | aspects:<br>• Analytical similarity study;<br>• Use of vial presentation only in comparative clinical study. |

## 1.2. Eligibility to the centralised procedure

The applicant Intas Third Party Sales 2005 S.L. submitted on 2 June 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Rexatilux (ranibizumab), 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:

Rexatilux is indicated in adults for:
- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

## 1.3. Legal basis and dossier content

**The legal basis for this application refers to:**

Article 10(4) of Directive 2001/83/EC – relating to applications for biosimilar medicinal products

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with European Union provisions in force for not less than 10 years in the EEA.

| | |
|---|---|
| ***Product name, strength, pharmaceutical form:*** | Lucentis 10mg/ml solution for injection |
| ***Marketing authorisation holder:*** | Novartis Europharm Limited |
| ***Date of authorisation:*** | 22/01/2007 |
| ***Marketing authorisation granted by:*** | European Union |
| ***Marketing authorisation number:*** | 000715 |

## 1.4. Information on paediatrics

Not applicable

## *1.5. Information on orphan market exclusivity*

### 1.5.1. Similarity with authorised orphan medicinal products

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 from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *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:*** | Simona Badoi |

| | |
|---|---|
| TThe application was received by the EMA on | 02 June 2025 |
| The procedure started on | 19 June 2025 |
| The CHMP rapporteur's first assessment report was received on | 08 September 2025 |
| The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on | 17 September 2025 |
| The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on | 22 September 2025 |
| The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on | 16 October 2025 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 17 December 2025 |
| The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the quality/safety/efficacy assessment of the product:<br>A request for a routine GCP inspection was adopted for the pivotal clinical study. The integrated inspection report (EMA/IN/0000287966) was issued on | 11 February 2026 |
| The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on | 02 February 2026 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 12 February 2026 |
| The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on | 26 February 2026 |
| The applicant submitted the responses to the CHMP list of outstanding issues on | 22 March 2026 |
| The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on | 08 April 2026 |

| | |
|---|---|
| The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on | 16 April 2026 |
| 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 Rexatilux on | 23 April 2026 |

## *1.7. CHMP outcome*

### 1.7.1. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rexatilux is favourable in the following indication(s):

- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

### 1.7.2. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Rexatilux is considered biosimilar to Lucentis. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

### 1.7.3. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

### 1.7.4. Other conditions and requirements of the marketing authorisation

#### *1.7.4.1. 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.

## 1.7.5. Conditions or restrictions with regard to the safe and effective use of the medicinal product

### *1.7.5.1. 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.

### *1.7.5.2. Additional risk minimisation measures*

Prior to launch in each Member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, following discussions and agreements with the National Competent Authorities in each Member State where Rexatilux is marketed, at launch and after launch all ophthalmological clinics where Rexatilux is expected to be used are provided with an up-to-date patient information pack.

The patient information pack should be provided in both the form of patient information booklets and an audio-file that contain following key elements:

- Patient information leaflet
- How to prepare for Rexatilux treatment
- What are the steps following treatment with Rexatilux
- Key signs and symptoms of serious adverse events including increased intraocular pressure, intraocular inflammation, retinal detachment, retinal tear and infectious endophthalmitis
- When to seek urgent attention from the health care provider

## 1.7.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

## 1.7.7. Proposed list of recommendations

| *Description of recommendation(s)* |
| --- |
| To implement the future transition from LAL to bacterial endotoxins testing using recombinant factor C (rFC) and use it for routine endotoxin testing, the applicant will need to submit a variation post-approval. |

# 2. Introduction

## *2.1. Therapeutic context*

Therapeutic indications

Rexatilux is indicated in adults for:

- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

Age-Related Macular Degeneration

AMD is a progressive neurodegenerative disease and a leading cause of visual loss in elderly patients. AMD is classified to two types: the non-exudative (or dry) form and the exudative (wet or neovascular) form. The dry form is the most prevalent, accounting for 90% of the cases. Wet AMD accounts for approximately 90% of severely impaired vision in AMD. Wet AMD begins with neovascularization from choroid due to defects in Bruch's membrane. Neovascular vessels proliferate underneath retinal pigment epithelium, and leakage from these vessels leads to retinal elevation and blurring of vision.

The efficacy and safety of ranibizumab was demonstrated in the MARINA and ANCHOR studies. Both the studies demonstrated that ranibizumab prevented vision loss and improved mean visual acuity, with low rates of serious adverse events, in patients with minimally classic or occult (with no classic lesions) choroidal neovascularization, secondary to age-related macular degeneration. Also, the CANTREAT study conducted to determine efficacy of ranibizumab using a Tand E (treat and extend) regimen to monthly dosing in treatment-naive patients with AMD after 24 months showed clinically meaningful improvements in BCVA despite fewer injections and visits.

Diabetic Macular Oedema

DME is characterised by the accumulation of fluid in the intra-retinal layers of the macula as a result of leakage from the retinal microvasculature. It is one of the most sight threatening complications in diabetes mellitus and occurs in 10% of the diabetic patients, with a high prevalence 30% in patients with more than 25-year history of diabetes. Because the population of people with diabetes is around 285 million worldwide and growing rapidly, vision loss from diabetes retinopathy is a significant public health issue, with considerable socioeconomic and quality-of-life impacts.

The natural progression of DME leads to vision loss of 2 or more lines (≥10 letters) of visual acuity within 2 years in approximately 50% of patients. The current standard of care in the treatment of DME is laser photocoagulation that has been demonstrated to slow the progression of vision loss. The RISE and RIDE studies demonstrated that IVT injections of inhibitor of VEGF agents are a safe and effective therapy for DME. The open-label extension phase of RIDE and RISE showed that the efficacy and safety achieved with monthly ranibizumab as treatment for DME can be maintained with less-than-monthly treatment. Vision gains achieved after 1 or 3 years of monthly ranibizumab therapy were maintained with a marked reduction in treatment frequency; some patients required no additional treatment.

Diabetic Retinopathy

DR is a progressive microangiopathy associated with both type 1 and type 2 diabetes mellitus that is mediated by hypoxia-induced upregulation of proangiogenic, proinflammatory, and vascular permeability factors, including VEGF-A.

The post hoc analysis of the RIDE and RISE studies demonstrated that ranibizumab reduced the risk of DR progression in eyes with diabetic macular oedema, and many ranibizumab-treated eyes experienced improvement in DR severity. In another study comparing ranibizumab with panretinal photocoagulation treatment, ranibizumab was demonstrated as non-inferior for the endpoint of visual acuity, at 2 years.

Retinal Vein Occlusion

RVO describes the narrowing or blockage of a retinal vein, the origins of which are multifactorial. In general, RVO presents with variable degrees of visual loss with any combination of fundal findings consisting of retinal vascular tortuosity, retinal haemorrhages, cotton wool spots, optic disc swelling and macular oedema. RVO is classified by the site of the venous occlusion as either branch RVO, where a branch retinal vein is occluded, central RVO, where the central retinal vein is occluded, or hemiretinal RVO, in which one or two of the trunks of the central retinal vein are occluded.

In the BRAVO and CRUISE studies, ranibizumab showed greater improvements in vision-related function compared with sham-treated patients through 6 months, even when a majority of patients present with RVOs in the worse-seeing eye.

Choroidal Neovascularization

CNV is one of the most severe causes of visual impairment in patients with uveitis. When the disruption of the homeostasis between the retinal pigment epithelium and Bruch's membrane occurs, a vicious circle leads to the choroidal neo-angiogenesis. Myopic CNV develops in approximately 5% to 10% of patients with pathological myopia. The overall prevalence of myopic CNV is therefore estimated to be approximately 0.04% to 0.05% in the general population.

The REPAIR and RADIANCE studies demonstrated that ranibizumab was effective in improving and sustaining best corrected visual acuity (BCVA) and was generally well tolerated in patients with myopic CNV. Also, a retrospective, observational study was conducted with East-Asian mCNV patients treated with ranibizumab in RADIANCE trial to establish real-world long-term effectiveness and safety of ranibizumab. It showed that patients with myopic CNV treated with ranibizumab maintained good visual outcomes for up to 48 months of follow-up within clinical practice settings.

## 2.2. Aspects of development

INTP18 (i.e. Intas Ranibizumab; INN: ranibizumab) is a recombinant, humanised IgG1 kappa isotype monoclonal antibody Fab fragment, expressed in *Escherichia coli* in form of inclusion bodies of heavy chain and light chain followed by refolding and purification processes.

Ranibizumab binds to the receptor site of active forms of vascular endothelial growth factor A (VEGF-A). Ranibizumab binds with high affinity to the VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and CNV or visual impairment caused by diabetic macular oedema secondary to RVO in adults.

INTP18 has been developed by Intas Pharmaceuticals Limited, India, as a biosimilar of EU-approved Lucentis, for the treatment of wet age-related macular degeneration.

Stepwise comparative studies against the reference medicinal product have been performed aiming to generate evidence substantiating the biosimilarity claim. The focus of the INTP18 development program was to establish analytical (structure) and *in-vitro* functional similarity to EU- and US-licensed Lucentis, and to further establish clinical similarity between INTP18 and Lucentis with respect to PK, efficacy, safety, and immunogenicity to support the approval of Intas Ranibizumab for the same approved indications.

To generate **clinical evidence** establishing the biosimilarity between the test and reference product, Intas Pharmaceuticals Limited, India conducted a single comparative double masked, parallel group, randomised, multicentre, Phase 3 clinical study (Study 0504-19; CLARITY) with the aim to compare the efficacy and safety of INTP18 with that of Lucentis in patients with wet AMD.

**Scientific advice/Protocol assistance**

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

*Table 2: Scientific advice*

| Opinion-Date | Reference | SAWP co-ordinators |
|---|---|---|
| 12/12/2019 | EMA/CHMP/SAWP/648227/2019<br>Procedure No.: EMEA/H/SA/4312/1/2019/III | Kerstin Wickström<br>Jens Reinhardt |
| 19/05/2022 | Doc Ref:<br>EMADOC-1700519818-824736<br>Case No.: EMA/SA/0000086319 | Kerstin Wickström<br>Andrea Laslop |
| 22/02/2024 | Doc Ref:<br>EMADOC-1700519818-1282315<br>Case No.: EMA/SA/0000161827 | Kerstin Wickström<br>Sara Galluzzo |

**Quality**

It was recommended that the similarity program should be based on the use of a sufficient number of Lucentis batches. The analytical methods selected for the comparison of the structural and physicochemical attributes were considered acceptable at this stage of development. However, the applicant was advised to additionally confirm the absence of free sulfhydryl groups. Tests for sub-visible particles and a second method (to the CEX-HPLC) for quantification and comparison of charged variants like capillary isoelectric were expected to be included. The application of a SPR-based binding method for evaluation of the binding affinity to VEGF isoforms VEGF 165, VEGF 121, VEGF 110 and VEGF 189 was recommended.

Slight differences in charge variants were considered probably acceptable provided functional parameters such as biological activity, binding activity etc. are comparable between the proposed biosimilar and the reference product. A sufficiently large pool of reference batches and the application of second, orthogonal method e.g. mass spectrometry (MS) and/or capillary isoelectric focusing (cIEF) besides the CEX-HPLC was recommended.

Application of a tiered approach for the similarity assessment was considered acceptable. The proposed panel of methods seemed appropriate for establishing an acceptable quality bridge of the EU-RMP to the US-sourced comparator.

**Non-clinical**

It was assumed that there is no need for a local tolerance study. Provided the comparability exercise in the *in vitro* studies would be considered satisfactory and no factors of concern were identified, or these factors of concern would not block direct entrance into humans, an *in vivo* animal study was not considered necessary. The conduct of a "general" *in vivo* study was discouraged for the MAA.

**Clinical**

The CHMP agreed that one clinical efficacy/safety equivalence study in patients should be sufficient to support biosimilarity. A study duration of 52 weeks and monthly dosing was supported. Masking of patients was strongly recommended in addition to assessor masking. It was agreed to evaluate biosimilarity in **patients with nAMD** as it was expected to render a population sensitive to detect differences between the treatments. The proposed **sample size** of 460 participants was considered too low. Study population was planned of being recruited in India exclusively. In principle, conduct of a clinical study outside of the EU was considered acceptable if the trial adheres to EMA guidance, GCP and ICH standards.

Regarding primary endpoints, the evaluation of BCVA vs. baseline was endorsed. The proposed range of secondary endpoints was agreed. However, the applicant was advised to evaluate efficacy in general at 8 weeks instead of 12 weeks. The evaluation of **CRT** was considered a key secondary endpoint, and it was suggested of being evaluated before the efficacy plateau is reached at a very early timepoint. In addition, the applicant was strongly advised to evaluate BCVA, and preferably also CRT, at every monthly visit.

The **equivalence margin** of ±4 letters for the proposed primary endpoint was considered somewhat wide. A margin lower than ±3.5 letters was recommended. The use of a two-sided 95% confidence interval for the difference in means was endorsed.

A masked **interim analysis** at the completion of 12 weeks treatment was clearly discouraged.

The **time points for sampling** and analysis for immunogenicity at Weeks 2, 4, 8, 12, 24, 36 and 52 were considered acceptable.

It was furthermore considered acceptable to evaluate systemic exposure (PK) in a subset of patients. The proposed number (10%) was assumed to be in a reasonable range but should be justified appropriately. Descriptive statistics for reporting the results were agreed to be sufficient. Sampling at BL and around expected Tmax at steady state was considered sufficient.

It was agreed that data obtained in nAMD patients would reasonably allow extrapolation to other approved therapeutic indications of Lucentis.

**EMA/SA/0000086319**

While a staggered submission was considered possible, the CHMP preferred to receive all data necessary for thorough assessment at the time of the initial submission of an MAA. However, an interim analysis could potentially be acceptable, provided strict masking is maintained at the study site/patient level throughout the duration of the study and full reassurance in this regard is given.

The applicant was advised to provide the updated data with the Day 120 responses to the CHMP List of Questions. Any impact of the new figures on the total outcome should be discussed, e.g., by including a separate section in the dossier.

The use of US-sourced Lucentis was considered acceptable provided the applicant demonstrates comparability at quality level. A three-way analytical similarity assessment comparing INTP18, EU- and US-sourced Lucentis was planned. Pooling of analytical data resultant from the analyses of multiple lots of EU-sourced Lucentis PFS and vials and comparison with US-sourced Lucentis vials as well as pooled INTA18 PFS and vials for the conduct of the three-way comparison seemed appropriate.

The overall strategy to handle randomisation and statistical analysis of patients who will be switched from vials to PFS was considered adequate. The randomisation scheme was considered acceptable.

**EMA/SA/0000161827**

Proposed analytical methods to establish analytical comparability between INTP18 (Vial and PFS) and EU-/US-sourced Lucentis (Vial and PFS) seemed suitable for demonstrating analytical similarity. Generally, at the time of MAA confirmation of sensitivity, specificity, and discriminatory capability of each analytical method was expected. Also, the proposal of conducting forced degradation studies was highly endorsed. The applicant's proposal to test the US-sourced Lucentis batches was considered acceptable as a sound bridging between the US- and EU-sourced RMP is required.

The proposed amount of the reference batches seemed to be limited to generate a robust data pool for demonstration of biosimilarity.

The overall proposal to use only the vial presentation in the comparative Phase III clinical study seemed acceptable if the analytical comparability between the vials and PFS is unequivocally demonstrated.

Performing an appropriate extractable/leachable study was recommended to account for components of the PFS presentation that may affect the quality of the INTP18 drug product.

## *2.3. Description of the product*

Rexatilux (ranibizumab) was developed by Intas Pharmaceuticals Limited, India, as a biosimilar product to Lucentis.

Ranibizumab is a recombinant humanised IgG1 kappa isotype monoclonal antibody fragment targeting VEGF-A, preventing its binding to receptors VEGFR-1 and VEGFR-2, thus reducing endothelial cell proliferation and vascular leakage.

**Proposed indications for Rexatilux:**

- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

The indication for the treatment of retinopathy of prematurity (ROP) in preterm infants – granted to Lucentis – is not claimed.

## *2.4. Inspection issues*

### 2.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection was required.

### 2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection was required (no non-clinical studies submitted).

### 2.4.3. Good clinical practice (GCP) inspection(s)

A routine GCP inspection (Case title: EMA/IN/0000287966) for the clinical study 0504-19 has been triggered. No specific concerns are known to have been identified by the assessment at the time of adoption of the inspection request. General triggers have been used in the choice of this dossier and the sites involved in line with the guideline "Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for "routine" and/or "for cause" inspections, their investigation and scope of such Inspections". The reports for the 3 sites inspected (1 in Hungary, 2 in India) have been submitted. It was shown that the findings observed at the investigator sites, although they cover major deficiencies, especially at the Indian site, did not or only to a negligible (and acceptable) extent raise the possibility of incorrect data reporting. The clinical trial was conducted in accordance with international ethical and professional guidelines and standards and in compliance with GCP requirements. The data obtained was documented and reported in a reliable manner.

Hence, the clinical data quality is acceptable and can be used in support of the Rexatilux Marketing Authorisation Application.

# 3. Quality aspects

## *3.1. Introduction*

Rexatilux has been developed as a biosimilar to the reference medicinal product Lucentis.

The finished product (FP) is presented as solution for injection containing 10 mg/ml of Ranibizumab as active substance (AS).

Other ingredients are: L-histidine, α,α-trehalose dihydrate, polysorbate 20 (E 432), hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), and water for injections.

The product is available in two presentations:

- As 0.165 ml sterile solution in a pre-filled syringe (type I glass) with a bromobutyl rubber plunger stopper and a syringe cap consisting of a white, tamper-evident rigid seal with a grey bromobutyl rubber tip cap including a Luer lock adapter. The pre-filled syringe has a plunger rod and a finger grip, and is packed in a sealed tray.

- As a vial (type I glass) with a stopper (bromobutyl rubber) containing 0.23 ml sterile solution and 1 blunt filter needle (18G x 1½", 1.2 mm x 40 mm, 5 µm).

## *3.2. Active substance*

### 3.2.1. General information

The name INTP18 is used for both the active substance and finished product in this application. During development of the product, the active substance was also referred to as INTP18, Intas Ranibizumab.

Ranibizumab is a recombinant, humanized IgG1 kappa isotype monoclonal antibody fragment (Fab) that selectively binds and neutralizes VEGF-A. As a Fab fragment, Ranibizumab does not contain the Fc region, and is therefore devoid of antibody-mediated effector functions. VEGF is a heparin-binding glycoprotein with potent angiogenic, mitogenic and vascular permeability-enhancing activities specific for endothelial cells. The binding of Ranibizumab to VEGF-A blocks the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation. Ranibizumab (INN, international non-Proprietary name) results from the insertion of murine anti-Vascular Endothelial Growth Factor (VEGF-A) complementary-determining regions (CDRs) into a consensus human IgG1 framework. Amino-acid substitutions were made in order to increase the binding affinity to VEGF-A isoforms (eg: VEGF110, VEGF121 and VEGF165 and VEGF189). The 214-residue light chain linked by a disulfide bond at its C-terminus extremity to the 231- residue N-terminal segment of the heavy chain. The molecular weight of Ranibizumab is approximately 48 kDa (23 kDa and 25 kDa for the light and heavy chain, respectively). Ranibizumab contains 10 cysteine residues forming 4 intrachain and 1 inter-chain disulfide bonds.

### 3.2.2. Manufacture, characterisation, and process controls

Manufacture of the active substance is carried out at Intas Pharmaceuticals Limited Biopharma Division, Ahmedabad, India (IPL). Additional sites are listed for characterisation and storage of cell banks.

The information presented on manufacturers is regarded as sufficient.

Sufficient evidence of GMP compliance has been provided for the sites involved with manufacture and testing of the active substance.

*Description of manufacturing process and process controls*

The ranibizumab heavy and light chain (HC and LC) are expressed separately in an *Escherichia coli* cell line and produced in a production scale fermenter, yielding inclusion bodies (IBs). The purification is targeting at refolding scale.

Manufacture of a batch starts with seed cultivation. Seed flasks containing sterilized seed medium are incubated with thawed working cell bank (WCB)/master cell bank (MCB) inoculum.

Cells are harvested and lysed. The lysate is then centrifuged and resuspended and further washing and centrifugation steps with buffers led to the inclusion bodies.

The purification starts with IB solubilization to make it available for the next refolding step. A first Ultrafiltration/Diafiltration (UFDF) step follows to concentrate and condition the proteins for chromatography steps. A second UFDF step is performed to concentrate the active substance. A final 0.2 µm filtration step is applied to prevent microbial growth.

An adequate batch numbering system is in place, which enables batch traceability. The system includes codes for active substance, product stage, territories and a sequential number.

Information on Critical process parameters (CPP), Key process parameters (KPP), Critical performance attributes (CPA) and Key performance attributes (KPA) is included.

The applicant provided a detailed description of the manufacturing process steps that is accompanied by flow charts. Within the flow charts, relevant process parameters and performance attributes are described. The description and purposes of the respective steps is also separated from the flow charts and depicted separately in tables, which is acceptable. Use of raw materials is also described in tables with process steps and their purpose. Reprocessing is not described and hence, not allowed.

In conclusion, the applicant provided a detailed description of the manufacturing process and controls that is in line with regulatory expectations.

*Control of materials*

Raw materials used for cell culture, purification, and formulation are listed together with their quality standard (in-house specification, compliant with Ph. Eur., USP and/or JP) and their intended use. Acceptable in-house specifications are provided for the non-compendial raw materials. Raw materials were further categorized and grouped according to their criticality.

Resins, filters and containers used during manufacture of INTP18 active substance are listed with their suppliers and related manufacturing steps. The applicant states that there is no use of ruminant derived material in the manufacturing of the chromatography columns. Altogether, there are no raw materials used in the manufacturing process of INTP18 active substance of human or animal origin. Corresponding Transmissible Spongiform Encephalopathies (TSE) free statements from the suppliers are depicted in 3.2.A.2.

The construction of the expression plasmids and their genetic elements are described in sufficient detail. Also, the information on the host cell line is satisfactory. Clones for HC and LC that were positive for incorporation of the desired genetic elements were depicted. Positive Clones were further optimized for protein expression,

with finally choosing the respective best ones for HC and LC respectively for further work. Primary cell banks were prepared from these clones and from there on WCBs were generated.

A two-tiered cell bank system with MCB (from research cell bank described above) and WCB has been established in accordance with ICH Q5D. The MCB and WCB are both stored at different locations, which is endorsed. In addition, a third-party location to store MCB/WCB in the case of extreme adverse events has been implemented upon request.

The applicant has established end of production cell banks (EPCB) for HC and LC. Stability of the cell banks is monitored by periodic determination of growth, viability and retention of recombinant construct; taking into account the available stability data for the WCB, the proposed intervals are acceptable.

The characterisation and testing of the expression construct and cell substrate including MCB, WCB, and EPCB is in line with current regulatory guidance, and state-of-the-art analytical methods were applied. The nucleotide sequence of the expression plasmids was confirmed by sequencing. Testing for lytic and lysogenic bacteriophages is described.

Manufacture and qualification procedures for future WCBs derived from the current MCB have been described in the dossier.

*Controls of critical steps and intermediates*

The active substance control strategy is based on a planned set of controls, derived from current product and process understanding that assures process performance and product quality (ICH Q10). INTP18 active substance process performance and product quality control strategy includes, but is not limited to, the following:

• Controls on material attributes, including raw materials and components, starting materials, source and starting materials of biological origin, reagents, and primary packaging material

• Controls on the design of the manufacturing process

• In-process manufacturing process controls

• Key/Critical Process Parameters (Inputs)

• Process Attributes/ Process performance parameters (Outputs)

• Controls on the Critical Intermediate

The applicant focusses on controls on material attributes (raw materials, reagents, packaging material), control of the active substance manufacturing process and its intermediates and defines Key inputs (CPP and non-critical process parameters (nCPP)) and outputs (process performance parameters; CPA, key performance attributes (KPA) and monitored attributes (MA)). This is a common strategy in line with ICH Q10 and thus is considered acceptable.

If in-process controls are out of acceptance, the out of specification (OOS) triggers investigation of the root causes. Results outside of the pre-defined action limits will moreover lead to execution of the deviation management procedure.

The analytical methods used for in-process testing are adequately described and the validation data therefrom are provided to demonstrate their suitability for the intended purpose.

Altogether, the process is considered in control and the controls, and their respective ranges/limits, are set adequate.

*Process validation*

Release testing results of all Process Performance Qualification (PPQ) batches passes pre-defined specification criteria indicating consistent and reproducible quality of process intermediates.

The PPQ campaign was carried out with PPQ batches, incorporating a matrix approach using different LC and HC batches at the commercial facility (IPL).

A classification as action limits and operating ranges were used alongside acceptance criteria throughout the pivotal PPQ campaign. With this setting, it was evaluated if the process is capable of constant reproducible commercial manufacturing. The validation criteria are acceptable. All PPQ batches met the active substance specifications applicable at time of validation and comply with the proposed commercial active substance specifications. Further, CPPs/KPPs were within their acceptable ranges and met operating ranges. In summary, the presented process verification data demonstrates that the intended commercial manufacturing process performs consistently and delivers active substance complying with the release specifications under commercial operating conditions.

A description of continued process verification is in place, with validation supporting studies of Clearance of process-related impurities, Clearance of bacterial endotoxin (BET), Clearance of bioburden, Clearance of product related impurities, Reuse of resin and membrane, Sanitization and storage of resin and membrane and Manufacturing component compatibility evaluation. As a final remark, shipment validation of INTP18 active substance is omitted, since the active substance and finished product manufacturing takes place within same facility.

*Manufacturing process development*

The process development of INTP18 active substance manufacturing process has been performed at one manufacturing site, IPL, which is the same site proposed for the INTP18 AS commercial production. A Quality by Design (QbD)-like approach was adopted for the process development and characterisation. Proven Acceptable Ranges (PARs) were derived for each parameter considering the effect of parameter on various quality attributes and performance attributes relevant for the corresponding unit operation. Operating within the PAR is considered as the control strategy to ensure consistent process performance and desired product quality.

The applicant started with identification of the critical quality attributes (CQA) and evaluating the impact of unit operations on key process attributes and critical quality attributes. Failure mode and effects analysis was performed to reveal impacts of parameters on the performance assigning risk priority numbers. The categorization is considered acceptable. The process development and characterisation approach was following quality by design principles with PARs acting as control strategies for process performance and desired product quality. The approach is considered meaningful. As requested, a description of the quality target product profile has been included, outlining the quality attributes related to safety and efficacy of the final product.

Scale-down models (SDMs) were used for the upstream and downstream process to support development studies to reduce input material, time and investment. Their qualification was assessed by comparison of small scale batch key quality attributes with manufacturing scale quality attributes. In conclusion, with the presented

data the SDMs for the cell culture process and purification procedures stand qualified and are representative of the commercial scale process. Further, range finding studies which led to acceptance ranges of operating parameters are sufficiently described. The manufacturing control strategy is made visible for upstream and downstream processes in flowcharts, which is endorsed as it enables a condensed overview of the whole process development approach.

With process scale-up no significant changes were observed in process performance and product quality attributes. Overall, the upscaling is described in sufficient detail. From there on, all batches were manufactured at the proposed commercial manufacturing scale. Some process improvements and adaptations that mainly concerned set points and operating ranges were made and these are sufficiently described. An extensive process comparability study encompassing clinical, representative and PPQ batches could convincingly show that the process changes did not have impact on the quality, safety and functional characteristics of INTP18 active substance. Therefore, comparability between process versions could be shown.

*Characterisation*

With the exception of the determination of the amino acid sequence and extinction coefficient, INTP18 lots have been used for the characterisation studies. This includes clinical trial lot, PPQ batch and primary reference standard batch. For the investigation of the amino acid sequence and extinction coefficient, a clinical trial INTP18 lot has been included, which is acceptable. In addition, batches of each EU and US Lucentis have been analysed within the characterisation studies, which is not foreseen to be part of the active substance characterisation, as the biosimilarity study is a separate study presented in 3.2.R.

The same analytical tests have been applied for the characterisation of INTP18 as applied for the biosimilarity study presented in 3.2.R. Overall, a broad testing panel including orthogonal and state-of the art methods has been used as follows:

- The evaluation of the primary structure includes the determination of the amino acid composition and extinction coefficient, sequence conformation by qualitative peptide map using LCMS, N-terminal sequencing by LCMS, intact mass, reduced mass, peptide mapping by RP-UPLC-UV, pI by iCIEF.
- The higher order structure has been investigated by disulfide bond analysis by MS, free cysteine analysis by Elman's method, far UV CD spectropolarimetry, fluorescence spectroscopy and DSC.
- Functional characteristics have been evaluated by HUVEC proliferation inhibition assay, KDR/NFAT-RE HEK293 cell based assay, VEGF165 binding assay by ELISA, VEGF isoform (165) binding by SPR, VEGF isoform (110) binding by SPR, VEGF isoform (121) binding by SPR, VEGF isoform (189) binding by SPR.
- The characterisation of product-related variants includes the determination of the impurity profile by RP-UHPLC, charge variant profile by IEX-HPLC, non-reduced CE-SDS, capillary zone electrophoresis, levels of noncanonical amino acids and post-translational modifications.
- Aggregates have been determined by SE-HPLC, SEC-MALS and analytical ultracentrifugation (AUC).
- Pharmaceutical properties that have been determined are the protein concentration, pH, physical appearance and osmolality.

Primary order structure

The amino acid composition and empirically evaluated extinction coefficient of INTP18 are similar to EU and US Lucentis batches. The sequence confirmation of ranibizumab has been assessed by peptide mapping by LC-MS. The sequence coverage is identical for INTP18, EU Lucentis and US Lucentis. The N-terminal sequence has been identical for INTP18, EU and US Lucentis batches. The intact mass data as well as subunit mass data correspond to the theoretical average mass. The primary amino acid sequence determined by peptide mapping

resulted in similar major peaks for all three INTP18 batches as well as EU and US Lucentis batches. The pI values have been similar for all three INTP18 and EU as well as US Lucentis lots.

Higher order structure

The disulfide bonds have been analysed by LC-MS and the results are comparable within all INTP18 lots, EU and US Lucentis batches. No free cysteines have been detected by the Ellman's method. The secondary structure detected by far UV circular dichroism spectroscopy is comparable for all tested batches. The tertiary structure has been characterised sufficiently by fluorescence spectroscopy. The protein stability has been assessed by the determination of the transition-midpoint temperature (Tm) via differential scanning calorimetry (DSC).

Functional characteristics

% Relative potency determined by the HUVEC proliferation inhibition assay and KDR/NFAT-RE HEK293 cell-based assay for INTP18 batches were within range. VEGF isoforms binding (VEG165, VEGF110, VEGF121, VEGF165 and VEGF189) have been sufficiently characterised.

Product-related variants/impurities

Relative amounts of product-related variants including hydrophobic variants, charged variants, low molecular weight impurities and monomer, noncanonical amino acids and post-translational modifications have been characterised sufficiently. In addition, product-related impurities generated during the downstream process have also been characterised, which is endorsed.

Particulates and Aggregates

HMW impurities have been characterised by SE-HPLC. It has been demonstrated that the HMW impurities are rather low. The molecular weight of size variants in native solution conditions has been assessed by SEC-MALS. The aggregates and monomer content have also been determined by SV AUC.

Pharmaceutical properties

The protein concentration, pH, physical appearance and osmolality have been appropriately characterised.

Process related variants/impurities

Impurities as HCP and HCD as well as residual process additives have been identified as process-related impurities. It has been demonstrated that impurities are sufficiently cleared by the chromatographic steps of the manufacturing process. It is agreed that the chromatographical methods applied remove process related impurities.

## 3.2.3. Specification

The INTP18 active substance specifications include tests for general characteristics, identity, quantity, purity, impurities, safety and potency. The release and stability acceptance criteria for INTP18 active substance are the same. However, certain tests are not included in stability specifications.

The release specification includes compendial tests for physical appearance (colour, clarity of solution), pH and osmolality and safety (bioburden and Endotoxin (LAL)). Quantification (OD280), identity (in-vitro bioassay, RP-UHPLC and iCIEF), purity (RP-UPLC, SE-HPLC, CEX-HPLC and CE-SDS NR) and process related impurity testing by HCP content testing and residual DNA is also included.

The acceptance criteria and the overall control strategy have been established based on:

- ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products, guidance
- ICH Q5C: Stability Testing of Biotechnological/Biological Products
- Lucentis EPAR
- Information available on US sourced Lucentis
- The variability of analytical methods.
- Currently available batch release and real-time stability data from the INTP18 active substance commercial scale batches (which also includes clinical batches)
- Compendial guidelines, as appropriate for general characteristics, process-related impurities, and safety parameters.

Limits have been justified by evaluating the batch data with appropriate statistics. Overall, setting of specifications is acceptable.

*Analytical procedures, validation of analytical methods*

The general and microbial attributes are tested according to the respective Ph. Eur. monographs; all other attributes are tested using in-house analytical methods, which are described in sufficient detail. Principally, the analytical methods appear adequate for their intended purpose.

The applicant has outlined details of the analytical test procedures used for the in-process control, lot release and stability testing of INTP18 active substance. This includes instrument/equipment use, procedure, calculations, system suitability and data reporting. The analytical methods developed in-house are validated for the intended purpose as per ICH Q2(R1) guideline. Validation summaries and detailed validation reports have been submitted. The validation results demonstrate suitability of the analytical procedures for their intended use. The relevant parameters have been assessed in accordance with ICH Q2(R1). Robustness of the methods has been satisfactorily demonstrated for a limited set of relevant variables. The validation experiments were performed with representative active substance batches. Method identifiers for the in-house analytical methods have been included. The general compendial methods have been verified to show the suitability of the methods for their intended use.

The potency assay is an *in vitro* bioassay based on the inhibition of VEGF induced proliferation of HUVEC-C cells. Ranibizumab very specifically inhibits the inducing activity of VEGF in a dose dependent manner. Relative potency of test sample is determined by comparing its dose response to that of reference solution.

With regard to bacterial endotoxin testing, the efforts of the applicant to transition to the Ph. Eur. 2.6.32 test for bacterial endotoxins using recombinant factor C is strongly supported. The formal implementation of the method will require the submission of a post-approval variation (Recommendation (REC)).

*Batch analysis*

All batches are manufactured at IPL. Batch analysis data has been provided for over 30 batches, which includes the PPQ batches, batches used to conduct stability studies, batches for developmental and characterisation or similarity studies and batches used to manufacture the finished product used in clinical studies. All results comply with the specifications valid at time of testing and with the proposed commercial specifications (if applicable).

The presented batch data demonstrate that the manufacturing process reliably delivers active substance with consistent quality.

*Container closure system*

The bulk INTP18 active substance is stored in 250 mL, 1000 mL, 2000 mL sterile square media PETG (Polyethylene terephthalate glycol modified copolyester) bottles, certified to ISO 13485:2003 with HDPE (High density polyethylene) screw caps. Each bottle is filled with INTP18 active substance, capped and labelled. The primary packaged active substance is stored in a black bag or any alternative material to minimize the direct exposure to intense light (white and UV) and transferred to the warehouse for storage.

Technical drawings as well as a representative Certificate of compliance with ISO 13485:2003 are provided.

Extractable studies were carried out on representative bottles and considered acceptable. The results showed that none of the extractable are found above analytical evaluation threshold (AET) for PETG bottles. Further, each extractable per dose under worst case scenarios was found lower than the permitted daily exposure (PDE) limit. Thus, the PETG bottles are safe and acceptable for storage of the INTP18 active substance. Moreover, the storage conditions further decrease the risk of leachables coming into the product. The active substance container closure complies with relevant Ph. Eur. monographs.

*Reference standards*

In line with ICH Q6B, a two-tiered system of primary reference standard (PRS) and working reference standard (WRS) has been implemented for the analysis of INTP18 active substance and finished product.

An international standard for ranibizumab is not available, so the applicant presented qualifications against in-house reference standards and against Lucentis. The history of the developmental and primary internal reference standards used throughout development of INTP18 is adequately described. All the reference standards were manufactured from INTP18 active substance batches representing the commercial development scale.

The analytical program for the qualification of the reference standards is principally acceptable and set against the specifications that were available at the time of qualification. The WRS is qualified against the same acceptance criteria as set for the active substance release specification. The establishment and the (re-) qualification of the reference standards are overall well described.

## 3.2.4. Stability

*Stability Study - At-scale Batches*

At-scale batches stored in PETG bottles were placed on real time stability at the intended storage conditions for 24 months and 18 months and on accelerated stability (5 ± 3 °C) for 6 months. One batch stored in PETG bottle was placed on stress stability (25° C ± 2° C) for 28 days.

*Stability Study - Clinical Batches*

Clinical batches stored in PETG bottles were placed on real time stability at the intended storage conditions for 24 months and 18 months, respectively. Some of the batches were also placed on accelerated stability at 5 ± 3 °C for 6 months.

*Stability Study - PPQ Batches*

The PPQ batches stored in PETG bottle were placed on real time stability at the intended storage conditions of for 24 months, and at accelerated stability at 5 ± 3 °C for 6 months.

The PPQ batches will continue to be monitored for stability up to 24 months at real-time storage condition according to the stability program in order to firmly establish the expiration date. Any out-of-specification (OOS) results obtained for real time stability study for the above specified batches and for annual batches will be notified to the Health Authorities. In addition, at least one commercial active substance batch will be placed annually on stability studies at real-time storage condition for follow-up purpose according to the post-approval stability monitoring program.

The batches were tested against the stability specifications that comprise stability indicating parameters controlled with the same stringency as for active substance release. No noteworthy changes or trends over the storage period were observed. The container used for stability studies is composed of the same material as that used for the commercial product and stored in an upright position.

The clinical phase 3 batches represent the intended commercial manufacturing scale. Based on a comparability study the clinical batches can be considered as being representative of the PPQ/commercial batches. As such and in accordance with Q5C and Q1A(R2) these batches can be used as primary stability batches in order to support the shelf life.

In summary, the data provided supports the proposed shelf life for the active substance.

## *3.3. Finished medicinal product*

### 3.3.1. Description of the product and pharmaceutical development

INTP18 finished product is a sterile, clear and colourless to pale yellow liquid formulation (pH 5.5, and solution for injection). INTP18 finished product (10 mg/mL) has two presentations, a vial and a pre-filled syringe (PFS). The vial consists of 2 mL USP type-I glass vial stoppered with a sterilized bromobutyl rubber stopper and sealed with an aluminium flip off seal. The PFS consists of a sterile type I glass syringe with a plunger stopper. Each vial contains 2.3 mg of Ranibizumab in 0.23 mL solution for intravitreal injection. Each pre-filled syringe contains 1.65 mg of Ranibizumab in 0.165 mL solution.

INTP18 finished product contains ranibizumab as an active pharmaceutical ingredient along with L-histidine, α, α-Trehalose dihydrate, hydrochloric acid, sodium hydroxide, polysorbate 20 and water for injections as excipients. The proposed presentation and strength of INTP18 are developed to have similar quantitative and qualitative composition as that of EU-approved and US-licensed Lucentis. The quantitative composition of vial and PFS presentation is given.

All excipients used for INTP18 are stated to be of Ph. Eur. grade and match the excipients used in the reference medicinal product Lucentis.

*Pharmaceutical development*

INTP18 vial and PFS and its composition are sufficiently described. Active substance is supplied at a concentration of 12.0 mg/mL ± 2.0 mg/mL. Excipients and their concentrations were selected based on the reference medicinal product. All excipients are already approved for intravitreal administration. There are no novel excipients or excipients of animal or human origin.

Formulation studies were performed. The presented data from these formulation robustness studies show that the intended formulation is robust and provides adequate stability of the finished product.

There are no overages applied for INTP18 finished product. Physicochemical and biological properties of INTP18 have been properly addressed.

*Manufacturing process development*

INTP18 finished product has been developed in two presentations: vial and PFS. Both presentations use the same active substance, same formulation, same concentration, and both have the same deliverable dose. The primary container of the vial is a 2 mL USP type-I clear glass vial and of the PFS a 0.5 mL type-I glass borosilicate syringe with silicone oil lubrication.

Clinical batches were manufactured with the same process and scale as process validation batches. The manufacturing process used for clinical and PPQ batches will be used for commercial manufacturing.

Comprehensive process development studies have been conducted to evaluate the robustness of the finished product manufacturing process. These studies demonstrate that the manufacturing process is under control and can deliver the required product quality and process consistency when operated within acceptable ranges.

A filter adsorption study was performed to determine the filter flush volume required for saturation of the filter. Tubing compatibility study demonstrated that tubing can be used in manufacturing up to 24h in static conditions. Hold time studies were performed for formulation buffer and formulated bulk solution.

A mixing study was performed to determine effect of mixing on formulated bulk solution. No significant change was observed on pH, osmolality, protein concentration, PS20 content and purity.

A freeze/thaw study was conducted to determine active substance thaw time and freeze/thaw cycles of active substance.

In addition, thermal cycling and agitation studies were performed.

The control strategy was developed using a systematic, scientific and risk-based approach for parameter classification, and criticality determination. For each unit operation, all process parameters were identified and ranked according to Failure Mode and Effects Analysis. The approach is considered acceptable.

A comparability study between vial and PFS was performed and comparability was demonstrated.

*Container closure system*

The container closure system for the vial presentation is composed of a 2 mL USP type-I clear glass vial, bromobutyl rubber stopper, aluminium flip-off seal, and a blunt filter needle. The PFS container closure consists of a 0.5 mL glass borosilicate syringe with silicone oil lubrication, plunger stopper, plunger rod, and plunger backstop.

Container closure components from vial and PFS that are in direct contact with the finished product are either provided as sterile (syringe barrel, rubber stopper) or sterilized in house (vial, rubber stopper, aluminium flip off seal) and comply with latest Ph. Eur. And USP requirements. The suitability of vial and PFS was tested with regards to product protection, safety, compatibility, and performance.

Product protection was evaluated by container closure integrity, stability testing, and photostability testing.

Safety was tested by extractable and leachable studies. The vial and rubber stopper, and PFS glass barrel, tip cap, and plunger stopper were evaluated in extractable studies. The results from the extractable study were

then further evaluated as part of a risk analysis to define potential leachables for further leachable testing. All compounds detected in glass vial and rubber stopper above the limit of quantitation/AET were below acceptable limits according to ICH guidelines Q3D (R1) and M7 (R1).

Regarding leachable study for the vial, isopropanol was detected in the formulated bulk above AET. However, the amounts were significantly below PDE according to ICH Q3D. Trace amounts were also found in the control sample with no increasing trend, suggesting that it was not migrating from the primary packaging components, which can be agreed.

Compatibility was evaluated by a compatibility assessment, stability testing, agitation study, and thermal cycling study.

Stability data are provided and compatibility of INTP18 has been demonstrated through accelerated and stressed conditions, which can be agreed.

An agitation study was conducted for the vial and PFS to mimic shipping conditions followed by a stability study at real time conditions. All results were within acceptance criteria, and no impact of agitation was observed.

A thermal cycling study was performed for the vial and PFS. No significant changes or trends were observed after three thermal cycles.

Performance of the vial and PFS was tested by PFS functionality, stopper positioning, and dose accuracy testing.

PFS functionality was performed to define the specifications of break loose and glide force. The specifications are included in release and stability testing, which is endorsed.

A stopper position study was conducted to define acceptance criteria of plunger stopper position.

Dose accuracy testing was analysed for PFS batches.

The PFS functionality at release is found to be acceptable. Compatibility and functionality of the PFS with the recommended needle (30G ½) has been assessed and was acceptable.

Regarding PFS, the single-use device components and the medicinal product form a single integral product. According to the Article 117 of the Medicinal Device Regulation (EU) 2017/745 (MDR), a CE certificate or Notified body opinion confirming full compliance of the integral device part with the relevant general safety and performance requirements set out in Annex I of the MDR should be provided. As this was not included in the initial submission a major objection (MO) was raised. The applicant submitted the Notified Body Opinion with the Day 120 responses. The objectives of the assessment were found to have been met and the technical documentation for the device was considered adequate to support compliance with the relevant General Safety and Performance requirements of the Medical Device Regulation (EU) 2017/745. The major objection was therefore considered satisfactorily resolved.

A comparability study demonstrating that the overall performance of the device (dose delivered) used during pivotal clinical development is equivalent with the device intended for marketing was missing, as well as device comparability with the respective reference medicinal product presentation. Due to this, a multidisciplinary MO was raised. During the procedure, the applicant clarified that the INTP18 PFS used in the development phase is identical in design and function to the one intended for commercial use, and the comparability between the biosimilar and reference medicinal product PFS was demonstrated. The MO was therefore resolved.

In summary, the suitability of the container closure system for vial and PFS was sufficiently demonstrated.

*Microbiological attributes*

INTP18 vial and PFS are manufactured as sterile products, as single dose treatments.

The measures set to ensure microbiological integrity of the vial and PFS are considered sufficient.

*Compatibility*

INTP18 finished product is intended for intravitreal (IVT) injection and no reconstitution or dilution with infusion solution is required for its administration. No further compatibility studies are required, which can be agreed. Stability data support the compatibility of the product and product contact components.

## 3.3.2. Manufacture of the product and process controls

For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

*Manufacturing process description*

The manufacturing process of INTP18 vial consists of preparation of formulation buffer, active substance thaw, preparation of formulated bulk solution, filtration of formulated bulk solution (bioburden reduction filtration), sterile filtration and filling, visual inspection, labelling packaging and dispatch.

The manufacturing process of INTP18 PFS consists of preparation of formulation buffer, active substance thaw, preparation of formulated bulk solution, filtration of formulated bulk solution (bioburden reduction filtration), sterile filtration and filling, visual inspection, labelling, plunger rod and backstop fixation, blister packaging, PFS surface sterilization, packaging and dispatch.

The manufacturing process of INTP18 vial and PFS is adequately described. Process parameters are sufficiently justified based on process characterisation and validation data. A flow diagram of the INTP18 manufacturing process and descriptions for each step including operating process parameters and performance attributes are provided.

Hold times are sufficiently justified with validated hold-time studies.

The batch numbering system of INTP18 vial and PFS is explained. There are no reprocessing steps. In the batch disposition strategy, the applicant states that if a CPP has exceeded the defined PAR or if a CQA has failed, the batch will be rejected with detailed investigation. If a KPP exceeded the limit, an investigation will be performed, and appropriate action will be taken. This is endorsed.

*Process controls*

The manufacturing process controls are sufficiently described. In-process manufacturing controls are differentiated in operating parameters and performance parameters. The criticality is defined as critical process parameters (CPPs), and non-critical process parameters (NCPP). NCPPs are further defined as key process parameters (KPP), non-key process parameters (NKPP), and monitoring process parameters (MPP). Performance parameters are classified into action limits, specifications, and acceptance criteria.

For performance parameters (i.e. in process tests), sufficiently justified acceptance criteria/action limits and for operational parameters, appropriate operating ranges have been defined.

No intermediate storage steps have been defined for the finished product manufacturing process.

*Process validation*

Process validation was conducted for INTP18 vial with consecutive batches 1 batch was manufactured by pooling two different active substance lots. The PPQ batches were manufactured using dedicated equipment and filling line.

The process validation covered all manufacturing steps including preparation of formulation buffer, active substance thaw, preparation of formulated bulk solution, filtration of formulated bulk solution, filling, and visual inspection. All acceptance criteria for process parameters were met.

Process validation for INTP18 PFS was conducted with consecutive batches. One PFS batch was pooled from 2 active substance batches.

The process validation covered all manufacturing steps including preparation of formulation buffer, active substance thaw, preparation of formulated bulk solution, filtration of formulated bulk solution, filling, visual inspection, secondary packaging and sterilization. All acceptance criteria for process parameters were met.

Hold times for filtered formulation buffer and unfiltered and filtered formulated bulk solution were validated with vial and PFS PPQ batches. In addition, hold time for filtered bulk in manifold was validated. All results met acceptance criteria and no impact on quality attributes was observed.

Filling homogeneity and consistency of the fill weight was demonstrated.

Suitability of the sterile filter has been sufficiently demonstrated.

Media fill simulation studies were performed, and results are presented for both vial and PFS presentations indicating the date when these studies were performed. Sufficient information has been provided on qualification of the sterilization processes.

*Shipping validation*

The applicant provided detailed shipping validation reports for INTP18 vial and PFS. The shipping process was successfully validated, and the temperature is routinely monitored throughout shipping of PFS and vial.

## 3.3.3. Product specification

Specifications for routine release of finished product (vial and PFS) include compendial tests (Ph.Eur/USP) for appearance (colour, clarity), pH, osmolality, particulate matter (visible and sub-visible particles), and adventitious agents (bacterial endotoxins, sterility). Non-compendial specification include gross content, extractable volume, identity (potency, iCIEF), purity/impurities (RP-UPLC, CEX-HPLC, SE-HPLC, CE-SDS), potency (*in vitro* cell-based assay), quantity (protein concentration), polysorbate 20, PFS surface sterility and PFS functionality tests (break loose and glide force).

The proposed finished product specifications have been provided and the choice of methods is considered appropriate. The proposed release specifications are in line with the requirements of general monographs Ph. Eur. 2031 (Monoclonal Antibodies for human use) and 0520 (Parenteral Preparations) as well as guideline ICH Q6B and EMA/CHMP/BWP/532517/2008.

Acceptance criteria are justified based on Lucentis product information, variability of the analytical methods, lot release and stability data from clinical and at-scale batches, and compendial requirements. To set specific acceptance criteria, no statistical evaluation was performed to estimate ranges, min-max ranges from release and stability data were evaluated to define each parameter.

The proposed acceptance criteria are appropriately justified.

The applicant conducted a risk assessment in relation to elemental impurities in line with ICH Q3D.. Based on the information provided, it can be concluded that the overall risk as regards elemental impurities is negligible.

To address nitrosamine impurities in INTP18, the applicant performed a risk assessment. The risk evaluation covered the active substance and finished product manufacturing processes including raw materials and excipients. No risk was identified for the presence of nitrosamines in INTP18 finished product. In conclusion, it is agreed that the risk arising from nitrosamine impurities can be considered as negligible.

In conclusion, the finished product specifications are considered adequate.

*Analytical procedures*

Analytical methods for finished product release and stability are listed. All methods are sufficiently described including equipment/reagents, sample preparation, assay procedure, system suitability criteria and reporting. For compendial test methods, the relevant pharmacopeia reference has been provided.

Validation/verification of analytical procedures common to the active substance and finished product are presented in the active substance part of the dossier.

Finished product specific compendial methods were verified, and adequate verification reports were provided. For the validation of finished product specific non-compendial methods, adequate summaries of validations and validation reports were provided. Results demonstrate suitability of the analytical procedures for their intended use. The relevant parameters have been assessed in accordance with ICH Q2(R2).

Since the product formulation contains a combination of a surfactant (polysorbate) and a chelator (histidine), low endotoxin recovery (LER) was investigated and no endotoxin masking effect was observed.

In summary, the validations and verifications of the analytical methods for vial and PFS are adequate and according to ICH Q2(R2) and demonstrate the suitability of the analytical procedures for their intended use.

*Reference standards*

The same reference standards are used for control of INTP18 active substance and finished product. Reference is therefore made to the active substance section.

*Batch analysis*

Batch analyses data was provided for vial (at-scale batches, clinical batches, and PPQ batches) and PFS batches (at-scale batches, PPQ batches). Results complied with acceptance criteria valid at the time of testing for all batches. All lots complied with commercial specifications.

The provided batch data confirm INTP18 finished product manufacturing process consistency.

## 3.3.4. Stability of the product

The applicant proposes a shelf-life of 36 months for the vial and 24 months for the PFS when stored at 5 ± 3 °C. The proposed shelf-life for vial is based on 36 months long-term and 6 months accelerated stability data. The proposed shelf-life for PFS is based on 24 months long-term and 6 months accelerated stability data for batches which were not terminally sterilized and 9 months long-term and 6 months accelerated stability data for the post-terminal sterilization study batches.

Comparability between pre- and post- surface sterilization was demonstrated and no impact on product quality and stability was observed.

The stability sampling strategy applied is in line with ICH Q5C and the container closure system used for stability studies is identical to that proposed for commercial distribution.

Shelf-life specifications for the vial and PFS consist of a subset of the release specifications. The stability specifications include several stability-indicating methods. The stability-indicating capabilities of these methods have been demonstrated in forced stress degradation studies.

No obvious relevant trends are present at long-term conditions up to the 36M time-point. Accelerated conditions were evaluated at 25 ± 2 °C for up to 6 months. A slight trend to higher impurities can be observed. The applicant provided a sufficient justification on trends and OOS results. All results for the other attributes were within acceptance criteria.

Stressed storage conditions were evaluated at 40 ± 2 °C up to 28 days and results were similar for all INTP and Lucentis batches.

In addition, stability studies were performed to evaluate out of fridge stability and photostability. Photostability studies resulted in product degradation at intense light exposure, which was comparable to the reference medicinal product. The SmPC includes instructions to keep the product in the outer carton in order to protect from light. Out of fridge stability was performed with finished product batches near the end of shelf-life (34 months) at accelerated conditions (25 ± 2 °C) for 30 days. All results were within acceptance criteria and support the statement in the SmPC that the product may be kept at room temperature (25°C) for up to 30 days.

Forced degradation studies were performed to evaluate degradation pathways in comparison to the reference medicinal product and results have been presented in the dossier.

Overall, the proposed shelf-life for INTP18 finished product vial of 36 months and for finished product PFS of 24 months when stored at 5 ± 3 °C is sufficiently justified based on the provided stability data.

The provided post-approval stability protocol and commitment is acceptable.

## 3.3.5. Comparability exercise for finished medicinal drug product

### *3.3.5.1. Biosimilarity*

Rexatilux has been developed as a biosimilar to the reference medicinal product Lucentis.

Overall, the number of batches included into the analytical similarity exercise are appropriated. The included INTP18 batches are representative for the commercial process.

The testing scheme provided is acknowledged. The applicant states that the number of lots tested per methods has been decided based on the tested quality attribute, criticality ranking, method purpose and/or material availability at the time of study. Overall, the testing scheme is considered acceptable. Thus, the applicant outlines that tests that provide qualitative information have not been performed on all lots. The highest criticality ranked quality attributes have been assessed over a maximum number of lots. In contrast, the lowest criticality ranked quality attributes have been assessed with a limited number of lots, which is in principle acceptable.

Concerning the analytical methods, it is acknowledged that the recommendations given by the CHMP in the Scientific Advice from 2019 and 2024 (procedure number EMEA/H/SA/4312/1/2019/III and

EMA/SA/0000161827) have been taken into account. Thus, a broad and state-of-the-art testing panel of analytical and functional tests have been applied for the biosimilarity evaluation. Sufficient orthogonal methods have been used in order to determine potential differences in the quality attributes.

The analytical methods used in the biosimilarity exercise are in line with the recommendation given in the EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) (EMA/CHMP/BWP/247713/2012).

The approach for the criticality ranking of the quality attributes has been outlined in sufficient detail.

The overall conclusion on biosimilarity is based on the measured values and results provided. Therefore, no question is raised on the statistical approach.

A three-way comparison has been performed, including INTP18, EU Lucentis and US Lucentis. The analytical similarity between the two presentations of INTP18 PFS and vial has been demonstrated and in addition, analytical similarity between the two presentation of EU Lucentis has been presented.

All test methods applied for the biosimilarity study have been validated or qualified appropriately. A summary of the suitability for their intended purpose has been provided. Overall, the provided summary of the method qualification or validation demonstrates that the methods are either sufficiently qualified or validated. It is noted that some test methods have been further developed between the biosimilarity studies. A document demonstrating sufficiently the bridging of analytical methods has been provided.

*Biosimilarity study results*

Overall, the provided results support the biosimilarity claim. For most of the quality attributes similarity was demonstrated; observed differences in certain quality attributes are minor and could be sufficiently justified to have no impact on the clinical performance of the product. A summary of the results is provided in the Table below.

Primary structure

Several orthogonal methods have been applied to demonstrate that the primary structure of INTP18 is similar to EU Lucentis and US Lucentis. Hence, the applicant demonstrated sufficiently that the amino acid composition and the extinction coefficient are comparable.

The sequence coverage has been identical for INTP18, EU Lucentis and US Lucentis. The N-terminal sequence of both the light and the heavy chain are identical for INTP18, EU Lucentis and US Lucentis.

Intact mass and subunit masses including the light and heavy chain are comparable between INTP18, EU Lucentis and US Lucentis.

The peptide mapping pattern of INTP18 is similar to EU Lucentis and US Lucentis. The isoelectric point of INTP18 are similar to EU Lucentis and US Lucentis.

Higher order structure

The secondary and tertiary structure has been compared between INTP18, EU Lucentis and US Lucentis as follows:

INTP18, EU Lucentis and US Lucentis are comparable with regard to the disulphide bonds and it can be concluded that the disulphide bonds have been appropriately characterised. Almost no free cysteine determined by Ellman’s method has been found for INTP18, EU Lucentis and US Lucentis.

The secondary structure has also been analysed by Far UV CD spectroscopy, which is endorsed. INTP18, EU Lucentis and US Lucentis are comparable concerning the secondary structure assessed by Far UV CD spectroscopy.

All three products are comparable with regard to their tertiary structure determined by fluorescence spectroscopy.

DSC analysis data show that the transition-midpoint temperature (Tm) values for INTP18, EU Lucentis and US Lucentis are similar. The higher order structure evaluated by 1D NMR and 2D NMR spectroscopy are highly similar.

In conclusion, the higher order structure of INTP18 can be considered similar to the higher order structure of EU Lucentis.

Functional characteristics

Ranibizumab inhibits the interaction of VEGF-A to its receptors and VEGFR1 and VEGFR. Hence, targets of ranibizumab are VEGF-A and its isoforms including $VEGF_{110}$, $VEGF_{121}$, $VEGF_{165}$ and $VEGF_{189}$. The functional characterisation of INTP18 has been performed by various orthogonal methods including HUVEC proliferation inhibition assay, KDR/NFAT-RE HEK293 cell-based assay, $VEGF_{165}$ binding assay by ELISA along with its binding to different isoforms ($VEGF_{110}$, $VEGF_{121}$, $VEGF_{165}$ and $VEGF_{189}$) using SPR.

% Relative potency values in HUVEC assay, KDR/NFAT-RE HEK293 cell-based assay, VEGF165 binding activity are similar for INTP18, EU- and US- Lucentis. $K_D$ values are highly similar for INTP18, EU- and US- Lucentis indicating highly similar binding activity for VEGF110 isoform, VEGF121 isoform, VEGF165 isoform and VEGF189 isoform.

Particulate and aggregate

Particulates and aggregates have been analysed by orthogonal methods such as SE-HPLC and SEC-MALS as well as analytical ultracentrifuge and all results were comparable for INTP18, EU Lucentis and US Lucentis PFS and vial presentations. Subvisible particles have been analysed between INTP18 PFS and vial, which is acceptable. The particle count has been well below the USP limits of NMT 50 and NMT 5 particles per container for particles $\geq$ 10 µm and $\geq$ 25 µm.

Product related variants

Within the product related variants, amino acid modifications such as oxidation, deamidation, aggregates (high molecular weight impurities) and truncations have been investigated by different orthogonal methods.

The purity and hydrophobic as well as hydrophilic impurities have been assessed by RP-HPLC. It is agreed that based on the data provided all lots of INTP18, EU approved and US approved Lucentis are comparable.

Charge-related variations assessed by cation exchange chromatography (CEX-HPLC) resulted in a similar peak pattern as well as relative amounts of basic and acidic variants. The relative amounts of low molecular weight (LMW) impurities and the monomer have been assessed by non-reducing CE-SDS. Besides CEX-HPLC, capillary zone electrophoresis (CZE) has been applied for the determination of charge variants and purity. All results showed a similar peak pattern. There were no mis-incorporated noncanonical amino acids and post-translational modifications, as assessed by reduced peptide mapping followed by LCMS and MSMS data for all samples.

Pharmaceutical properties

The extractable volume of the PFS as well as vial presentation, pH, physical appearance and osmolality were comparable as well.

Forced degradation

Within the forced degradation studies the following conditions have been investigated: high temperature, chemical oxidation, light exposure, low pH and high pH. It is acknowledged that stability-indicating quality attributes and methods have been selected for the forced degradation studies. In conclusion, the degradation profile of INTP18, EU Lucentis as well as US Lucentis show a similar degradation pathways, when exposed to thermal stress, low pH, high pH, oxidation and photo stress.

*Conclusions*

In summary, a comprehensive analytical similarity study was performed by the applicant in order to demonstrate biosimilarity at the quality level between the proposed biosimilar and reference medicinal product Lucentis. The results indicate high similarity between the biosimilar INTP18 and EU Lucentis, as well as US Lucentis. The data also confirms that the non-EU comparator (US Lucentis) can be considered representative of the EU reference medicinal product.

*Table 3: Summary of the analytical comparability results*

| *Molecular parameter* | *Attribute* | *Methods for control and characterisation* | *Key findings* |
|---|---|---|---|
| Primary structure | Amino acid sequence | Amino acid composition and extinction coefficient analysis | The primary amino acid composition is identical for INTP18 and EU- and US- Lucentis. |
| | | Sequence confirmation by qualitative peptide map using LCMS | Sequence coverage with trypsin enzyme for all samples of INTP18, EU-Lucentis and US-Lucentis at MS level is identical |
| | | N-Terminal sequencing by LCMS | The amino acid sequence of N-terminal peptides of light and heavy chains of INTP18 is same as that of EU- Lucentis and US- Lucentis lots. |
| | | Peptide mapping by RP-UHPLC-UV | The peptide mapping profiles of INTP18 lots at UV-280 nm are overlapping with the profiles of EU- and US-Lucentis lots. All three products are concluded to be highly similar. |
| | Molecular weight determination | Intact mass analysis | The data demonstrates that INTP18 is same as EU- and US- Lucentis in terms of intact mass |

| *Molecular parameter* | *Attribute* | *Methods for control and characterisation* | *Key findings* |
|---|---|---|---|
| | | Subunit mass analysis | The data demonstrates that INTP18 is same as EU- and US-Lucentis in terms of subunit mass. |
| | Isoelectric point | pI by iCIEF | All three products are same in terms of pI. |
| Higher order structure | Disulphide bridge assessment | LC-MS | The disulphide bonding pattern is identical in INTP18, EU- and US-Lucentis |
| | Free cysteine | Elman's test | The mole of cysteine present per mole of Ranibizumab is found to be similar for INTP18 and EU- and US-Lucentis. |
| | Secondary structure | Far UV CD spectroscopy | The far UV CD spectra for minima of INTP18 lots are comparable with that of EU- and US-Lucentis confirming similar secondary structures. |
| | Tertiary structure | Fluorescence Spectroscopy | INTP18 and EU- and US- Lucentis show comparable emission spectra of excitation wavelength confirming similar tertiary structures. |
| | Secondary structure | DSC | The $T_m$ values of INTP18 are highly similar to that of EU- and US-Lucentis indicating their similar higher order structure and thermal stability. |
| | Dimensional structure | 1D and 2D NMR | INTP18 and EU- Lucentis and US-Lucentis lots have comparable folding as analysed by 1D and 2D NMR. |
| Functional characteristic analysis | Potency | HUVEC proliferation inhibition assay | % Relative potency values are similar for INTP18, EU- Lucentis and US- Lucentis in HUVEC assay. |
| | Target binding activity | KDR/NFAT-RE HEK293 cell based assay | % Relative potency values are similar for INTP18, EU- and US-Lucentis in KDR/NFAT-RE HEK293 cell-based assay |

| *Molecular parameter* | *Attribute* | *Methods for control and characterisation* | *Key findings* |
|---|---|---|---|
| | | $VEGF_{165}$ binding assay by ELISA | % Relative potency values are comparable for INTP18, EU- and US-licensed Lucentis for VEGF165 binding activity. |
| | | $VEGF_{110}$ isoform binding by SPR | $K_D$ values are highly similar for INTP18, EU- and US- Lucentis indicating highly similar binding activity for VEGF110 isoform. |
| | | $VEGF_{121}$ isoform binding by SPR | $K_D$ values are highly similar for INTP18, EU-Lucentis and US-Lucentis indicating highly similar binding activity for VEGF121 isoform. |
| | | $VEGF_{165}$ isoform binding by SPR | $K_D$ values are similar for INTP18, EU- and US-Lucentis indicating similar binding activity for VEGF165 isoform. |
| | | $VEGF_{189}$ isoform binding by SPR | $K_D$ values are highly similar for INTP18, EU- and US- Lucentis indicating highly similar binding activity for VEGF189 isoform. |
| Product related variants | Variant profile | RP-UPLC | % Main Peak Purity and % Total Impurities, and Chromatographic profiles observed from RP-UPLC analysis it can be inferred that INTP18 are highly similar to EU-Lucentis and US-Lucentis lots. |
| | Charge variants | CEX-HPLC | The % principal peak purity, % total acidic variants, % total basic variants, % total charge variants observed from CEX-HPLC analysis of INTP18 are similar to EU-Lucentis and US-Lucentis lots. |
| | LMW variants | CE-SDS (NR) | The electropherogram profile and relative % main peak and % LMW observed using CE-SDS (NR) analysis of INTP18 batches are highly similar to EU- and US-Lucentis lots. |

| *Molecular parameter* | *Attribute* | *Methods for control and characterisation* | *Key findings* |
|---|---|---|---|
| | Charge variants | Capillary Zone Electrophoresis (CZE) | The electropherogram profile and % acidic variants, % main peak, % basic variants observed using CZE analysis of INTP18 batches is comparable to EU- and US-Lucentis lots. |
| | Relative percentage of peptides containing normal and noncanonical amino acids | LC-MS and MS/MS | Non-canonical amino acid levels of INTP18 batches are highly similar to EU- Lucentis and US-Lucentis lots. |
| | Relative percentage of post translational modifications | LC-MS and MS/MS | The post translational modifications such as acetylation, glycation, S-->N, cysteinylation, thioether and trisulfide were not detected and PTMs such as total deamidation, tryptophan oxidation, methionine oxidation are highly similar for INTP18, EU- and US- Lucentis. |
| Particulates and aggregates | HMW variants | SE-HPLC | The chromatographic profile and % HMW and % Monomer observed using SE-HPLC analysis of INTP18 batches are comparable to EU-Lucentis and US-Lucentis lots. |
| | High molecular weight variants/ Oligomeric species | SEC-MALS | The observed molecular weight ranges of monomer peak is comparable for INTP18, EU- and US-Lucentis. |
| | | Aggregates by analytical ultracentrifugation (AUC) | The sedimentation profiles of monomer and other molecular weight species (OMWS: LMW and HMW) are qualitatively similar between INTP18, EU- Lucentis and US-Lucentis. The sedimentation profile, Sw (20, w) and % Abundance of main peak observed using AUC analysis of INTP18 batches are comparable to EU-Lucentis and US-Lucentis lots. |

| *Molecular parameter* | *Attribute* | *Methods for control and characterisation* | *Key findings* |
|---|---|---|---|
| | Sub-visible particle count | Light obscuration test | INTP18 have particle count well less than below the USP limits of NMT 50 particles and NMT 5 particles per container for particles ≥ 10 µm and ≥ 25 µm, respectively. |
| Pharmaceutical properties | Protein concentration | UV by $A_{280}$ | Protein concentration for INTP18 and EU- and US- Lucentis are highly similar which indicates that strength of INTP18 is same as that of EU- and US- Lucentis. |
| | Formulation and other characteristics | Extractable volume | All INTP18 samples are within the specification for PFS presentation and vial presentation. |
| | | pH | It was observed that all the results of INTP18 lots are within the in-house specification |
| | | Physical appearance | All lots of INTP18 and EU- and US-Lucentis are observed to be clear and colourless. Thus, INTP18 and EU- and US-Lucentis are similar in terms of physical appearance. |
| | | Osmolality | All INTP18 samples are within the in-house specification. |

## 3.3.6. Post approval change management protocol(s)

Not applicable

## 3.3.7. Adventitious agents

INTP18 is manufactured by bacterial fermentation in E. coli. Biological materials used during cell banking and manufacturing of INTP18 are listed in Module 3.2.A.2. No materials of human or animal origin were used during cell banking and the manufacturing process of INTP18. There are no excipients of animal or human origin. The materials are of plant, vegetable or microbial origin and are certified BSE/TSE free by the suppliers.

No TSE certificates for single raw materials were provided, however, a general BSE/TSE statement has been included in the dossier stating that active substance and finished product are free from any risk of TSE and BSE based on review of information provided by the suppliers. Ranibizumab active substance and finished product are fully compliant with the requirements set out in guidance EMA/410/01. This is considered acceptable.

The cell banks have been screened for microbiological purity and absence of bacteriophages has been confirmed. Active substance and finished product are tested for bioburden and endotoxin throughout the process and all equipment is cleaned and sterilized using standard procedures. Aseptic filling techniques and sterile filtration are conducted during the finished product manufacturing process.

In summary, it is agreed that the risk of viral contamination and TSE transmission is negligible. The information provided is sufficient.

### 3.3.8. Genetically modified organisms (GMO)

Not applicable

## *3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects*

Rexatilux (INTP18) has been developed as a similar biological medicinal product (biosimilar) to Lucentis, having ranibizumab, a recombinant humanized monoclonal antibody, as active substance.

The information about the AS manufacturing process and process controls is considered sufficient. Information on used raw materials used in the manufacturing processing are sufficiently provided. The overall control strategy of the relevant critical quality attributes including risk assessment tools is described. The methodology as well as the proposed classification of quality attributes in critical and non-critical attributes is agreed. The in-process controls and their acceptance criteria/action limits are considered adequate and sufficiently described.

Process characterisation and process verification (PPQ) data support the conclusion that the manufacturing process reliably generates active substance meeting its predetermined specifications and quality attributes.

A comprehensive characterisation of the active substance has been performed based on broad panel of standard and state-of-the-art methods and a discussion of the AS potential impurities has been provided. The proposed active substance specifications are acceptable and the analytical methods appropriately validated.

Reference standards are described and characterised.

The AS container closure system is considered suitable. Based on the submitted stability data, the proposed shelf-life is considered acceptable.

INTP18 finished product is a sterile solution for IVT administration available in two presentations: in a pre-filled syringe and in a single-use vial.

There are no differences in the formulation of finished product vial and PFS. The excipients are of compendial quality and controlled in compliance with tests and acceptance criteria of compendial monographs. There are no novel excipients, and no excipients of human or animal origin. Formulation development studies were conducted with the vial presentation. The chosen formulation is sufficiently supported by the studies performed.

Process parameters are sufficiently justified based on process characterisation and validation data. Manufacturing process development studies have been conducted to evaluate the robustness of the finished product manufacturing process. These studies demonstrate that the finished product manufacturing process is under control and can deliver the required product quality and process consistency when operated within

acceptable ranges. Comparability between different vial manufacturing processes and between vial and PFS was demonstrated.

Process validation has been performed for the vial and for the PFS and batch data demonstrate that the manufacturing process reliably generates finished product meeting its predetermined specifications and quality attributes.

Finished product-specific methods are suitable for their intended purpose and finished product specifications are considered acceptable.

Compatibility and suitability of the primary container closure systems (vial and PFS) with INTP18 finished product over the proposed shelf-life claim is demonstrated. Extractable/leachable studies were performed for vial and PFS and are sufficient. The risk as regards elemental impurities and nitrosamines can be considered as low.

In relation to the PFS, a major objection was raised during the procedure due to the absence of a CE certificate or Notified body opinion confirming full compliance of the integral device part with the relevant general safety and performance requirements set out in Annex I of the MDR. In response, the applicant provided a suitable Notified Body Opinion and the major objection was therefore considered satisfactorily resolved.

A comparability study demonstrating that the overall performance of the device (dose delivered) used during pivotal clinical development is equivalent with the device intended for marketing was missing, as well as device comparability with the respective Reference medicinal product presentation. Due to this, a multidisciplinary MO was raised. During the procedure, the applicant clarified that the INTP18 PFS used in the development phase is identical in design and function to the one intended for commercial use and the comparability between the biosimilar and RMP PFS was demonstrated. The MO was therefore resolved.

The stability data sufficiently support the proposed shelf-life for finished product vial of 36 months and finished product PFS of 24 months when stored at 2° to 8°C. The provided post-approval stability protocol and commitment is acceptable.

To implement the future transition from LAL to bacterial endotoxins testing using recombinant factor C and use it for routine endotoxin testing, the applicant agreed that they will need to submit a variation post-approval (REC).

A comprehensive analytical similarity study was performed by the applicant in order to demonstrate biosimilarity at the quality level between the proposed biosimilar and reference medicinal product Lucentis. The results indicate high similarity between the biosimilar INTP18 and the EU Lucentis. The data also confirms that the non-EU comparator (US Lucentis) can be considered representative of the EU reference medicinal product.

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

# 4. Non-clinical aspects

## *4.1. Introduction*

Intas ranibizumab (INTP18) non-clinical development program was designed to meet the recommendations in EMA's and United States FDA's regulatory guidelines on biosimilars. Stepwise comparative studies against the reference medicinal product have been performed to generate evidence substantiating the similar nature, in terms of quality/structural characteristics, biological activity, PK, efficacy, safety, and immunogenicity.

INTP18 is manufactured according to Good Manufacturing Practice (GMP), and it has been characterised by an extensive physicochemical and functional similarity/comparability program whereby it was compared in a side-by-side manner with EU-approved Lucentis and US-licensed Lucentis. The comparative analytical assessment of INTP18 to Lucentis based on primary structure, higher order structure (HOS), product variants, particulates and aggregates and pharmaceutical properties indicated that ranibizumab is comparable in both the products. As a result, the attributes for which similarity has been established between INTP18 and Lucentis are molecular weight, amino acid composition, peptide mapping profile, disulfide bond, purity, charge variants and HMW variants.

Furthermore, analytical similarity studies include *in-vitro* PD studies which was carried out using multiple INTP18 batches and multiple EU- Lucentis and US- Lucentis batches, demonstrating similarity between INTP18 and Lucentis and demonstrated that INTP18 is highly similar to reference product Lucentis

Based on scientific principles outlined in the US FDA "Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, (FDA, 2015) and the EMA *Guideline on similar biological medicinal products containing monoclonal antibodies – nonclinical and clinical issues* (EMA/CHMP/BMWP/403543/2010, December 2012), a step-wise approach should be followed for the MAA of biosimilar medicinal products. *In-vivo* study/studies (PD and/or PK and/or safety) are not warranted if the comparability exercise between the test product and the reference product is deemed satisfactory in the *in-vitro* studies, and no other factors of concerns are identified. Thus, animal studies are in principle only warranted in case the results of *in-vitro* comparability are not considered satisfactory.

Safety pharmacology, metabolism and disposition studies (distribution, metabolism, excretion PD/PK interaction), acute toxicity, genotoxicity, carcinogenicity and reproduction toxicology studies were not conducted as these are not required for nonclinical testing of similar biological medicinal products.

The overview of the key supportive non-clinical program consisting of primary pharmacology studies, based on the primary mechanism of action of the product, is described.

Analytical similarity exercise was designed to integrate the characterisation of both the presentations of INTP18 (2.3mg/0.23mL (10mg/mL) vial and 1.65mg/0.165mL (10mg/mL) PFS), by comparing INTP18 with EU-Lucentis (2.3mg/0.23mL (10mg/mL) vial and 1.65mg/0.165mL (10mg/mL) PFS) and INTP18 with US-Lucentis (2.3mg/0.23mL (10mg/mL) vial and 1.65mg/0.165mL (10mg/mL) PFS) to support the similarity of INTP18 with EU- and US-Lucentis. Multiple lots of EU- and US-Lucentis have been evaluated for key product quality characteristics.

## *4.2. Analytical methods*

See Quality section 3.3.5 – Comparability exercise for finished medicinal drug product for details on analytical

methods.

## *4.3. Pharmacology*

## 4.3.1. Pharmacodynamics

#### *4.3.1.1. Primary pharmacodynamics*

APD studies (*in-vitro*) were conducted as part of non-clinical program to demonstrate biosimilarity of INTP18 and EU- and US-Lucentis.

#### *4.3.1.2. Biosimilarity Conclusions based on Analytical and Functional in-vitro tests*

The comparative analytical assessment data (presented in Section 3.2.R.4.1 of eCTD Quality Module 3)assures that the profile of products is similar for a comprehensive panel of product quality attributes tested. Thus, data collectively support the conclusion of interchangeable biosimilar of INTP18 to EU- and US-Lucentis. The comparison data from the analytical similarity assessment demonstrated that INTP18 PFS and Vials are highly similar to EU- and US- Lucentis, notwithstanding minor differences in clinically inactive components. Based on the above provided comparative analytical assessment, it can be concluded that there are no residual uncertainties from a product quality perspective and hence could be considered interchangeable.

#### *4.3.1.3. Secondary pharmacodynamics*

No secondary pharmacodynamics studies were performed. These studies are not required for registration of biosimilar medicinal products.

#### *4.3.1.4. Safety pharmacology*

No safety pharmacology studies were performed. These studies are not required for registration of biosimilar medicinal products.

#### *4.3.1.5. Pharmacodynamic drug interactions*

No PD drug interaction studies were performed. These studies are not required for registration of biosimilar medicinal products.

## 4.3.2. Pharmacokinetics

In accordance with the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010), no *in-vivo* PK studies have been submitted.

## *4.4. Toxicology*

In accordance with the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010), no safety pharmacology, metabolism and disposition studies (absorption, distribution, metabolism, excretion, PD/PK interaction), acute toxicity, genotoxicity, carcinogenicity and reproduction toxicology studies were not conducted.

### 4.4.1. Ecotoxicity/environmental risk assessment

Ranibizumab is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, INTP18 ranibizumab is not expected to pose a risk to the environment.

## *4.5. Overall discussion and conclusions on non-clinical aspects*

### 4.5.1. Discussion

The applicant provided an extensive *in-vitro* functional similarity/comparability program. The applicant´s approach on using *in-vitro* assays as part of their biosimilarity exercise is in line with the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010).

For *in-vivo* studies, Intas had reached an agreement with the CHMP (Scientific Advice: EMEA/H/SA/4312/1/2019/III) for not conducting *in-vivo* animal studies as *in-vivo* animal studies are not warranted if the comparability exercise between the test product and the reference product is deemed satisfactory in the *in-vitro* studies, and no other factors of concerns are identified. Thus, no *in-vivo* primary pharmacodynamics, secondary pharmacodynamics, safety pharmacology studies, pharmacodynamic drug interaction or pharmacokinetics were conducted.

According to "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/42832/2005 Rev1), non-clinical reproductive and developmental toxicity studies are not warranted when the proposed and reference product have been demonstrated to be highly similar through extensive structural and functional characterisation. No studies were performed to address reproductive and developmental toxicity of INTP18. This is acceptable. However, as stated in the SmPC for Lucentis due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryo-/foetotoxic. This is sufficiently addressed in the SmPC.

In line with the reference product, ranibizumab Intas is indicated for the treatment of retinopathy of prematurity. No non-clinical juvenile toxicity studies were required as part of the PIP for the reference product, and none have been performed for Rexatilux.

A suitable justification for the absence of ERA studies has been provided.

Overall, the non-clinical package for Rexatilux is considered adequate, comprehensive and acceptable and no unexpected results were observed.

### 4.5.2. Conclusions

The applicant provided an extensive *in-vitro* functional similarity/comparability program on non-clinical aspects of INTP18.

The results of the non-clinical program for Rexatilux are acceptable and support the MAA.

# 5. Clinical aspects

## *5.1. Introduction*

### 5.1.1. Good Clinical Practice (GCP) aspects

The clinical trial was performed in accordance with GCP as claimed by the applicant.

The applicant confirms that the clinical study report submitted is in compliance with the guidance ICH Topic E3 Structure and Content of Clinical Study Reports as well as the Note for guidance on the inclusion of appendices to clinical study reports in marketing authorisation applications. The applicant, furthermore, claims that this study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and the applicable regulatory requirements, including the archiving of essential documents.

**GCP inspections** have been conducted in the following sites in India by the respective authorities:

- 2011, 2016: Sankara Nethralaya No.18, College Road, Numgambakkam, Chennai-600006 – Central Drugs Standard Control Organization (CDSCO, India)
- Feb 2024: Chopda Medicare & Research Centre Pvt. Ltd, Magnum Heart Institute 3/5, Patil Lane No.1, Laxmi Nagar, Near K.B.H Vidyalaya, Canada corner, Nashik-422005, Maharashtra – CDSCO
- 2011, 2018: Narayana Nethralaya 1211C, Chord Road 1st R block, Rajajinagar, Bangalore – 560010 - CDSCO
- 26-28/10/2023: Netralaya Super Speciality Eye Hospital, 1st Floor Kaydee house, above Andhra bank, opposite Gujarat gas, Parimal Garden Cross Road, Ellisbridge, Ahmedabad-380006 - U.S. Food and Drug Administration (USFDA, United States of America)
- 2013: Amrita Institute of Medical Sciences & Research Centre Department of Ophthalmology Amrita Institute of Medical Sciences & Research Centre, AIMS Ponekkara, P. O, Kochi - 682041 – CDSCO
- 2015: Arvind Eye Hospital and Postgraduate Institute of Ophthalmology No. 1 Anna Nagar, Madurai-625020. Tamil Nadu - European Medicines Agency (EMA, European Union)

The respective certificates or statements regarding the outcome of listed GCP inspections have been provided.

For the clinical trial 0504-19 (CLARITY), a request for a routine GCP inspection was adopted. The integrated inspection report (EMA/IN/0000287966) was issued on 11 February 2026.

Based on the review of clinical data and the above-mentioned reports, CHMP did not identify the need for a

further GCP inspection of the clinical trials included in this dossier.

### 5.1.2. Tabular overview of clinical trials

*Table 4: Tabular overview of main clinical studies*

| Study | Design, control type, duration | Treatment | Subject population | Study objectives and primary endpoint | Number of subjects total and per group randomised (treated)/completed study |
|---|---|---|---|---|---|
| Phase 3 – Single pivotal Efficacy and Safety Study | | | | | |
| Study 0504-19 (CLARITY) | RD/DB/parallel group/multicentre<br><br>Comparator controlled<br><br>21-day Screening Phase; 48-week Intervention Phase; Post-intervention follow-up visit (4 weeks after last dose) → Duration of individual participation ca. 55 weeks in total | 0.5 mg intravitreal injection of ranibizumab (INTP18 or EU- or US-sourced Lucentis) Q4W | Adult patients aged 50-92 yrs with neovascular (wet) AMD | Objectives: Establishing therapeutic equivalence of INTP18 versus Lucentis; Comparing efficacy, safety, tolerability, immunogenicity and systemic levels of INTP18 with Lucentis<br><br>Primary Endpoint: Mean change in BCVA in the study eye from baseline to Week 8 using the ETDRS protocol | 546 randomised /<br>546 treated /<br>461 completed<br>INTP18: 273 (273)/235<br>Lucentis: 273 (273)/226 |

RD = randomised; DB = double blind; Q4W = every 4 weeks; yrs = years

## *5.2. Clinical pharmacology*

### 5.2.1. Methods

**Pharmacokinetics**

Determination of Ranibizumab in Human Serum by ELISA Method

The assay for detection and quantification of Ranibizumab was based on indirect ELISA principle.

The method was validated at Bioanalytical (Proteins-Biosimilar) Laboratory of Lambda Therapeutic Research Ltd., Ahmedabad, Gujarat, India.

The assay was validated for calibration curve range of 200.000 pg/mL to 6400.000 pg/mL.

Results of matrix screening, accuracy & precision, calibration curve comparability, QC comparability, selectivity, sensitivity, specificity, prozone or hook effect, qualification run, qualification of kit and stability parameters

**PD biomarkers**

Not applicable

**Immunogenicity**

ELISA Based Method for Anti-Ranibizumab Antibody in Normal Human Serum

The assay was based on bridging ELISA format.

The assay was validated for determination of screening cut point, confirmatory cut point, titre cut point, sensitivity, precision, selectivity, titration assay reproducibility, prozone effect, specificity, stability, drug tolerance, and antigenic equivalence

ELISA Based Method for Neutralizing Antibodies of Ranibizumab in Normal Human Serum

The NAb assay was based on a competitive ELISA format.

The assay was validated for determination of neutralizing cut point, precision, selectivity, titration assay reproducibility, selectivity, specificity, prozone effect, stability, drug tolerance, and antigenic equivalence,

| | | |
|---|---|---|
| | SpectraMax i3x Plate Reader) | |

Abbreviations: HPC, high positive control; LPC, low positive control; MPC, medium positive control; NC, negative control; PC, positive control.
Source: MV(I)-601-22 Table 14

*Table 5: Validation summary of accepted experiments in report MV(I)-601-22 addendum-I*

| No. | Validation Parameters | Results/Data |
|---|---|---|
| 1 | Long term stability of analyte | 151 days at −65 ± 10 °C and at −22 ± 5 °C |
| 2 | Confirmation of sensitivity in diseased matrix | Sensitivity was unaffected by matrix effect and remained same in diseased human serum matrix at LPC level (1640.000 ng/mL) |
| 3 | Selectivity in diseased matrix | Method found selective to detect Anti-Ranibizumab antibody diseased human serum matrix. |

Abbreviation: LPC, low positive control.
Source: MV(I)-601-22 Addendum-I Table 05

## 5.2.2. Pharmacokinetics

### *5.2.2.1. Introduction*

As ranibizumab is administered via intravitreal injection and is supposed to act locally in the respective eye, the pharmacokinetics of ranibizumab are of limited relevance due to the low clinical systemic exposure. Thus, pharmacokinetics of INTP18 is of secondary interest.

### *5.2.2.2. Evaluation and qualification of models*

#### 5.2.2.2.1. Population pharmacokinetics

Not applicable

#### 5.2.2.2.2. Physiology based pharmacokinetic model

Not applicable

### *5.2.2.3. Absorption*

Not applicable

### *5.2.2.4. Bioequivalence*

No dedicated PK studies have been conducted in healthy volunteers. Nevertheless, comparable systemic exposure was planned to be shown as a secondary endpoint in a subset of patients with neovascular AMD within the comparative clinical safety and efficacy study 0504-19.

According to the most recent version of the Clinical Study Protocol (Version 4.0) for study 0504-19, the peak serum concentrations of INTP18 and Lucentis were planned to be characterised after single dose and after repeat dose administration. Of each treatment arm, 25 participants (a total of 50 participants) were planned to be considered for PK sample collection. PK sampling was however applicable exclusively for participants at sites in India and not for participants of other countries.

A total of 16 blood samples (approximately 3.5 mL) were scheduled of being drawn at pre-dose of the first dose (within 60 min before dosing), pre-dose of dose 07 at Visit 10 (Week 24; within 5 min before dosing) and post-dose at 8.00, 12.00, 16.00, 20.00, 24.00, 28.00 and 32.00 hours (within ± 5 min) from selected participants for pharmacokinetic analysis.

Blood samples were collected through an indwelling intravenous cannula placed in the forearm vein of the participants or through a fresh vein puncture. An instruction manual was planned of being prepared with detailed information on blood sample collection, separation, storage and shipment of bioanalytical samples for PK and Immunogenicity analysis.

The following pharmacokinetic parameters were computed as secondary endpoints at first dose and after dose 07 (Week 24), using non-compartmental model of Phoenix® WinNonlin® Version 8.3 (Certara L.P.) and statistical analysis were performed using SAS® 9.4 (SAS Institute Inc., USA).:

| **Pharmacokinetic Parameters:** | | |
|---|---|---|
| $T_{max}$ | : | Time of the maximum measured concentration. |
| $C_{max}$ | : | Maximum measured concentration. |

Descriptive statistics were provided for pharmacokinetic parameters and concentration data of ranibizumab IMP and RMP accordingly with the final analysis.

Actual time points of the sample collection were used. All concentration values below the lower limit of quantification were set to zero for the pharmacokinetic and statistical calculations.

All collected samples were planned to be analysed. If any participant was dropped out after dosing and no post-dose samples were collected, then pre-dose samples of such participants were not to be analysed.

The primary aliquot used for study sample analysis was discarded after completion of analysis. Any missing samples were reported as `M' and non-reportable concentration values due to insufficient volume or any other reason as per in-house procedure will be reported as 'NR'.

PK-Results from pivotal Phase 3 study 0504-19

A total of 48 patients were enrolled for PK analysis [INTP18 vs. Lucentis: 22 vs. 26 patients, respectively]. Two patients (one of each treatment arm) have been excluded from the PK set as all analysed samples were reported as NR due to the unavailability of the required stability data.

*Table 6: Pharmacokinetic parameters of ranibizumab (PK set, N=48)*

| **Parameters (Units)** | **Mean ± SD (untransformed data)** | | | |
|---|---|---|---|---|
| | **After dose 1 (N=48)** | | **After dose 7 (N=43)** | |
| | **Intas Ranibizumab (N=22)** | **Lucentis (N=26)** | **Intas Ranibizumab (N=21)** | **Lucentis (N=22)** |
| $T_{max}$ (h)[#] | 8.017 (7.933-31.083) | 19.959 (0.000-32.050) | 8.050 (8.000-32.050) | 22.025 (7.950-32.033) |
| $C_{max}$ (pg/mL) | 3703.633±2577.0472 | 3451.920±2435.3948 | 3237.669±364.0728 | 3299.398±2442.9072 |

**(Refer Table No. 14.2.3.1, 14.2.3.2, 14.2.3.3 and 14.2.3.4)**

[#]$T_{max}$ is represented as median (min-max) value.

Note: Two patients in test arm (Intas Patient no. R005 and R009) were excluded from statistical analysis due to insufficient data of calculate PK parameters.

After the 1st dose, mean (±SD) **Tmax** was 14.151 (±8.5469) h for the INTP18 group and 18.163 (±10.3795) h for the Lucentis group, median **Cmax** (min-max) was 3056.917 (999.188-12798.307) pg/mL for the INTP18 group and 3358.974 (0.000-9002.442) pg/mL for the Lucentis group.

After the 7th dose, mean (±SD) **Tmax** was 15.643 (±10.3322) h for the INTP18 group and 20.380 (±8.8269) h for the Lucentis group, median **Cmax** (min-max) was 2581.281 (467.429-9909.616) pg/mL for the INTP18 group and 2726.719 (323.077-10218.999) pg/mL for the Lucentis group.

#### *5.2.2.5. Distribution*

Not applicable

#### *5.2.2.6. Metabolism*

Not applicable

#### *5.2.2.7. Elimination*

Not applicable

#### *5.2.2.8. Dose proportionality and time dependency*

Not applicable

#### *5.2.2.9. Pharmacokinetics in the target population*

For PK data in the target population, refer to section 5.2.2.4. Bioequivalence above.

#### *5.2.2.10. Special populations*

Not applicable.

#### *5.2.2.11. Pharmacokinetic interaction studies*

Not applicable.

### 5.2.3. Pharmacodynamics

No dedicated (comparative) clinical pharmacodynamic (PD) studies have been performed as part of the clinical biosimilarity programme for INTP18. No accepted specific pharmacodynamic (PD) markers exist, being predictive of efficacy/safety of ranibizumab in patients.

However, central retinal thickness (foveal centre point (FCP) retinal thickness and foveal central subfield (FCS) retinal thickness), which addresses the PD aspects of ranibizumab, was evaluated by spectral domain optical coherence tomography (SD-OCT) in study 0504-19. Lesion characteristics such as total area of choroidal

neovascularization (CNV) and total area of leakage from CNV were evaluated using fluorescein angiography (FA).

#### *5.2.3.1. Mechanism of action*

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and CNV or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO.

#### *5.2.3.2. Primary and secondary pharmacology*

Not applicable

#### *5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances*

Not applicable

#### *5.2.3.4. Genetic differences in PD response*

Not applicable

#### *5.2.3.5. Immunological events*

See below section 5.4.7. Immunological events.

### 5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Not applicable

### 5.2.5. Dose selection and therapeutic window

Not applicable

### 5.2.6. Overall discussion and conclusions on clinical pharmacology

#### *5.2.6.1. Discussion*

#### *5.2.6.2. Conclusions*

The clinical development program did not include a dedicated PK study in healthy volunteers, which is

considered acceptable, since systemic exposure levels of ranibizumab after intravitreal administration are expected to be low and highly variable. Nevertheless, the pharmacokinetic profile of the proposed biosimilar was assessed within the Phase III clinical efficacy and safety study. Overall, study design aspects such as sampling schedule, chosen PK parameters or presentation of results via descriptive statistics are considered acceptable. Mean **Tmax** was shown to be generally lower in the INTP18 group than in the Lucentis group. However, considering the high inter-subject variability in both treatment arms this difference seems to be of no concern. Also, reported values for Cmax were overall comparable between treatment arms and, regarding their magnitude, comparable with the range predicted for the originator drug Lucentis. Thus, reported values for Cmax seem acceptable.

No dedicated (comparative) clinical **pharmacodynamic** studies have been performed as part of the clinical biosimilarity exercise for INTP18, which is acceptable as the primary focus of the biosimilarity exercise was laid on functional and anatomical outcomes. As the respective endpoints are directly linked to therapeutic efficacy, additional surrogate PD markers are not considered necessary.

## *5.3. Clinical efficacy*

### 5.3.1. Dose response study

No dedicated dose response studies were performed during the clinical development of INTP18.

### 5.3.2. Main study

#### *5.3.2.1. Pivotal Efficacy Study - 0504-19 (CLARITY)*

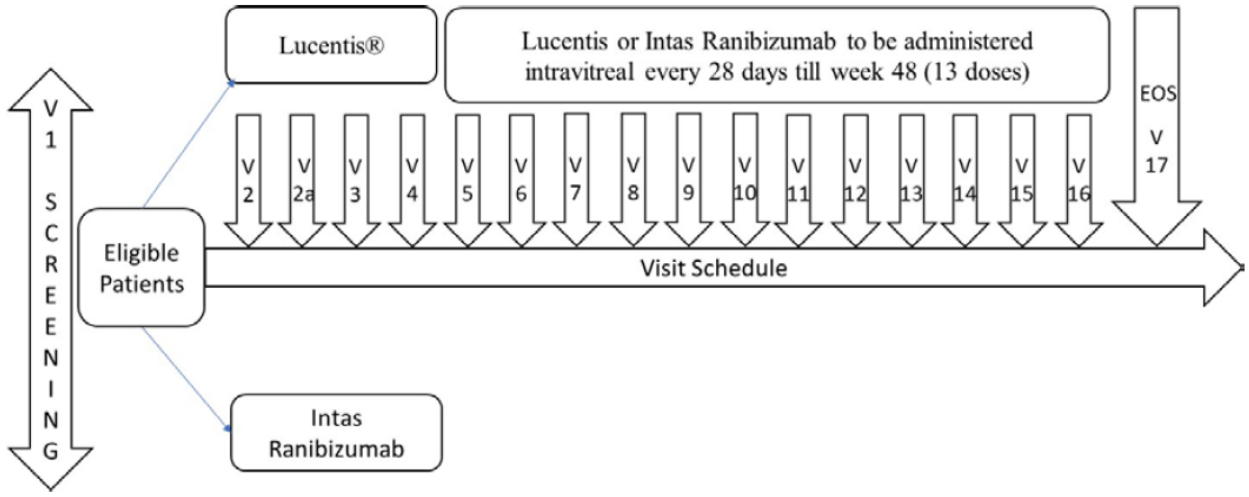
##### 5.3.2.1.1. Study title

A Double Masked, Parallel Group, Randomised, Multicentre, Clinical Study to Compare Efficacy and Safety of Intas Ranibizumab with Lucentis® in Patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD)

##### 5.3.2.1.2. Study design

The study is being conducted in **3 phases**: a Screening Phase (21 days), an Intervention Phase (48 weeks), and a post-intervention follow up visit (4 weeks after the participant's last dose of study intervention).

*Figure 1: Study schema*




**Patient population**

Study 0504-19 was conducted in patients with neovascular (wet) AMD.

The study was conducted at a total of 60 investigational sites across 5 countries (Czech Republic, Hungary, India, Latvia, Poland).

**Main Inclusion Criteria**

1. Male or female participants aged 50 years or more at the time of screening

4. Newly diagnosed, treatment naïve patients with active subfoveal CNV lesion secondary to neovascular (wet) age-related macular degeneration (AMD) in the study eye at Screening and confirmed by the Central Reading Centre (CRC)

   Note: Active CNV indicated the presence of leakage as evidenced by Fluorescein Angiography (FA) and intra- or subretinal fluid as evidenced by Optical Coherence Tomography (OCT) and must involve central subfield:

   a. The area of CNV must be ≥50% of the total lesion area in the study eye confirmed by the CRC, and

   b. Total lesion area ≤9 Disc Areas (DA) in size (including blood, scars and neovascularization) as assessed by FA in the study eye

   c. All subtypes of nAMD CNV lesions were permissible (i.e., classic CNV, occult CNV, or with some classic CNV component)

6. BCVA of 20/40 to 20/200 (≤ 73 and ≥ 34 ETDRS letter score) in the study eye using ETDRS chart at a distance of 4 meters at Screening and Baseline

7. Fellow eye should not be expected to need any anti-vascular endothelial growth factor (VEGF) treatment during the initial 8 weeks period of study participation.

**Main Exclusion Criteria**

4. Central subfield of the study eye affected by fibrosis or geographic atrophy assessed by colour fundus photography and confirmed by the CRC at Screening
5. Total area of scarring ≥50% of the total lesion in the study eye at Screening and confirmed by the CRC, in the study eye
6. Subretinal haemorrhage in the study eye that involved the centre of the fovea and/or the size of the haemorrhage was either >50% of the total area of the lesion or ≥1-disc area in size at screening as confirmed by CRC
7. Any infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis in either eye within 4 weeks prior to Baseline
8. Any active intraocular inflammation (grade trace or above) in the study eye within 4 weeks prior to Baseline
9. History of idiopathic or autoimmune-associated uveitis in either eye
10. CNV in either of the two eyes due to causes other than AMD such as diabetic macular oedema, retinal vein occlusion, histoplasmosis, trauma, multifocal choroiditis, angioid streaks, history of choroidal rupture or pathologic myopia (spherical equivalent of –6 diopters or more negative)
11. Prior interventions in the study eye
    a. Prior Treatment with verteporfin, External beam radiation treatment and Transpupillary thermotherapy in the study eye
    b. Prior any intravitreal injection in the study eye
    c. Prior laser photocoagulation in the study eye
    d. Prior vitrectomy in the study eye
    e. Prior Glaucoma filtration surgery in the study eye
    f. Prior Corneal Transplant in the study eye
    g. Submacular surgery or any surgical intervention for AMD in study eye
    h. Prior ocular surgery (including cataract) within the previous 3 months from baseline in the study eye
12. Prior treatment with:
    a. Any prior anti-VEGF including ranibizumab, bevacizumab, aflibercept and pegaptanib (intravitreal or systemic) in either eye
    b. Any prior intraocular use of corticosteroids in the study eye
    c. Use of topical ocular corticosteroids in the study eye for 60 or more consecutive days within the 90 days period prior to Baseline
    d. Use of systemic corticosteroids in the past 6 months. Note: Inhaled, nasal or dermal steroids are permitted
14. Current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol
15. History or evidence of the following in the study eye at Screening and/or baseline visit:

a. Retinal pigment epithelium (RPE) rip/tear involving the macula at Screening or Baseline in the study eye

b. Current vitreous haemorrhage or history of vitreous haemorrhage within 4 weeks prior to Baseline in the study eye

c. Any macular abnormality (including a history of macular hole stage 2 and above) other than AMD at Screening

d. Uncontrolled glaucoma in the study eye (defined as intraocular pressure (IOP) ≥30 mmHg or a cup to disc ratio ≥ 0.8, despite treatment with antiglaucoma medication) and any such condition for which the investigator feels may require a glaucoma filtering surgery while in the study

e. For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye does not exceed 6 diopters of myopia

f. Advanced glaucoma or optic neuropathy that involve(s) or threaten(s) the central visual field in the study eye at Screening or Baseline

g. Aphakia and/or absence of the posterior capsule at Screening or Baseline in the study eye. Absence of an intact posterior capsule was allowed if it occurred as a result of Yttrium-Aluminum-Garnet (YAG) laser posterior capsulotomy in association with prior posterior chamber intraocular lens (IOL) implantation

h. Rhegmatogenous retinal detachment in the study eye at Screening or Baseline

16. Use of other investigational drugs (excluding vitamins, minerals) within 30 days (or as per local regulation) or 5 half-lives prior to Baseline whichever was longer, and for neovascular AMD (other than vitamin supplements) in the study eye at any time

18. Significant illness within two (2) weeks prior to baseline

19. History of immunodeficiency diseases, including a positive HIV (ELISA or Western blot) test result. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result

20. Presence of uncontrolled systolic blood pressure >160 mmHg or uncontrolled diastolic blood pressure >100 mmHg based on the average of 3 readings taken with the patient in a resting state (Patients with controlled blood pressure (<140/90) with stable antihypertensive treatment regimen were eligible)

21. Documented medical history (i.e., within 6 months of screening) of thromboembolic events, stroke, congestive heart failure, myocardial infarction, uncontrolled atrial fibrillation

22. Documented medical history of bleeding disorders, including platelet disorders, acquired or hereditary coagulations disorders, and acquired or hereditary vascular disorders

23. History of active malignancy except for appropriately treated carcinoma in situ of the cervix, nonmelanoma skin carcinoma, and prostate cancer with a Gleason score of < 6 and a stable prostate-specific antigen for > 12 months

24. Any history or evidence of a concurrent intraocular condition in the study eye, including retinal diseases other than neovascular AMD, that in the judgment of the Investigator, could either require medical or surgical intervention during the course of the study to prevent or treat visual loss that might result from that condition or that limits the potential to gain visual acuity upon treatment with the investigational

product (e.g. diabetic retinopathy, cataract, uncontrolled glaucoma, uveitis, previous corneal transplant, recent cataract surgery etc.)

25. History of a medical condition (disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding) that, in the judgment of the Investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product, affect interpretation of the results of the study, or renders the patient at high risk of treatment complications.

Determination of the study eye

The study eye was defined as the eye meeting all of the inclusion criteria and none of the exclusion criteria (i.e. the enrolment criteria).

**Randomisation**

Randomisation numbers were generated using **central randomisation**. At the randomisation visit (i.e. Visit 2, Day 1) after ensuring that a patient met all eligibility criteria, participants were assigned 1:1 to 1 of 2 intervention groups, to receive INTP18 or Lucentis at a dose of 0.5 mg by intravitreal (IVT) injection every 28 days until Week 48 (total 13 doses) in the study eye, based on an algorithm implemented in the interactive web response system (IWRS) before the study.

Randomisation was in the end stratified based on baseline BCVA (≤54 and >54), iris colour (dark iris and light iris), region (India and Europe), and in addition had initially been planned to be also stratified by device (PFS and vial).

Recruitment was planned such that at least 30% of the subjects of the total sample size were with light iris colour. Recruitment of approximately 200 subjects from the EU, and initially also 120 to 150 subjects from the US (30 subjects on PFS of the test and reference products each and 30 subjects on vials of the test and reference products each) was planned. Based on the algorithm, the IWRS assigned a unique intervention code, which would dictate the intervention assignment and matching study intervention kit for the participant.

Central randomisation schedule was generated using SAS® Version 9.4 or higher (SAS Institute Inc., USA) before the commencement of the study by the biostatistician who was not involved in the conduct of the study. The randomisation schedule was prepared by a vendor or third party as per their SOPs.

Unmasked study staff involved in dispensing of study drug and verification of dispensed study drugs were accountable for ensuring compliance to randomisation schedule.

**Blinding**

Participants, investigator staff, and persons performing the assessments were planned to remain masked to the identity of the treatment from the time of randomisation until final database lock after study completion. Also, in principle, all members of the **site** team were to be masked to treatment assignments while the study is in progress. However, in case of "unexpected extreme situations", the Medical Monitor could grant a switch of a study staff member from the masked role to the unmasked role, but not the other way around. In the event an alternate study staff member was required to be added or substituted, that alternate study staff member could assume only one role for the duration of the study.

At the **CRO**, there were separate groups of masked and unmasked study personnel foreseen and their roles were clearly defined in the project management plan, separating the roles and responsibilities for masked and unmasked personnel throughout the study.

Interim analysis

To maintain the blind for the remaining part of the trial, after interim analysis at 6 months, a separate **unblinded study team** was set up. This team was responsible for the unblinded analysis and reporting of the 6 months results for submission.

This unblinded team was granted access to an unblinded directory to ensure that the study team which continued to manage the study did not have access to unblinded information and remain blinded to the activities until the 12-month analysis.

The blinded study team was responsible for all data cleaning activities required to freeze the database for the analysis of the 6 months data.

Any contacts with the sites were executed in a blinded manner by the blinded study team. The unblinded team did not interact with investigators or the site personnel.

Furthermore, designated unmasked study staff provided the IP to the unmasked injecting investigator/site personnel in accordance with the randomisation schedule.

During the study, the unmasked injecting investigator/site personnel were required to maintain records of IP dispensation and collection for each participant. This record was made available to the unmasked study monitor for the purpose of verifying the accounting of clinical supplies.

Emergency unmasking of treatment assignment

The IWRS was planned to be programmed with mask-breaking instructions that have not been reported in detail.

After an emergency unmasking an assessment whether or not study drug should be discontinued for the respective participant was done by the site personnel and the study lead.

In general, full disclosure of randomisation codes was planned if the study is completed and the clinical database is closed.

**Description of trial intervention**

Participants received either INTP18 (i.e. Intas Ranibizumab/Rexatilux) or EU- and US-sourced Lucentis at a dose of 0.5 mg by intravitreal (IVT) injection administered as 0.05 mL of a 10 mg/mL solution drawn of a single-use vial. The first dose was administered on Day 1 (Visit 2), consecutive injections were given every 28 days/4 weeks until Week 48 (resulting in a planned total of 13 doses) in the study eye.

Study treatment was to be administered in the study eye on the day of the study visit, or within the visit window as described in the Schedule of Activities (i.e., ±1 day (Visit 2a, Day 4); ±2 days (Visit 3, Day 8); ±3 days (Visit 4, Day 15); ±7 days for the remaining visits). A delay of more than 7 days was considered a protocol deviation. However, the participant was allowed to continue in the study. An injection free interval of at least 21 days was to be kept.

Following the study treatment, participants remained in the clinic for a post-injection assessment by the injecting investigator to ensure that the procedure and/or the study medication have not endangered the health

of the eye. The post-injection assessments included gross assessment of vision by finger counting test, measurement of IOP and indirect ophthalmoscopy [to assess the central retinal artery perfusion, presence of retinal detachment, presence of new intraocular haemorrhage(s)].

Only 1 eye was treated at a time. However, AMD therapies not interfering with study efficacy assessments were allowed in the other (fellow) eye.

Treatment of the fellow eye

In case the fellow eye required treatment during the study with an anti-VEGF, a drug approved for the treatment of neovascular AMD in the respective country could be applied at the discretion of the Investigator and following the procedures established at the respective site (bevacizumab was not considered acceptable; ranibizumab was the last option to avoid potential immunogenicity interactions).

If treatment of the fellow eye was required at any time point before 8 weeks (Visit 6), the Investigator was required to discuss treatment application in advance with the medical monitor.

Any fellow eye treatment had to be captured on the eCRF.

**Concomitant and rescue therapies**

Prior therapies

Medications considered relevant and significant non-drug therapies administered **up to 30 days before the first dose** of study intervention, as well as all medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant started treatment with the study drug to the last study intervention were listed on the Prior/Concomitant medications/Significant non-drug therapies eCRF.

Protocol-specific medications (e.g., dilating drops, fluorescein dyes) and pre- and post-injection medications (e.g., topical anesthetics) used by a participant during the study were not considered concomitant medications but standard of care and were therefore not documented in the eCRF.

Permitted therapies

- In case the fellow eye required treatment during the study with an **anti-VEGF**, a drug approved for the treatment of neovascular AMD in the respective country was applied at the discretion of the Investigator (bevacizumab was no treatment option; ranibizumab was allowed as a last option).
- **Systemic medications** with a stable dosing regimen to control a systemic disease (e.g., rheumatoid arthritis) were allowed.
- The use of **topical corticosteroids** in the study eye to treat an active ocular condition other than CNV was permitted.
- **Antimicrobials** for self-administration by the participant could be given based on local clinical practice.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention had to be recorded in the CRF.

Prohibited therapies

- **Anti-angiogenic drugs**, including any anti-VEGF agents' therapy other than IMP in the study eye

- **Anti-angiogenic drugs**, including any anti-VEGF agents' therapy other than IMP in the fellow eye within first 8 weeks of Baseline
- **Intra-ocular or periocular** (subtenon, retrobulbar, subconjunctival) **treatment of CNV** in the study eye, e.g. ocular corticosteroids, etc.
- Unapproved (intravitreal bevacizumab was not allowed) or investigational treatment in the fellow eye
- **Systemic anti-angiogenic drugs**, including any anti-VEGF agents' therapy
- **Systemic corticosteroids** (oral, intramuscular, intravenous) for 15 or more consecutive days (low stable doses of corticosteroids [defined as ≤10 mg prednisolone or equivalent dose], inhaled, nasal or dermal steroids are permitted) if initiated during the study
- **Systemic medications known to be toxic to the lens, retina or optic nerve**, e.g., deferoxamine, chloroquine/hydroxychloroquine
- **Any other treatment for choroidal neovascularization for the study eye**, including, but not limited to, laser photocoagulation, photodynamic therapy, Macugen® therapy, transpupillary thermotherapy, external beam radiation therapy, submacular surgery, or other surgical intervention for AMD
- Elective vitrectomy surgery in the study eye

No **rescue medication** was allowed during the study. Any participant who was in need of rescue treatment, in the judgement of the investigator, were to be withdrawn from the study treatment.

Study intervention discontinuation criteria

A participant's study intervention was to be discontinued after:

- Emergence of the following AEs:
  a. Stage 3 or 4 macular hole
  b. Rhegmatogenous retinal detachment
  c. Stroke or transient ischemic attack
  d. Myocardial infarction
  e. Participants with ≥2+ intraocular inflammation in the study eye
- If any other clinically significant finding was identified which affected overall capability of the participant to follow protocol-defined assessments and schedule.
- Investigator's discretion based on his/her clinical judgment the participant requires rescue treatment.
- Appearance of a new health condition suspected to require appropriate care or require medications or treatment prohibited by the protocol.

Participants who discontinued study treatment were not to be considered withdrawn from the study and were expected to continue their scheduled follow-up assessments until End of Study. Participants were expected to continue with the study visits and procedures as long as such procedures do not pose a risk to the well-being of the participant.

Withdrawal criteria

- Consent was withdrawn: Participants had the right to withdraw from the trial at any time for any reason. If withdrawal occurred, the participant was requested to come for a complete follow-up examination.
- Non-compliance: The participant could be withdrawn from the trial at the discretion of the Investigator if it was judged that participant was non-compliant to study assessment and schedule and it could cause safety concerns.
- Positive pregnancy test: A female participant with a positive pregnancy test was to be withdrawn from the trial.
- If a participant missed any of the two consecutive doses during the study period.
- Lost to follow-up
- Death

Withholding of study intervention

Ranibizumab treatment was to be withheld, and treatment was not to be resumed earlier than the next scheduled treatment in the event of:

- A decrease in BCVA of ≥ 30 letters in the study eye compared with the last assessment of VA prior to most recent treatment.
- Vitreous haemorrhage in the study eye. Treatment was to be permitted when the vitreous haemorrhage had improved to allow a visual acuity score improvement to a <30-letter decrease.
- Intraocular inflammation (iritis, iridocyclitis or vitritis) is ≥1+ in the study eye.
- An IOP of ≥30 mmHg. Treatment was to be permitted when intraocular pressure had been lowered to <30 mmHg, either spontaneously or by treatment, as determined by the Investigator.
- Sensory rhegmatogenous retinal break: New retinal break was identified in the study eye. Treatment could be resumed ≥23 days after the retinal break has been successfully treated.
- Interruption of study treatment if any of the following were present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye, or if the participant was currently receiving treatment for an active local or systemic infection. Participants with endophthalmitis in either eye were to be discontinued from the study.
- Performed or planned intraocular surgery within the previous or next 28 days. Cataract surgery in the study eye could be performed if clinically indicated and should occur >30 days after the previous study injection; the next study injection was to be held for ≥30 days following cataract surgery.

Interruptions of study treatment due to other reasons were not permitted, unless they were deemed necessary by the Investigator due to AEs.

**Study assessment**

BCVA assessed on ETDRS chart at a starting distance of 4 m

Best corrected visual acuity (BCVA) was measured by trained and certified personnel at the study sites to allow assessment of the change from baseline in BCVA in the study eye. The BCVA examiner was masked to treatment arm assignment. BCVA was measured from Visits 1 to 17 (EoS), with exemption of Visit 2a.

ETDRS visual acuity testing preceded any examination requiring the administration of eye drops to dilate the eye or any examination requiring contact with the eye. Visual acuity testing was performed following refraction.

Fluorescein Fundus Angiography (FFA)

FFA was conducted for the assessment of leakage for both eyes at Screening, at Week 8, 24 and 52/EoS, in the study eye only before dosing. At Screening, the images were submitted to the CRS for determination of eligibility (within 24 hours, if possible). FA images from previous routine evaluations were used, provided they were performed within 3 days of the screening visit using CRC-certified equipment and examiners.

Spectral Domain Optical Coherence Tomography Imaging (SD-OCT)

SD-OCT was used to assess persistent or worsening disease activity, which included the presence of sub-retinal fluid, persistent or increased number, size or total volume of IRCs, or increased central retinal or foveal thickness, or similar quantitative retinal imaging data recorded within the individual participant record. For the assessment of FCP/FCS SD-OCT was conducted in both eyes at Screening. At all visits (except Day 4 = Visit 2a and Week 2 = Visit 4), SD-OCT assessment was conducted in the study eye only before dosing. At Screening, the images were submitted to the CRS for determination of eligibility (within 24 hours, if possible).

Participants were assessed using the same machine throughout the course of the study. The information collected was used by the Investigator to assess the status of disease activity based on their own evaluation.

Colour fundus photography (CFP)

The CFP was conducted for both eyes at Screening, at Week 8, 24 and 52/EoS, in the study eye only before dosing. At Screening, the images were submitted to the CRS for determination of eligibility (within 24 hours, if possible).

#### 5.3.2.1.3. Objectives and estimands

**Primary objective**

Primary objective of study 0504-19 was to establish therapeutic equivalence of INTP18 versus Lucentis with respect to the change in best corrected visual acuity (BCVA) from Baseline to Week 8 using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale in adult patients with wet AMD.

Primary Efficacy Endpoint

Mean change in BCVA in the study eye from baseline to Week 8 using the ETDRS protocol.

Acceptance criterion (for EMA)

Therapeutic equivalence was concluded if the 95% CI of the difference between treatments for mean change in BCVA from baseline to Week 8 falls within ±3.4 for the PP set.

Hypothesis

The primary hypothesis of this study was that INTP18 is therapeutically equivalent to Lucentis in the treatment of nAMD.

**Estimand for the primary objective**

The applicant did not define the estimand for the primary objective or discuss the potential occurrence of intercurrent events and associated handling strategies.

*Table 7: Estimand for primary objective*

| | |
|---|---|
| Population | Adult patients with wet AMD meeting all specified eligibility criteria. |
| Treatment condition | Assignment to INTP18, in the case of completion of the primary evaluation phase of the study without major protocol deviations, compared to assignment to Lucentis, in the case of completion of the primary evaluation phase of the study without major protocol deviations |
| Endpoint (variable) | BCVA at week 8 |
| Population-level summary | Difference in means |
| Intercurrent events and strategy to handle them | |
| Intercurrent event | Not discussed by the applicant |

**Statistical methods for estimation and sensitivity analysis on primary estimand**

Analysis Sets

| Analysis Set | Definition |
|---|---|
| Safety set | All randomized participants who received at least one dose of study medication. |
| Modified Intent-To-Treat (mITT) set | All randomized participants who received at least one dose of study medication and underwent at least one post-dose efficacy evaluation. Participants in the mITT set who missed efficacy data for a particular visit, the missing data was imputed using last observation carried forward (LOCF) techniques. |
| Per protocol (PP) set | All randomized participants who completed the week 8 primary efficacy assessment with no major protocol deviations impacting the primary efficacy endpoint. |

Source: Interim Clinical Study Report, Section 9.7.3 Analysis Populations

The safety set was used for the safety analysis. Participants included in the per protocol (PP) and modified intent-to treat (mITT) sets were used for the evaluation of the efficacy endpoints.

Primary Analysis

The mean change in BCVA in the study eye from baseline to week 8 was planned to be analysed on the PP set using an Analysis of Covariance (ANCOVA) model. The model was to include the baseline BCVA level, iris color, country/region and the treatment group as covariates. The 90% and 95% CIs for the difference between treatments for mean change in BCVA from baseline to Week 8 was planned to be calculated and reported.

Therapeutic equivalence was to be concluded if the 95% CI of the difference between treatments for mean change in BCVA from baseline to week 8 fell within the equivalence margin of ±3.4.

Supporting/Sensitivity Analysis

The ANCOVA analysis was also planned to be performed for the (m)ITT set to corroborate the results obtained from the PP set, and the missing efficacy data at week 8 to be imputed using the LOCF (last observation carried forward) method. As a sensitivity analysis, an ANCOVA on the mITT set that included all stratification variables used for randomisation as covariates and used multiple imputation to address missing values and Rubin's rules to combine multiple imputation results was provided. Additionally, a sensitivity analysis for missing data was planned to be performed on the mITT set using a Mixed Model for Repeated Measures (MMRM) with an unstructured correlation matrix assuming that the data are Missing at Random (MAR). This MMRM was complemented with a tipping point analysis.

Planned subgroup analyses

Subgroup analyses were planned for the primary endpoint, specifically for each age group and each country / region as applicable.

Sample size determination

An equivalence test of means using two one-sided equal-variance t-tests with a sample size of 218 completers in each treatment group achieves 90% power at a 5% significance level when the equivalence limits are -3.4 and 3.4, the actual difference between the means is 0.0, and the standard deviation is assumed to be 10.76 in each group. Assuming ~20% dropouts/withdrawals, 546 patients were planned to be recruited.

**Secondary objectives**

Secondary Objectives:

- To compare the efficacy of Intas Ranibizumab versus Ranibizumab-Ref at week 24 and 52
- To compare the efficacy of Intas Ranibizumab with Ranibizumab-Ref based on central foveal thickness, area of choroidal neovascularization and leakage from choroidal neovascular lesion
- To assess the safety and tolerability Intas Ranibizumab relative to Ranibizumab-Ref
- To compare the systemic levels of Intas Ranibizumab with Ranibizumab-Ref
- To compare immunogenicity of Intas Ranibizumab with Ranibizumab-Ref

Secondary Efficacy Endpoints:

- Mean change from baseline in BCVA in the study eye up to 52 weeks using the ETDRS protocol
- Proportion of patients who gained ≥5, ≥10 and ≥15 letters in the study eye using ETDRS protocol up to 52 weeks
- Proportion of patients who lost ≥5, ≥10 and ≥15 letters in the study eye using ETDRS protocol up to 52 weeks
- Mean change from baseline in the total area of **leakage** from choroidal neovascularization (CNV) measured by fluorescein angiography (FA) at Weeks 8 and 52

- Mean change from baseline in total area of CNV measured by FA at Weeks 8 and 52 in the study eye
- Mean change from baseline in central retinal thickness (foveal centre point (FCP) retinal thickness and foveal central subfield (FCS) retinal thickness) as in the study eye measured by SD-OCT (optical coherence tomography) up to 52 weeks

Secondary Safety/Immunogenicity Endpoints:

- Incidence of ocular adverse events over 52 weeks
- Incidence of non-ocular adverse events over 52 weeks
- Systemic blood levels of ranibizumab
- Incidence of anti-drug antibodies

**Estimand for the secondary objectives**

No estimand for the secondary objectives have been pre-defined.

**Statistical methods for estimation and sensitivity analysis on the secondary estimands**

The mean change in BCVA, in total area of leakage from CNV measured by FA, in total area of CNV measured by FA, and in central retinal thickness (foveal centre point (FCP) and foveal central subfield (FCS)) measured by SDOCT from baseline to week 52 were planned to be evaluated using independent t-tests and the corresponding p-values were planned to be reported.

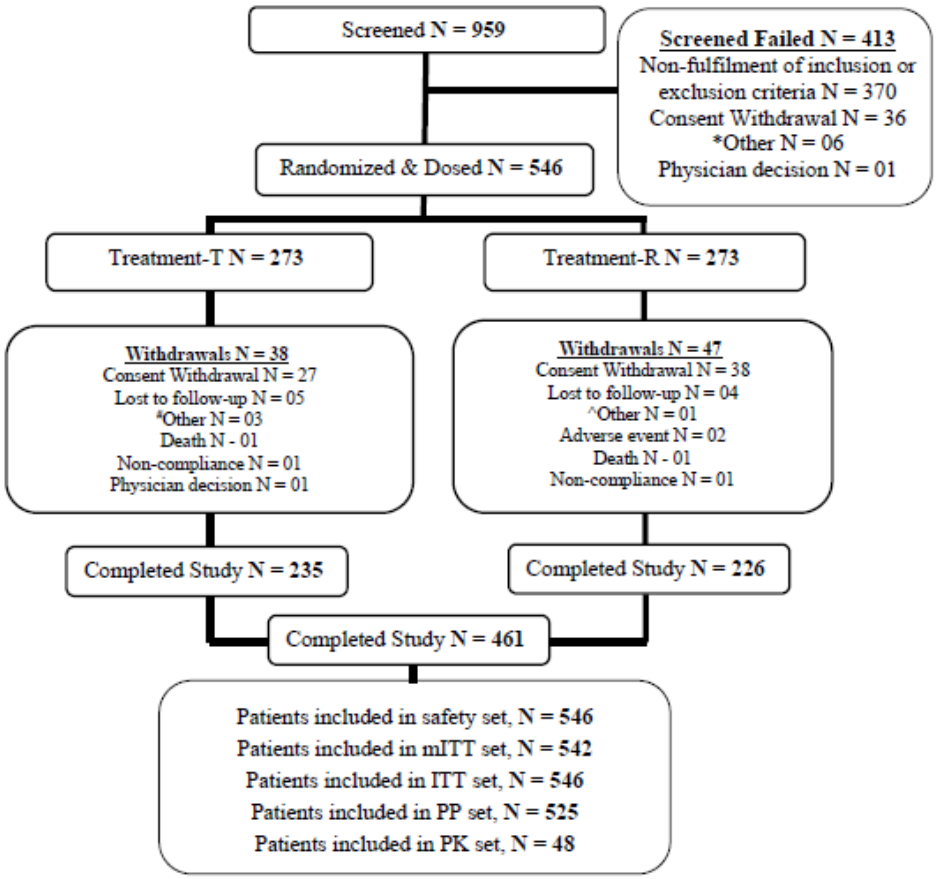
The number of patients who gained ≥5, ≥10 and ≥15 letters in the study eye and the number of patients who lost ≥5, ≥10 and ≥15 letters in the study eye was planned to be compared between treatment groups using the Chi-Squared/Fisher's Exact test and the corresponding p-values reported.

### 5.3.2.1.4. Results

**Participant flow and numbers analysed**

| | |
|---|---|
| Study Initiation Date: | 13/04/2021 (first patient first visit) |
| Interim Analysis Database Cutoff Date: | 16/01/2025 |
| Interim Clinical Study Report Date: | 11/03/2025 |
| Study Completion Date: | 27/05/2025 (last patient last visit) |
| Final Database Cutoff Date: | 20/08/2025 |
| Final Clinical Study Report Date: | 26/09/2025 |

*Figure 2: Participant flow*




* Imaging related reason for 5 patients and 1 patient was COVID-19 positive.
#Patients met study exclusion criteria and withdrawn from the study.
^Patient missed IP doses.

Source: Final Clinical Study Report, Section 10.1 Disposition of patients

## Patient disposition & Discontinuations

Patient disposition and datasets analysed

*Table 8: Summary of patient disposition and datasets analysed*

| | Statistics | Intas Ranibizumab (N=273) | Lucentis (N=273) | Total (N=546) |
|---|---|---|---|---|
| Number of patients enrolled | n (%) | - | - | 546 (100.0) |
| Patients included in Safety set | n (%) | 273 (100.0) | 273 (100.0) | 546 (100.0) |
| Patients included in mITT set | n (%) | 271 (99.3) | 271 (99.3) | 542 (99.3) |
| Patients included in ITT set | n (%) | 273 (100.0) | 273 (100.0) | 546 (100.0) |
| Patients included in PP set | n (%) | 260 (95.2) | 265 (97.1) | 525 (96.2) |
| Patients included in PK set | n (%) | 22 (8.1) | 26 (9.5) | 48 (8.8) |
| Patients who completed study | n (%) | 235 (86.1) | 226 (82.8) | 461 (84.4) |
| Patients who discontinued study | n (%) | 38 (13.9) | 47 (17.2) | 85 (15.6) |
| Reason for discontinuing study | | | | |
| Consent is withdrawn | n (%) | 27 (9.9) | 38 (13.9) | 65 (11.9) |
| Lost to follow-up | n (%) | 5 (1.8) | 4 (1.5) | 9 (1.6) |
| Adverse Event | n (%) | 0 (0.0) | 2 (0.7) | 2 (0.4) |
| Death | n (%) | 1 (0.4) | 1 (0.4) | 2 (0.4) |
| Non-compliance | n (%) | 1 (0.4) | 1 (0.4) | 2 (0.4) |
| Other : Patient withdrawal as exclusion 23 met and inclusion 6 not met | n (%) | 1 (0.4) | 0 (0.0) | 1 (0.2) |
| Other : Subject Withrow form the study. | n (%) | 1 (0.4) | 0 (0.0) | 1 (0.2) |
| Other : excusion criteria 23 and 12 met | n (%) | 1 (0.4) | 0 (0.0) | 1 (0.2) |
| Other : protocol criteria, 2 missed IP doses | n (%) | 0 (0.0) | 1 (0.4) | 1 (0.2) |
| Physician decision | n (%) | 1 (0.4) | 0 (0.0) | 1 (0.2) |

Note 1: N = Number of patients in respective treatments.
Note 2: n = Number of patients in respective categories.
Note 3: Percentages are based on total number of patients in each treatment.
Reference listing: 16.2.1.1 and 16.2.1.2

Source: *Final Clinical Study Report, Section 14.3 Safety data*

Four subjects were excluded from the mITT set since at least one post-baseline efficacy BCVA data point was not available (2 subjects each from the two treatment arms).

A total of 21/546 (3.8%) patients were excluded from the PP set as they either did not complete the study and missed the BCVA assessment at Week 8 (Visit 6; INTP18 vs. Lucentis: 9/273 (3.3%) vs. 6/273 (2.2%) patients, respectively) or Visit 6 was not performed and hence BCVA data were not available for the primary efficacy analysis (INTP18 vs. Lucentis: 4/273 (1.5%) vs. 2/273 (0.7%) patients, respectively).

Discontinuations

A total of 38/273 (13.9%) subjects in the Intas Ranibizumab arm and 47/273 (17.2%) subjects in the Lucentis arm discontinued the study.

The most common reason for subject discontinuation in both the treatment arms was 'withdrawal of consent' (INTP18 vs. Lucentis: 27/273 (9.9%) vs. 38/273 (13.9%) patients).

***Protocol deviations***

Of the total of 1646 protocol deviations, 1606 were categorised as minor, 40 were categorised as major (INTP18 vs. Lucentis: 18 vs. 22 major protocol deviations, respectively). As 37 protocol deviations were reported as "site level deviations", 1609 protocol deviations remain on patient level. Of the latter, 808 protocol deviations were reported for the INTP18 group, and 801 protocol deviations were reported for the Lucentis group. Minus the 40 protocol deviations categorised as major, that leaves 790 minor protocol deviations in the INTP18 group and 779 minor protocol deviations in the Lucentis group on patient level.

Major protocol deviations

Of the 40 major protocol deviations, 26 were "randomisation and masking related" (INTP18 vs. Lucentis: 8 vs. 18 major protocol deviations), 7 were "inclusion-exclusion criteria related" (7 vs. 0 major protocol deviations), 3 were "discontinuation of study intervention and participant discontinuation and withdraw related" (2 vs. 1 major protocol deviation), 2 were "treatment of the fellow eye related" (0 vs. 2 major protocol deviations), and 1 was "schedule of activity related" (1 vs. 0 major protocol deviation) or "study intervention related" (0 vs. 1 major protocol deviation) each.

Deviations from study plan

The original protocol (Version 1.0) was amended 5 times resulting in the final CSP (Version 4.0).

The study initiation date was on 01/05/2021 (date of first patient visit). The database cutoff date for interim analysis was 16/01/2025. Thus, amendments 3.1, 3.1/CZE-1 and 4.0 lie after the start of the study.

The following key amendments have been implemented:

*Table 9: Summary of key changes in each protocol amendment*

| Document Version and Date | Summary of Key Changes |
|---|---|
| Original protocol<br>Version 1.0<br>Dated 28 January 2020 | N/A |
| Amendment 2.0<br>Dated 07 July 2020 | •Updated formulation details to remove PFS<br>•Updated the number of blood samples taken for PK analysis based on regulatory advice<br>•Updated the therapeutic equivalence definitions for US FDA and EMA based on regulatory advice<br>•Added randomization stratified by Iris color based on regulatory advice<br>•Iris color examination was added to the complete ophthalmic examination based on regulatory advice |
| Amendment 3.0<br>Dated 11 August 2020 | •Updated formulation details to add PFS as a form<br>•Updated to state both EU and US sourced Lucentis as reference product<br>•Updated recruitment plan to have at least 30% subjects of total sample size with light iris color<br>•Updated country specific stratification for geographic region/country considering balance administration of PFS & vials to be done through IWRS<br>•Updated sample size details to state recruitment of approximately 120 to 150 patients from the US (30 subjects on PFS of the test and reference products each and 30 patients on vials of the test and reference products each). |
| Amendment 3.1<br>Dated 19 May 2021 | •Clarifying text was added to the schedule of activities table<br>•Clarifying text was included for region specific enrolment to state that recruitment of approximately 200 subjects from EU, and 120 to 150 subjects from the US (30 subjects on PFS of the test and reference products each and 30 subjects on vials of the test and reference products each)<br>•Clarifying text was added to participant discontinuation/withdrawal from the study<br>•Clarifying text was added to state that PK assessment was not applicable for participants in the EU<br>•Added text to relevant sections for management of study in COVID-19 or similar pandemic |
| Amendment 3.1/CZE-1<br>Dated 03 February 2022 | •Based on regulatory requirement, deleted text in the section Emergency unmasking of treatment assignment |
| Aamendment 4.0<br>Dated 10 February 2022 | •Added planned interim analysis strategy endorsed by regulatory advice<br>•Exclusion criterion was updated based on the current summary of product characteristics of Lucentis<br>•Clarified the exclusion criterion to state documented medical history (i.e., within 6 months of screening) of thromboembolic events, stroke, congestive heart failure, myocardial infarction, uncontrolled atrial fibrillation<br>•Based on regulatory advice covered under protocol version 3.0/CZE-1, text was deleted in the section emergency unmasking of treatment assignment<br>•A section was included for management of study in COVID-19 or similar pandemic |

Source: Interim Clinical Study Report, Version 4.0, Section 9.8.1 Protocol Amendments

Although it was planned to conduct the study in India, US and Europe, subjects were enrolled from India and Europe based on the Sponsor's decision.

The interim analysis was based on the interim SAP version 1.0, dated 02 January 2025. Details of the final analysis to be conducted after study completion are provided in the original SAP version 00, dated 19 December 2023.

**Baseline data**

**Demographic Data**

*Table 10: Demographic data and baseline characteristics (safety set)*

| | Statistics | Intas Ranibizumab (N=273) | Lucentis (N=273) | Total (N=546) | p-value |
|---|---|---|---|---|---|
| Age (years) | n | 273 | 273 | 546 | 0.0214 |
| | Mean (SD) | 69.4 (9.55) | 71.3 (9.18) | 70.3 (9.40) | |
| | Median | 70.0 | 72.0 | 71.0 | |
| | Min, Max | 50, 88 | 50, 92 | 50, 92 | |
| Gender | | | | | |
| Female | n (%) | 136 (49.8) | 112 (41.0) | 248 (45.4) | 0.0391 |
| Male | n (%) | 137 (50.2) | 161 (59.0) | 298 (54.6) | |
| Race | | | | | |
| Asian | n (%) | 174 (63.7) | 172 (63.0) | 346 (63.4) | 0.859 |
| White | n (%) | 99 (36.3) | 101 (37.0) | 200 (36.6) | |
| Ethnicity | | | | | |
| Not Hispanic or Latino | n (%) | 273 (100) | 273 (100) | 546 (100) | Null |
| Region/Country | | | | | |
| India | n (%) | 174 (63.7) | 172 (63.0) | 346 (63.4) | 0.859 |
| Europe | n (%) | 99 (36.3) | 101 (37.0) | 200 (36.6) | |
| Czech Republic | n (%) | 10 (3.7) | 6 (2.2) | 16 (2.9) | |
| Hungary | n (%) | 31 (11.4) | 29 (10.6) | 60 (11.0) | |
| Latvia | n (%) | 14 (5.1) | 11 (4.0) | 25 (4.6) | |
| Poland | n (%) | 44 (16.1) | 55 (20.1) | 99 (18.1) | |
| Weight (Kgs) | n | 273 | 273 | 546 | 0.218 |
| | Mean (SD) | 68.79 (15.343) | 70.40 (15.245) | 69.59 (15.301) | |
| | Median | 67.90 | 68.00 | 68.00 | |
| | Min, Max | 33.0, 130.0 | 36.3, 150.0 | 33.0, 150.0 | |
| Height (cms) | n | 273 | 273 | 546 | 0.3811 |
| | Mean (SD) | 162.0 (9.76) | 162.8 (9.97) | 162.4 (9.86) | |
| | Median | 162.0 | 163.0 | 162.5 | |
| | Min, Max | 132, 185 | 134, 192 | 132, 192 | |
| BMI ($kg/m^2$) | n | 273 | 273 | 546 | 0.3689 |
| | Mean (SD) | 26.077 (4.6870) | 26.425 (4.3674) | 26.251 (4.5293) | |
| | Median | 25.810 | 25.810 | 25.810 | |
| | Min, Max | 15.06, 47.63 | 17.53, 47.34 | 15.06, 47.63 | |
| BCVA | | | | | |
| <=54 | n (%) | 118 (43.2) | 126 (46.2) | 244 (44.7) | 0.4911 |
| >54 | n (%) | 155 (56.8) | 147 (53.8) | 302 (55.3) | |
| Iris Color | | | | | |
| Dark iris | n (%) | 186 (68.1) | 183 (67.0) | 369 (67.6) | 0.7839 |
| Light iris | n (%) | 87 (31.9) | 90 (33.0) | 177 (32.4) | |
| Formulation | | | | | |
| Single use vial | n (%) | 273 (100) | 273 (100) | 546 (100) | Null |

n = Number of subjects in respective categories; N = Number of subjects in respective treatments.
Percentages were calculated based on total number of subjects for each treatment.
For categorical data, p-value was calculated using a chi-square test. If any cell has counts less than 5, then the Fisher's exact test was used instead. For continuous data, p-value is calculated using independent t-test for the comparison between two treatments.
Source: Table 14.1.1

Baseline characteristics for the **mITT set** and the **PP set** showed comparable numbers.

For the **PK set**, the mean age for the 48 included patients was 67 ± 10.8 years, 30 (62.5%) patients were male and 18 (37.5%) patients were female. All 48 patients were Asians (India). The mean weight was 64.8 ± 14.75 kg. The mean height was 160 ± 8.2 cm. The mean BMI was 25.36 ± 5.155 $kg/m^2$. BCVA of 17 (35.4%)

patients was >54 and 31 (64.6%) patients was ≤54. Iris colour of all 48 patients was dark. Single use vial was used for all 48 patients during the study.

Baseline Disease Characteristics

Mean (±SD) **total area of leakage from CNV** (measured by fluorescein angiography) at baseline as presented for the PP set: INTP18 vs. Lucentis: 2.18 (±2.057) vs. 2.28 (±1.970) $mm^2$.

Mean (±SD) **total area of CNV** (measured by fluorescein angiography) at baseline as presented for the PP set: INTP18 vs. Lucentis: 5.18 (±4.051) vs. 5.48 (±3.915) $mm^2$.

Mean (±SD) **central retinal thickness (CRT) of Foveal Central Point** (measured by SD-OCT) at baseline as presented for the PP set: INTP18 vs. Lucentis: 411.2 (±171.47) vs. 395.2 (±153.60) µm.

Mean (±SD) **central retinal thickness (CRT) of Foveal Central Subfield** (measured by SD-OCT) at baseline as presented for the PP set: INTP18 vs. Lucentis: 431.967 (±146.0012) vs. 414.008 (±129.5760) µm).

Comparable baseline characteristics have been shown for the mITT Set. Values for CRT of FCS and FCS originate from the interim analysis since no data was presented separately for CRT of FCP and FCS in the final CSR.

Concomitant medication

A total of 440/546 (80.6%) patients had **at least one concomitant medication** (INTP18 vs. Lucentis: 212/273 (77.7%) vs. 228/273 (83.5%) patients).

Concomitant medications **reported in ≥10% of patients** (Safety set) were:

"Beta blocking agents, selective" (Total: 126/546 (23.1%) patients; INTP18 vs. Lucentis: 56/273 (20.5%) vs. 70 (25.6%) patients)

"HMG-CoA-reductase inhibitors" (Total: 123/546 (22.5%); INTP18 vs. Lucentis: 61/273 (22.3%) vs. 62/273 (22.7%) patients)

"Dihydropyridine derivatives" (Total: 115/546 (21.1%) patients; INTP18 vs. Lucentis: 46/273 (16.8%) vs. 69/273 (25.3%) patients)

"Angiotensin II antagonists, plain" (Total: 99/546 (18.1%) patients; INTP18 vs. Lucentis: 41/273 (15.0%) vs. 58/273 (21.2%) patients)

"Biguanides" (Total: 87/546 (15.9%) patients; INTP18 vs. Lucentis: 48/273 (17.6%) vs. 39/273 (14.3%) patients)

"Fluoroquinolones" (Total: 78/546 (14.3%) patients; INTP18 vs. Lucentis: 35/273 (12.8%) vs. 43/273 (15.8%) patients)

"Platelet aggregation inhibitors excl. heparin" (Total: 76/546 (13.9%) patients; INTP18 vs. Lucentis: 33/273 (12.1%) vs. 43/273 (15.8%) patients)

"Proton pump inhibitors" (Total: 68/546 (12.5%) patients; INTP18 vs. Lucentis: 32/273 (11.7%) vs. 36/273 (13.2%) patients)

Prohibited medication

*Table 11: Prohibited medication*

| Treatment | Medication Name | Dose per administration | Medication given for | Indication code |
|---|---|---|---|---|
| Lucentis | Bevacizumab | 1.25 mL | Non-Study Eye | Medical Condition |
| INTP18 | Betagen[1] | 24 mg | Other than eye | Medical Condition |
| Lucentis | Dexaven[2] | 4 mg | Other than eye | Adverse Event |
| Lucentis | Dexaven[2] | 8 mg | Other than eye | Adverse Event |
| Lucentis | Solu-Medrol[3] | 40 mg | Other than eye | Adverse Event |
| INTP18 | Prednisonum | 5 mg | Other than eye | Medical Condition |
| INTP18 | Bevacizumab | 1.25 mg | Study eye | Adverse Event |
| Lucentis | Avastin[4] | 0.05 mL | Non-Study Eye | Medical Condition |
| INTP18 | Hydrocortisonum | 10 mg | Other than eye | Medical Condition |

Source: Table has been provided with D120 responses by the applicant and has been modified by the Assessor.

[1] i.e., betamethasone dipropionate in combination with gentamicin sulfate

[2] i.e., dexamethasone sodium phosphate

[3] i.e., methylprednisolone sodium succinate

[4] i.e., bevacizumab

**Outcomes and estimation**

**Primary efficacy analysis**

Primary Efficacy Endpoint - Mean Change in BCVA from Baseline to Week 8

*Table 12: Analysis of mean change in BCVA from baseline to week 8 (ANCOVA)*

| **PP set (N=525)** | | | | | | |
|---|---|---|---|---|---|---|
| **Treatments** | **n** | **LS Mean** | **SE** | **Intas Ranibizumab Vs. Lucentis** | | |
| | | | | **LS Mean Difference** | **Confidence Interval** | |
| Intas Ranibizumab (N=260) | 260 | 7.0 | 0.49 | -0.7 | 90% CI | -1.8, 0.4 |
| Lucentis (N=265) | 265 | 7.7 | 0.48 | | 95% CI | -2.0, 0.6 |
| | | | | | | |
| **mITT set (N=542)** | | | | | | |
| **Treatments** | **n** | **LS Mean** | **SE** | **Intas Ranibizumab Vs. Lucentis** | | |

| | | | | **LS Mean Difference** | **Confidence Interval** | |
|---|---|---|---|---|---|---|
| Intas Ranibizumab (N=271) | 260 | 7.0 | 0.49 | -0.7 | 90% CI | -1.8, 0.4 |
| Lucentis (N=271) | 265 | 7.7 | 0.48 | | 95% CI | -2.0, 0.6 |
| | | | | | | |
| **ITT set (N=546)** | | | | | | |
| **Treatments** | **n** | **LS Mean** | **SE** | **Intas Ranibizumab Vs. Lucentis** | | |
| | | | | **LS Mean Difference** | **Confidence Interval** | |
| Intas Ranibizumab (N=273) | 260 | 7.0 | 0.49 | -0.7 | 90% CI | -1.8, 0.4 |
| Lucentis (N=273) | 265 | 7.7 | 0.48 | | 95% CI | -2.0, 0.6 |

Note 1: N = Number of patients in respective treatment and analysis set, n = Number of patients in respective categories.
Note 2: Change from baseline (CFB) = Post-baseline – Baseline
Note 3: 90% and 95% CI has been calculated by an Analysis of Covariance (ANCOVA) model.
Note 4: Baseline is defined as visit 2/week 0.

**Sensitivity Analyses of the Primary Endpoint**

To confirm robustness of the primary analyses, sensitivity analyses were performed:

*Table 13: Analysis of mean change in BCVA from baseline to week 8 using an ANCOVA with multiple imputation and Rubin's rules (mITT)*

| **mITT set (N=542)** | | | | | | |
|---|---|---|---|---|---|---|
| **Treatments** | **n** | **LS Mean** | **SE** | **Intas Ranibizumab Vs. Lucentis** | | |
| | | | | **LS Mean Difference** | **Confidence Interval** | |
| Intas Ranibizumab (N=271) | 260 | 6.7 | 0.51 | -0.8 | 90% CI | -1.8, 0.3 |
| Lucentis (N=271) | 265 | 7.5 | 0.41 | | 95% CI | -2.0, 0.5 |

Note 1: N = Number of patients in respective treatment and analysis set, n = Number of patients in respective categories.

Note 2: Change from baseline (CFB) = Post-baseline – Baseline

Note 3: 90% and 95% CI has been calculated by an Analysis of Covariance (ANCOVA) model.

Note 4: Baseline is defined as visit 2/week 0.

*Table 14:* Mean change from baseline to week 8 BCVA score (MMRM, tipping point analysis) part 1

| Penalty | Intas Ranibizumab (N=271) | | | Lucentis (N=271) | | | Point Estimate (Difference) | 95% Confidence Interval |
|---|---|---|---|---|---|---|---|---|
| | n | LS Mean | SE | n | LS Mean | SE | | |
| 0 | 260 | 6.7 | 0.50 | 265 | 7.5 | 0.41 | -0.7 | [-2.0, 0.5] |
| 10 | 260 | 7.4 | 0.55 | 265 | 7.5 | 0.41 | -0.1 | [-1.4, 1.2] |
| 20 | 260 | 7.7 | 0.60 | 265 | 7.5 | 0.41 | 0.3 | [-1.1, 1.7] |
| 50 | 260 | 8.2 | 0.66 | 265 | 7.5 | 0.41 | 0.7 | [-0.8, 2.2] |
| | | | | | | | | |
| 58 | 260 | 9.1 | 0.85 | 265 | 7.5 | 0.41 | 1.6 | [-0.3, 3.4] |
| Penalty | Intas Ranibizumab (N=271) | | | Lucentis (N=271) | | | Point Estimate (Difference) | 95% Confidence Interval |
| | n | LS Mean | SE | n | LS Mean | SE | | |
| 59 | 260 | 9.1 | 0.85 | 265 | 7.5 | 0.41 | 1.6 | [-0.2, 3.5] |

Note 1: N = Number of patients in respective treatment and analysis set, n = Number of patients in respective categories.

Note 2: Change from baseline (CFB) = Post-baseline – Baseline

Note 3: Baseline is defined as visit 2/week 0.

Note 4: Limit of imputed data for BCVA is set to 0 to 120 for MMRM Tipping point using 10 imputations.

*Table 15:* Mean change from baseline to week 8 BCVA score (MMRM, tipping point analysis) part 2

| Penalty | Intas Ranibizumab (N=271) | | | Lucentis (N=271) | | | Point Estimate (Difference) | 95% Confidence Interval |
|---|---|---|---|---|---|---|---|---|
| | n | LS Mean | SE | n | LS Mean | SE | | |
| 0 | 260 | 6.7 | 0.50 | 265 | 7.5 | 0.41 | -0.7 | [-2.0, 0.5] |
| -5 | 260 | 6.4 | 0.52 | 265 | 7.5 | 0.41 | -1.1 | [-2.4, 0.2] |
| -10 | 260 | 6.0 | 0.56 | 265 | 7.5 | 0.41 | -1.4 | [-2.8, -0.1] |
| -15 | 260 | 5.7 | 0.61 | 265 | 7.5 | 0.41 | -1.7 | [-3.2, -0.3] |
| -18 | 260 | 5.6 | 0.64 | 265 | 7.5 | 0.41 | -1.9 | [-3.4, -0.4] |
| -20 | 260 | 5.5 | 0.67 | 265 | 7.5 | 0.41 | -2.0 | [-3.5, -0.5] |

Note 1: N = Number of patients in respective treatment and analysis set, n = Number of patients in respective categories.

Note 2: Change from baseline (CFB) = Post-baseline – Baseline

Note 3: Baseline is defined as visit 2/week 0.

Note 4: Limit of imputed data for BCVA is set to 0 to 120 for MMRM Tipping point using 10 imputations.

Source: D180 responses, clinical – response to Q10

**Secondary Efficacy Endpoints**

Mean change from baseline in BCVA in the study eye up to 24 weeks using the ETDRS protocol

*Table 16: Change in BCVA in the study eye from baseline using the ETDRS protocol (PP set)*

| Visit / Week | Statistics | Intas Ranibizumab (N=260) | Lucentis (N=265) | p-value (between) |
|---|---|---|---|---|
| Visit 3/ Week 1 | n | 257 | 257 | |
| | Mean (SD) | 3.1 (5.23) | 3.2 (4.92) | |
| | Median | 2.0 | 2.0 | |
| | Q1, Q3 | 0.0, 5.0 | 0.0, 5.0 | |
| | Min, Max | -17.0, 28.0 | -8.0, 24.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.8895 |
| Visit 4/ Week 2 | n | 256 | 259 | |
| | Mean (SD) | 4.1 (5.97) | 4.4 (5.36) | |
| | Median | 3.0 | 3.0 | |
| | Q1, Q3 | 0.0, 7.0 | 0.0, 7.0 | |
| | Min, Max | -22.0, 39.0 | -6.0, 26.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.5375 |
| Visit 5/ Week 4 | n | 257 | 264 | |
| | Mean (SD) | 5.2 (6.98) | 5.8 (5.93) | |
| | Median | 4.0 | 5.0 | |
| | Q1, Q3 | 1.0, 10.0 | 1.0, 10.0 | |
| | Min, Max | -27.0, 39.0 | -7.0, 25.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.2797 |
| Visit 6/ Week 8 | n | 260 | 265 | |
| | Mean (SD) | 6.8 (8.35) | 7.5 (6.64) | |
| | Median | 5.5 | 6.0 | |
| | Q1, Q3 | 1.0, 12.0 | 3.0, 12.0 | |
| | Min, Max | -27.0, 45.0 | -7.0, 38.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.2836 |
| Visit 7/ Week 12 | n | 253 | 258 | |
| | Mean (SD) | 7.7 (8.56) | 8.0 (7.44) | |
| | Median | 7.0 | 7.0 | |
| | Q1, Q3 | 2.0, 13.0 | 3.0, 13.0 | |
| | Min, Max | -26.0, 46.0 | -13.0, 45.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.7081 |
| Visit 8/ Week 16 | n | 250 | 254 | |
| | Mean (SD) | 8.4 (8.73) | 8.9 (8.04) | |
| | Median | 7.5 | 8.0 | |
| | Q1, Q3 | 2.0, 14.0 | 4.0, 14.0 | |
| | Min, Max | -25.0, 49.0 | -17.0, 45.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.5405 |

| | | | | |
|---|---|---|---|---|
| Visit 9/ Week 20 | n | 241 | 250 | |
| | Mean (SD) | 8.9 (9.05) | 9.2 (8.75) | |
| | Median | 8.0 | 9.0 | |
| | Q1, Q3 | 3.0, 14.0 | 4.0, 15.0 | |
| | Min, Max | -21.0, 48.0 | -20.0, 45.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.6465 |
| Visit 10/ Week 24 | n | 243 | 243 | |
| | Mean (SD) | 9.5 (8.87) | 10.0 (9.43) | |
| | Median | 9.0 | 10.0 | |
| | Q1, Q3 | 5.0, 15.0 | 4.0, 15.0 | |
| | Min, Max | -19.0, 50.0 | -17.0, 47.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.5456 |
| Visit 11/ Week 28 | n | 241 | 242 | |
| | Mean (SD) | 10.0 (9.38) | 10.4 (9.52) | |
| | Median | 9.0 | 10.0 | |
| | Q1, Q3 | 5.0, 15.0 | 4.0, 15.0 | |
| | Min, Max | -22.0, 50.0 | -17.0, 47.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.6107 |
| Visit 12/ Week 32 | n | 237 | 241 | |
| | Mean (SD) | 10.1 (9.54) | 10.8 (9.62) | |
| | Median | 9.0 | 10.0 | |
| | Q1, Q3 | 4.0, 16.0 | 5.0, 16.0 | |
| | Min, Max | -18.0, 48.0 | -26.0, 47.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.4794 |
| Visit 13/ Week 36 | n | 237 | 239 | |
| | Mean (SD) | 10.3 (9.73) | 11.1 (9.96) | |
| | Median | 10.0 | 11.0 | |
| | Q1, Q3 | 5.0, 15.0 | 5.0, 17.0 | |
| | Min, Max | -22.0, 48.0 | -21.0, 47.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.4037 |
| Visit 14/ Week 40 | n | 234 | 229 | |
| | Mean (SD) | 10.5 (10.06) | 11.0 (10.33) | |
| | Median | 10.0 | 11.0 | |
| | Q1, Q3 | 4.0, 16.0 | 5.0, 17.0 | |
| | Min, Max | -16.0, 44.0 | -25.0, 47.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.5572 |

| | | | | |
|---|---|---|---|---|
| Visit 15/ Week 44 | n | 227 | 227 | |
| | Mean (SD) | 11.3 (9.98) | 11.9 (10.48) | |
| | Median | 11.0 | 12.0 | |
| | Q1, Q3 | 5.0, 16.0 | 5.0, 17.0 | |
| | Min, Max | -17.0, 41.0 | -25.0, 52.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.5698 |
| Visit 16/ Week 48 | n | 226 | 223 | |
| | Mean (SD) | 11.2 (10.61) | 11.9 (10.88) | |
| | Median | 11.0 | 11.0 | |
| | Q1, Q3 | 4.0, 16.0 | 6.0, 18.0 | |
| | Min, Max | -19.0, 45.0 | -41.0, 52.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.4672 |
| Visit 17 (EOS)/ Week 52 | n | 233 | 227 | |
| | Mean (SD) | 11.6 (10.99) | 12.1 (11.38) | |
| | Median | 11.0 | 11.0 | |
| | Q1, Q3 | 5.0, 17.0 | 6.0, 18.0 | |
| | Min, Max | -18.0, 48.0 | -42.0, 52.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.6324 |

Note 1: n = Number of patients in respective categories.
Note 2: N = Number of patients in respective treatments.
Note 3: p-value (between) has been calculated using independent t-test between two treatments.
Note 4: p-value (within) has been calculated using paired t-test for the comparison of each visit to baseline visit.
Note 5: Change from baseline (CFB) =Post baseline - Baseline.
Note 6: Baseline is defined as visit 2 / Week 0.
Reference listing: 16.2.6.1

Source: Final Clinical Study Report, Section 14.2.2 Secondary Efficacy Data

Furthermore, descriptive statistics for BCVA values in the study eye from baseline up to Week 24 have been provided:

INTP18 *versus* Lucentis (PP Set) – **Baseline/Week 0**: 55.1 (±12.37) vs. 55.0 (±11.37) letters; **Week 1**: 58.1 (±13.22) vs. 58.0 (±12.35) letters; **Week 2**: 59.2 (±13.63) vs. 59.3 (±12.92) letters; **Week 4**: 60.2 (±13.97) vs. 60.7 (±13.00) letters; **Week 8**: 61.9 (±14.38) vs. 62.4 (±13.34) letters; **Week 12**: 62.8 (±14.22) vs. 63.0 (±13.48) letters; **Week 16**: 63.6 (±14.02) vs. 64.2 (±13.64) letters; **Week 20**: 64.1 (±14.40) vs. 64.6 (±13.70) letters; **Week 24**: 65.1 (±13.67) vs. 65.3 (±13.59) letters; **Week 28**: 65.7 (±13.52) vs. 65.5 (±13.72) letters; **Week 32**: 65.6 (±14.03) vs. 66.3 (±13.97) letters; **Week 36**: 65.8 (±14.10) vs. 66.6 (±14.06) letters; **Week 40**: 66.1 (±13.65) vs. 66.6 (±14.21) letters; **Week 44**: 66.7 (±13.32) vs. 67.5 (±13.78) letters; **Week 48**: 66.6 (±14.01) vs. 67.4 (±14.14) letters; **Week 52 (EoS)**: 67.0 (±14.10) vs. 67.4 (±14.61) letters.

Comparable outcomes have been shown for the mITT population.

Proportion of subjects who gained ≥5, ≥10 and ≥15 letters in the study eye using ETDRS protocol up to 52 weeks

*Table 17: Proportion of subjects who gained ⩾5, ⩾10 and ⩾15 letters in the study eye using ETDRS protocol (PP set)*

| Visit / Week | Statistics | Gained letters | Intas Ranibizumab (N=260) | Lucentis (N=265) | p-value |
|---|---|---|---|---|---|
| Visit 3/ Week 1 | n (%) | ≥5 | 78 (30.0) | 68 (25.7) | 0.2672 |
| | n (%) | ≥10 | 31 (11.9) | 35 (13.2) | 0.6572 |
| | n (%) | ≥15 | 13 (5.0) | 9 (3.4) | 0.3592 |
| Visit 4/ Week 2 | n (%) | ≥5 | 102 (39.2) | 94 (35.5) | 0.3733 |
| | n (%) | ≥10 | 38 (14.6) | 44 (16.6) | 0.5304 |
| | n (%) | ≥15 | 16 (6.2) | 15 (5.7) | 0.8105 |
| Visit 5/ Week 4 | n (%) | ≥5 | 127 (48.8) | 141 (53.2) | 0.3176 |
| | n (%) | ≥10 | 66 (25.4) | 70 (26.4) | 0.7876 |
| | n (%) | ≥15 | 23 (8.8) | 25 (9.4) | 0.8153 |
| Visit 6/ Week 8 | n (%) | ≥5 | 146 (56.2) | 167 (63.0) | 0.1090 |
| | n (%) | ≥10 | 93 (35.8) | 94 (35.5) | 0.9433 |
| | n (%) | ≥15 | 32 (12.3) | 39 (14.7) | 0.4196 |
| Visit 7/ Week 12 | n (%) | ≥5 | 159 (61.2) | 167 (63.0) | 0.6597 |
| | n (%) | ≥10 | 99 (38.1) | 96 (36.2) | 0.6609 |
| | n (%) | ≥15 | 45 (17.3) | 51 (19.2) | 0.5658 |
| Visit 8/ Week 16 | n (%) | ≥5 | 161 (61.9) | 182 (68.7) | 0.1039 |
| | n (%) | ≥10 | 103 (39.6) | 105 (39.6) | 0.9986 |
| | n (%) | ≥15 | 50 (19.2) | 59 (22.3) | 0.3916 |
| Visit 9/ Week 20 | n (%) | ≥5 | 166 (63.8) | 174 (65.7) | 0.6635 |
| | n (%) | ≥10 | 103 (39.6) | 114 (43.0) | 0.4285 |
| | n (%) | ≥15 | 58 (22.3) | 66 (24.9) | 0.4835 |
| Visit 10/ Week 24 | n (%) | ≥5 | 183 (70.4) | 175 (66.0) | 0.2850 |
| | n (%) | ≥10 | 111 (42.7) | 123 (46.4) | 0.3909 |
| | n (%) | ≥15 | 64 (24.6) | 70 (26.4) | 0.6363 |
| Visit 11/ Week 28 | n (%) | ≥5 | 183 (70.4) | 179 (67.5) | 0.4823 |
| | n (%) | ≥10 | 116 (44.6) | 130 (49.1) | 0.3079 |
| | n (%) | ≥15 | 64 (24.6) | 79 (29.8) | 0.1812 |
| Visit 12/ Week 32 | n (%) | ≥5 | 177 (68.1) | 184 (69.4) | 0.7373 |
| | n (%) | ≥10 | 117 (45.0) | 132 (49.8) | 0.2697 |
| | n (%) | ≥15 | 70 (26.9) | 82 (30.9) | 0.3099 |
| Visit 13/ Week 36 | n (%) | ≥5 | 183 (70.4) | 181 (68.3) | 0.6049 |
| | n (%) | ≥10 | 122 (46.9) | 136 (51.3) | 0.3136 |
| | n (%) | ≥15 | 69 (26.5) | 82 (30.9) | 0.2649 |
| Visit 14/ Week 40 | n (%) | ≥5 | 174 (66.9) | 174 (65.7) | 0.7596 |
| | n (%) | ≥10 | 123 (47.3) | 130 (49.1) | 0.6884 |
| | n (%) | ≥15 | 76 (29.2) | 74 (27.9) | 0.7405 |

| | | | | | |
|---|---|---|---|---|---|
| Visit 15/ Week 44 | n (%) | ≥5 | 177 (68.1) | 176 (66.4) | 0.6850 |
| | n (%) | ≥10 | 122 (46.9) | 137 (51.7) | 0.2739 |
| | n (%) | ≥15 | 76 (29.2) | 87 (32.8) | 0.3728 |
| Visit 16/ Week 48 | n (%) | ≥5 | 169 (65.0) | 177 (66.8) | 0.6649 |
| | n (%) | ≥10 | 123 (47.3) | 132 (49.8) | 0.5661 |
| | n (%) | ≥15 | 80 (30.8) | 83 (31.3) | 0.8914 |
| Visit 17 (EOS)/ Week 52 | n (%) | ≥5 | 177 (68.1) | 179 (67.5) | 0.8966 |
| | n (%) | ≥10 | 124 (47.7) | 133 (50.2) | 0.5673 |
| | n (%) | ≥15 | 90 (34.6) | 95 (35.8) | 0.7673 |

Note 1: n = Number of patients in respective categories.
Note 2: N = Number of patients in respective treatments.
Note 3: p-value is calculated based on a chi-square test.
Note 4: If any cell has expected counts less than 5, then the Fisher's exact test is used instead.
Note 5: Change from baseline (CFB) =Post baseline - Baseline.
Note 6: Baseline is defined as visit 2 / Week 0.
Note 7: Percentages are based on total number of patients in each treatment.
Reference listing: 16.2.6.1

Source: Final Clinical Study Report, Section 14.2.2 Secondary Efficacy Data

Comparable outcomes have been shown for the mITT population.

Proportion of subjects who lost ≥5, ≥10 and ≥15 letters in the study eye using ETDRS protocol up to 52 weeks

*Table 18: Proportion of subjects who lost ⩾5, ⩾10 and ⩾15 letters in the study eye using ETDRS protocol (PP set)*

| Visit / Week | Statistics | Lost letters | Intas Ranibizumab (N=260) | Lucentis (N=265) | p-value |
|---|---|---|---|---|---|
| Visit 3/ Week 1 | n (%) | ≥5 | 8 (3.1) | 4 (1.5) | 0.2573 |
| | n (%) | ≥10 | 2 (0.8) | 0 (0.0) | - |
| | n (%) | ≥15 | 1 (0.4) | 0 (0.0) | - |
| Visit 4/ Week 2 | n (%) | ≥5 | 5 (1.9) | 3 (1.1) | 0.5008 |
| | n (%) | ≥10 | 2 (0.8) | 0 (0.0) | - |
| | n (%) | ≥15 | 1 (0.4) | 0 (0.0) | - |
| Visit 5/ Week 4 | n (%) | ≥5 | 11 (4.2) | 4 (1.5) | 0.0704 |
| | n (%) | ≥10 | 3 (1.2) | 0 (0.0) | - |
| | n (%) | ≥15 | 2 (0.8) | 0 (0.0) | - |
| Visit 6/ Week 8 | n (%) | ≥5 | 9 (3.5) | 2 (0.8) | 0.0351 |
| | n (%) | ≥10 | 5 (1.9) | 0 (0.0) | - |
| | n (%) | ≥15 | 3 (1.2) | 0 (0.0) | - |
| Visit 7/ Week 12 | n (%) | ≥5 | 11 (4.2) | 4 (1.5) | 0.0704 |
| | n (%) | ≥10 | 5 (1.9) | 1 (0.4) | 0.1197 |
| | n (%) | ≥15 | 2 (0.8) | 0 (0.0) | - |
| Visit 8/ Week 16 | n (%) | ≥5 | 9 (3.5) | 8 (3.0) | 0.7745 |
| | n (%) | ≥10 | 4 (1.5) | 3 (1.1) | 0.7224 |
| | n (%) | ≥15 | 1 (0.4) | 1 (0.4) | 1.0000 |
| Visit 9/ Week 20 | n (%) | ≥5 | 15 (5.8) | 10 (3.8) | 0.2830 |
| | n (%) | ≥10 | 6 (2.3) | 5 (1.9) | 0.7364 |
| | n (%) | ≥15 | 1 (0.4) | 2 (0.8) | 1.0000 |
| Visit 10/ Week 24 | n (%) | ≥5 | 8 (3.1) | 10 (3.8) | 0.6609 |
| | n (%) | ≥10 | 3 (1.2) | 2 (0.8) | 0.6834 |
| | n (%) | ≥15 | 2 (0.8) | 2 (0.8) | 1.0000 |
| Visit 11/ Week 28 | n (%) | ≥5 | 9 (3.5) | 10 (3.8) | 0.8482 |
| | n (%) | ≥10 | 5 (1.9) | 3 (1.1) | 0.5008 |
| | n (%) | ≥15 | 2 (0.8) | 2 (0.8) | 1.0000 |
| Visit 12/ Week 32 | n (%) | ≥5 | 9 (3.5) | 10 (3.8) | 0.8482 |
| | n (%) | ≥10 | 5 (1.9) | 5 (1.9) | 0.9757 |
| | n (%) | ≥15 | 3 (1.2) | 4 (1.5) | 1.0000 |
| Visit 13/ Week 36 | n (%) | ≥5 | 11 (4.2) | 13 (4.9) | 0.7113 |
| | n (%) | ≥10 | 6 (2.3) | 4 (1.5) | 0.5414 |
| | n (%) | ≥15 | 4 (1.5) | 3 (1.1) | 0.7224 |
| Visit 14/ Week 40 | n (%) | ≥5 | 12 (4.6) | 10 (3.8) | 0.6303 |
| | n (%) | ≥10 | 7 (2.7) | 7 (2.6) | 0.9712 |
| | n (%) | ≥15 | 3 (1.2) | 5 (1.9) | 0.7246 |

| | | | | | |
|---|---|---|---|---|---|
| Visit 15/ Week 44 | n (%) | ≥5 | 8 (3.1) | 9 (3.4) | 0.8363 |
| | n (%) | ≥10 | 7 (2.7) | 5 (1.9) | 0.5369 |
| | n (%) | ≥15 | 4 (1.5) | 5 (1.9) | 1.0000 |
| Visit 16/ Week 48 | n (%) | ≥5 | 11 (4.2) | 11 (4.2) | 0.9636 |
| | n (%) | ≥10 | 7 (2.7) | 6 (2.3) | 0.7523 |
| | n (%) | ≥15 | 5 (1.9) | 4 (1.5) | 0.7497 |
| Visit 17 (EOS)/ Week 52 | n (%) | ≥5 | 12 (4.6) | 11 (4.2) | 0.7949 |
| | n (%) | ≥10 | 7 (2.7) | 7 (2.6) | 0.9712 |
| | n (%) | ≥15 | 4 (1.5) | 5 (1.9) | 1.0000 |

Note 1: n = Number of patients in respective categories.
Note 2: N = Number of patients in respective treatments.
Note 3: p-value is calculated based on a chi-square test.
Note 4: If any cell has expected counts less than 5, then the Fisher's exact test is used instead.
Note 5: Change from baseline (CFB) =Post baseline - Baseline.
Note 6: Baseline is defined as visit 2 / Week 0.
Note 7: Percentages are based on total number of patients in each treatment.
Reference listing: 16.2.6.1

Source: Final Clinical Study Report, Section 14.2.2 Secondary Efficacy Data

Comparable outcomes have been shown for the mITT population.

Mean change from baseline in the **total area of leakage from CNV** measured by fluorescein angiography (FA) at Weeks 8 and 52

*Table 19: Change in total area of leakage from CNV ($mm^2$) measured by fluorescein angiography (FA) (PP set)*

| Visit / Week | Statistics | Intas Ranibizumab (N=260) | Lucentis (N=265) | p-value (between) |
|---|---|---|---|---|
| Visit 6/ Week 8 | n | 199 | 199 | |
| | Mean (SD) | 0.05 (2.042) | 0.13 (2.069) | |
| | Median | -0.03 | -0.06 | |
| | Q1, Q3 | -0.65, 0.73 | -0.83, 0.75 | |
| | Min, Max | -7.99, 7.72 | -5.79, 8.31 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.6883 |
| Visit 7/ Week 12 | n | - | 1 | |
| | Mean (SD) | - | 0.99 (0.000) | |
| | Median | - | 0.99 | |
| | Q1, Q3 | - | 0.99, 0.99 | |
| | Min, Max | - | 0.99, 0.99 | |
| | p-value (within) | - | - | - |
| Visit 10/ Week 24 | n | 144 | 132 | |
| | Mean (SD) | -0.08 (2.153) | 0.05 (2.628) | |
| | Median | -0.10 | -0.11 | |
| | Q1, Q3 | -0.80, 0.63 | -0.89, 0.87 | |
| | Min, Max | -7.27, 10.56 | -6.39, 18.77 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.6510 |
| Visit 11/ Week 28 | n | - | 2 | |
| | Mean (SD) | - | 0.44 (0.417) | |
| | Median | - | 0.44 | |
| | Q1, Q3 | - | 0.15, 0.74 | |
| | Min, Max | - | 0.15, 0.74 | |
| | p-value (within) | . | 0.4695 | - |
| Visit 17 (EOS)/ Week 52 | n | 67 | 53 | |
| | Mean (SD) | 0.02 (2.093) | 0.94 (4.095) | |
| | Median | -0.06 | 0.27 | |
| | Q1, Q3 | -0.79, 0.93 | -0.82, 1.55 | |
| | Min, Max | -5.87, 10.60 | -5.25, 25.27 | |
| | p-value (within) | <0.0001 | 0.0594 | 0.1149 |

Note 1: n = Number of patients in respective categories.
Note 2: N = Number of patients in respective treatments.
Note 3: p-value (between) has been calculated using independent t-test between two treatments.
Note 4: p-value (within) has been calculated using paired t-test for the comparison of each visit to baseline visit.
Note 5: Change from baseline (CFB) =Post baseline - Baseline(Screening Visit (Day -21 to 0)).
Reference listing: 16.2.6.2

Source: Final Clinical Study Report, Section 14.2.2 Secondary Efficacy Data

*Table 20: Total area of leakage from CNV ($mm^2$) measured by fluorescein angiography (FA) (PP set)*

| Visit / Week | Statistics | Intas Ranibizumab (N=260) | Lucentis (N=265) |
|---|---|---|---|
| Screening Visit (Day -21 to 0) | n | 252 | 260 |
| | Mean (SD) | 2.18 (2.057) | 2.28 (1.970) |
| | Median | 1.42 | 1.68 |
| | Q1, Q3 | 0.76, 2.91 | 0.76, 3.34 |
| | Min, Max | 0.06, 10.19 | 0.01, 9.41 |
| Visit 6/ Week 8 | n | 205 | 203 |
| | Mean (SD) | 2.27 (2.325) | 2.41 (2.312) |
| | Median | 1.54 | 1.56 |
| | Q1, Q3 | 0.65, 2.80 | 0.66, 3.64 |
| | Min, Max | 0.02, 14.33 | 0.04, 10.29 |
| Visit 7/ Week 12 | n | - | 1 |
| | Mean (SD) | - | 1.49 (0.000) |
| | Median | - | 1.49 |
| | Q1, Q3 | - | 1.49, 1.49 |
| | Min, Max | - | 1.49, 1.49 |
| Visit 10/ Week 24 | n | 147 | 135 |
| | Mean (SD) | 2.20 (2.436) | 2.51 (2.761) |
| | Median | 1.37 | 1.80 |
| | Q1, Q3 | 0.60, 2.78 | 0.64, 3.06 |
| | Min, Max | 0.01, 12.84 | 0.07, 20.91 |
| Visit 11/ Week 28 | n | - | 2 |
| | Mean (SD) | - | 4.06 (4.900) |
| | Median | - | 4.06 |
| | Q1, Q3 | - | 0.59, 7.52 |
| | Min, Max | - | 0.59, 7.52 |
| Visit 17 (EOS)/ Week 52 | n | 67 | 54 |
| | Mean (SD) | 2.28 (2.512) | 3.12 (4.190) |
| | Median | 1.30 | 1.70 |
| | Q1, Q3 | 0.54, 3.15 | 1.09, 3.65 |
| | Min, Max | 0.04, 12.88 | 0.23, 27.41 |

Note 1: n = Number of patients in respective categories.
Note 2: N = Number of patients in respective treatments.
Reference listing: 16.2.6.2

Source: Final Clinical Study Report, Section 14.2.2 Secondary Efficacy Data

Comparable outcomes have been shown for the mITT population.

Mean change from baseline in **total area of CNV** measured by FA at Weeks 8 and 52 in the study eye

*Table 21: Change in total area of CNV ($mm^2$) measured by fluorescein angiography (FA) (PP set)*

| Visit / Week | Statistics | Intas Ranibizumab (N=260) | Lucentis (N=265) | p-value (between) |
|---|---|---|---|---|
| Visit 6/ Week 8 | n | 206 | 209 | |
| | Mean (SD) | -2.22 (2.368) | -2.44 (2.711) | |
| | Median | -1.72 | -2.24 | |
| | Q1, Q3 | -3.21, -0.72 | -3.54, -0.75 | |
| | Min, Max | -10.09, 4.37 | -14.06, 7.55 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.3756 |
| Visit 7/ Week 12 | n | - | 1 | |
| | Mean (SD) | - | 0.52 (0.000) | |
| | Median | - | 0.52 | |
| | Q1, Q3 | - | 0.52, 0.52 | |
| | Min, Max | - | 0.52, 0.52 | |
| | p-value (within) | - | - | - |
| Visit 10/ Week 24 | n | 152 | 142 | |
| | Mean (SD) | -2.93 (2.952) | -3.00 (3.229) | |
| | Median | -2.01 | -2.72 | |
| | Q1, Q3 | -3.93, -0.91 | -4.46, -0.98 | |
| | Min, Max | -15.41, 2.60 | -14.70, 7.17 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.8342 |
| Visit 11/ Week 28 | n | - | 2 | |
| | Mean (SD) | - | -2.09 (2.666) | |
| | Median | - | -2.09 | |
| | Q1, Q3 | - | -3.97, -0.20 | |
| | Min, Max | - | -3.97, -0.20 | |
| | p-value (within) | . | 0.4542 | - |
| Visit 17 (EOS)/ Week 52 | n | 72 | 59 | |
| | Mean (SD) | -2.80 (2.907) | -1.95 (3.006) | |
| | Median | -2.32 | -1.79 | |
| | Q1, Q3 | -3.81, -0.68 | -3.19, -0.51 | |
| | Min, Max | -12.67, 2.14 | -13.08, 6.63 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.1036 |

Note 1: n = Number of patients in respective categories.
Note 2: N = Number of patients in respective treatments.
Note 3: p-value (between) has been calculated using independent t-test between two treatments.
Note 4: p-value (within) has been calculated using paired t-test for the comparison of each visit to baseline visit.
Note 5: Change from baseline (CFB) =Post baseline - Baseline(Screening Visit (Day -21 to 0)).
Reference listing: 16.2.6.2

Source: Final Clinical Study Report, Section 14.2.2 Secondary Efficacy Data

*Table 22: Total area of CNV ($mm^2$) measured by fluorescein angiography (FA) (PP set)*

| Visit / Week | Statistics | Intas Ranibizumab (N=260) | Lucentis (N=265) |
|---|---|---|---|
| Screening Visit (Day -21 to 0) | n | 258 | 265 |
| | Mean (SD) | 5.18 (4.051) | 5.48 (3.915) |
| | Median | 4.14 | 4.77 |
| | Q1, Q3 | 2.01, 7.18 | 2.39, 7.78 |
| | Min, Max | 0.11, 19.83 | 0.17, 25.79 |
| Visit 6/ Week 8 | n | 207 | 209 |
| | Mean (SD) | 2.94 (3.004) | 2.99 (2.930) |
| | Median | 1.89 | 1.95 |
| | Q1, Q3 | 0.74, 4.19 | 0.85, 4.33 |
| | Min, Max | 0.00, 17.24 | 0.00, 15.41 |
| Visit 7/ Week 12 | n | - | 1 |
| | Mean (SD) | - | 6.85 (0.000) |
| | Median | - | 6.85 |
| | Q1, Q3 | - | 6.85, 6.85 |
| | Min, Max | - | 6.85, 6.85 |
| Visit 10/ Week 24 | n | 152 | 142 |
| | Mean (SD) | 2.66 (2.671) | 2.83 (2.816) |
| | Median | 1.66 | 1.92 |
| | Q1, Q3 | 0.79, 3.80 | 0.78, 3.86 |
| | Min, Max | 0.00, 13.70 | 0.08, 15.25 |
| Visit 11/ Week 28 | n | - | 2 |
| | Mean (SD) | - | 2.68 (3.048) |
| | Median | - | 2.68 |
| | Q1, Q3 | - | 0.52, 4.83 |
| | Min, Max | - | 0.52, 4.83 |
| Visit 17 (EOS)/ Week 52 | n | 72 | 59 |
| | Mean (SD) | 3.35 (3.344) | 3.48 (3.020) |
| | Median | 2.31 | 2.64 |
| | Q1, Q3 | 1.04, 4.70 | 1.21, 4.77 |
| | Min, Max | 0.03, 13.82 | 0.21, 15.17 |

Note 1: n = Number of patients in respective categories.
Note 2: N = Number of patients in respective treatments.
Reference listing: 16.2.6.2

Source: Final Clinical Study Report, Section 14.2.2 Secondary Efficacy Data

Comparable outcomes have been shown for the mITT population.

Mean change from baseline in **central retinal thickness** (FCP retinal thickness and FCS retinal thickness) in the study eye measured by SD-OCT up to 24 weeks

*Table 23: Change in central retinal thickness (FCP) in the study eye measured by SD-OCT (PP set)*

| Visit / Week | Statistics | Intas Ranibizumab (N=260) | Lucentis (N=265) | p-value (between) |
|---|---|---|---|---|
| Visit 3/ Week 1 | n | 252 | 254 | |
| | Mean (SD) | -101.4 (123.48) | -91.8 (98.22) | |
| | Median | -70.0 | -69.0 | |
| | Q1, Q3 | -140.0, -25.0 | -134.0, -29.0 | |
| | Min, Max | -585.0, 159.0 | -565.0, 273.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.3341 |
| Visit 4/ Week 2 | n | 2 | - | |
| | Mean (SD) | -311.0 (216.37) | - | |
| | Median | -311.0 | - | |
| | Q1, Q3 | -464.0, -158.0 | - | |
| | Min, Max | -464.0, -158.0 | - | |
| | p-value (within) | NE | NE | NE |
| Visit 5/ Week 4 | n | 252 | 262 | |
| | Mean (SD) | -137.7 (141.27) | -101.3 (110.57) | |
| | Median | -100.0 | -79.5 | |
| | Q1, Q3 | -186.0, -50.0 | -159.0, -34.0 | |
| | Min, Max | -678.0, 242.0 | -598.0, 332.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.0012 |
| Visit 6/ Week 8 | n | 254 | 264 | |
| | Mean (SD) | -151.9 (153.61) | -126.2 (123.53) | |
| | Median | -114.0 | -104.5 | |
| | Q1, Q3 | -204.0, -50.0 | -186.5, -44.0 | |
| | Min, Max | -712.0, 234.0 | -592.0, 214.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.0360 |
| Visit 7/ Week 12 | n | 250 | 256 | |
| | Mean (SD) | -163.8 (159.76) | -137.8 (123.51) | |
| | Median | -120.5 | -117.0 | |
| | Q1, Q3 | -234.0, -65.0 | -199.5, -59.0 | |
| | Min, Max | -739.0, 373.0 | -626.0, 188.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.0406 |
| Visit 8/ Week 16 | n | 244 | 252 | |
| | Mean (SD) | -161.8 (160.31) | -146.7 (135.17) | |
| | Median | -126.5 | -120.0 | |
| | Q1, Q3 | -220.0, -56.0 | -211.0, -67.0 | |
| | Min, Max | -761.0, 311.0 | -653.0, 197.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.2581 |

| | | | | |
|---|---|---|---|---|
| Visit 9/ Week 20 | n | 236 | 249 | |
| | Mean (SD) | -168.2 (169.77) | -154.2 (135.14) | |
| | Median | -135.0 | -125.0 | |
| | Q1, Q3 | -231.5, -65.5 | -224.0, -67.0 | |
| | Min, Max | -817.0, 443.0 | -661.0, 168.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.3147 |
| Visit 10/ Week 24 | n | 239 | 243 | |
| | Mean (SD) | -167.1 (168.68) | -150.3 (137.77) | |
| | Median | -132.0 | -113.0 | |
| | Q1, Q3 | -235.0, -50.0 | -218.0, -59.0 | |
| | Min, Max | -817.0, 351.0 | -653.0, 160.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.2307 |
| Visit 11/ Week 28 | n | 235 | 241 | |
| | Mean (SD) | -177.7 (173.06) | -160.7 (142.25) | |
| | Median | -142.0 | -125.0 | |
| | Q1, Q3 | -262.0, -61.0 | -227.0, -67.0 | |
| | Min, Max | -828.0, 351.0 | -678.0, 250.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.2421 |
| Visit 12/ Week 32 | n | 233 | 239 | |
| | Mean (SD) | -179.7 (173.51) | -160.4 (147.78) | |
| | Median | -147.0 | -130.0 | |
| | Q1, Q3 | -267.0, -62.0 | -244.0, -60.0 | |
| | Min, Max | -827.0, 331.0 | -686.0, 243.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.1939 |
| Visit 13/ Week 36 | n | 232 | 237 | |
| | Mean (SD) | -189.4 (173.57) | -162.0 (146.67) | |
| | Median | -142.5 | -140.0 | |
| | Q1, Q3 | -284.5, -70.0 | -240.0, -62.0 | |
| | Min, Max | -828.0, 331.0 | -703.0, 252.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.0650 |
| Visit 14/ Week 40 | n | 228 | 227 | |
| | Mean (SD) | -184.7 (181.45) | -166.8 (153.38) | |
| | Median | -149.5 | -136.0 | |
| | Q1, Q3 | -278.0, -62.5 | -259.0, -64.0 | |
| | Min, Max | -828.0, 326.0 | -711.0, 220.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.2574 |

| | | | | |
|---|---|---|---|---|
| Visit 15/ Week 44 | n | 223 | 224 | |
| | Mean (SD) | -185.5 (171.50) | -170.3 (147.78) | |
| | Median | -145.0 | -144.5 | |
| | Q1, Q3 | -284.0, -67.0 | -239.5, -71.5 | |
| | Min, Max | -839.0, 311.0 | -711.0, 150.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.3167 |
| Visit 16/ Week 48 | n | 222 | 221 | |
| | Mean (SD) | -192.1 (187.32) | -171.5 (148.34) | |
| | Median | -157.5 | -143.0 | |
| | Q1, Q3 | -287.0, -77.0 | -238.0, -65.0 | |
| | Min, Max | -850.0, 541.0 | -719.0, 209.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.2005 |
| Visit 17 (EOS)/ Week 52 | n | 227 | 222 | |
| | Mean (SD) | -184.7 (180.92) | -168.5 (150.07) | |
| | Median | -143.0 | -145.0 | |
| | Q1, Q3 | -279.0, -75.0 | -235.0, -69.0 | |
| | Min, Max | -851.0, 491.0 | -728.0, 268.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.3038 |

Note 1: n = Number of patients in respective categories.
Note 2: N = Number of patients in respective treatments.
Note 3: p-value (between) has been calculated using independent t-test between two treatments.
Note 4: p-value (within) has been calculated using paired t-test for the comparison of each visit to baseline visit.
Note 5: Change from baseline (CFB) =Post baseline - Baseline.
Note 6: Baseline is defined as visit 2 / Week 0.
Note 7: NE=Not Evaluable
Reference listing: 16.2.6.2

*Table 24: Descriptive statistics for central retinal thickness (FCP) in the study eye measured by SD-OCT (PP set)*

| Visit / Week | Statistics | Intas Ranibizumab (N=260) | Lucentis (N=265) |
|---|---|---|---|
| Baseline/ Week 0 | n | 257 | 265 |
| | Mean (SD) | 413 (170.1) | 394 (154.5) |
| | Median | 369 | 366 |
| | Q1, Q3 | 292, 501 | 278, 492 |
| | Min, Max | 90, 1062 | 116, 950 |
| Visit 3/ Week 1 | n | 254 | 254 |
| | Mean (SD) | 310 (116.2) | 304 (120.4) |
| | Median | 291 | 285 |
| | Q1, Q3 | 226, 360 | 226, 351 |
| | Min, Max | 101, 846 | 104, 957 |
| Visit 4/ Week 2 | n | 2 | - |
| | Mean (SD) | 283 (26.2) | - |
| | Median | 283 | - |
| | Q1, Q3 | 264, 301 | - |
| | Min, Max | 264, 301 | - |
| Visit 5/ Week 4 | n | 254 | 262 |
| | Mean (SD) | 276 (114.6) | 292 (131.6) |
| | Median | 247 | 251 |
| | Q1, Q3 | 200, 318 | 209, 343 |
| | Min, Max | 92, 753 | 90, 896 |
| Visit 6/ Week 8 | n | 256 | 264 |
| | Mean (SD) | 262 (112.7) | 267 (116.6) |
| | Median | 234 | 234 |
| | Q1, Q3 | 184, 302 | 192, 310 |
| | Min, Max | 90, 771 | 73, 758 |
| Visit 7/ Week 12 | n | 252 | 256 |
| | Mean (SD) | 250 (104.5) | 255 (114.0) |
| | Median | 226 | 227 |
| | Q1, Q3 | 180, 285 | 184, 290 |
| | Min, Max | 92, 903 | 55, 750 |
| Visit 8/ Week 16 | n | 246 | 252 |
| | Mean (SD) | 251 (113.4) | 248 (104.0) |
| | Median | 218 | 218 |
| | Q1, Q3 | 176, 293 | 188, 289 |
| | Min, Max | 87, 826 | 73, 732 |
| Visit 9/ Week 20 | n | 238 | 249 |
| | Mean (SD) | 242 (103.9) | 241 (103.8) |
| | Median | 218 | 212 |
| | Q1, Q3 | 174, 276 | 180, 285 |
| | Min, Max | 85, 817 | 70, 697 |

| | | | |
|---|---|---|---|
| Visit 10/ Week 24 | n | 241 | 243 |
| | Mean (SD) | 243 (102.6) | 240 (109.3) |
| | Median | 217 | 211 |
| | Q1, Q3 | 170, 293 | 176, 276 |
| | Min, Max | 74, 702 | 48, 752 |
| Visit 11/ Week 28 | n | 237 | 241 |
| | Mean (SD) | 236 (95.9) | 237 (108.2) |
| | Median | 211 | 209 |
| | Q1, Q3 | 169, 275 | 176, 270 |
| | Min, Max | 95, 692 | 55, 852 |
| Visit 12/ Week 32 | n | 235 | 239 |
| | Mean (SD) | 231 (94.1) | 236 (105.3) |
| | Median | 209 | 211 |
| | Q1, Q3 | 168, 278 | 173, 261 |
| | Min, Max | 85, 682 | 61, 715 |
| Visit 13/ Week 36 | n | 234 | 237 |
| | Mean (SD) | 225 (92.8) | 232 (102.9) |
| | Median | 202 | 203 |
| | Q1, Q3 | 166, 267 | 169, 263 |
| | Min, Max | 85, 682 | 50, 778 |
| Visit 14/ Week 40 | n | 229 | 227 |
| | Mean (SD) | 227 (92.6) | 228 (102.3) |
| | Median | 201 | 201 |
| | Q1, Q3 | 167, 268 | 168, 259 |
| | Min, Max | 71, 672 | 42, 753 |
| Visit 15/ Week 44 | n | 225 | 224 |
| | Mean (SD) | 226 (93.5) | 224 (98.7) |
| | Median | 201 | 201 |
| | Q1, Q3 | 167, 272 | 167, 256 |
| | Min, Max | 71, 662 | 41, 753 |
| Visit 16/ Week 48 | n | 224 | 221 |
| | Mean (SD) | 225 (105.0) | 222 (97.3) |
| | Median | 200 | 193 |
| | Q1, Q3 | 163, 269 | 163, 260 |
| | Min, Max | 71, 892 | 45, 812 |
| Visit 17 (EOS)/ Week 52 | n | 229 | 222 |
| | Mean (SD) | 233 (102.2) | 226 (93.5) |
| | Median | 209 | 204 |
| | Q1, Q3 | 169, 277 | 167, 268 |
| | Min, Max | 53, 842 | 41, 619 |

Note 1: n = Number of patients in respective categories.
Note 2: N = Number of patients in respective treatments.
Reference listing: 16.2.6.2

Similar outcomes have been shown for the mITT Set.

*Table 25: Change in central retinal thickness (FCS) in the study eye measured by SD-OCT (PP set)*

| Visit / Week | Statistics | Intas Ranibizumab (N=260) | Lucentis (N=265) | p-value (between) |
|---|---|---|---|---|
| Visit 3/ Week 1 | n | 253 | 255 | |
| | Mean (SD) | -79.1 (96.75) | -78.3 (78.48) | |
| | Median | -54.2 | -64.2 | |
| | Q1, Q3 | -123.1, -21.7 | -118.9, -25.9 | |
| | Min, Max | -513.9, 275.6 | -363.4, 86.6 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.9225 |
| Visit 4/ Week 2 | n | 2 | - | |
| | Mean (SD) | -157.5 (22.64) | - | |
| | Median | -157.5 | - | |
| | Q1, Q3 | -173.5, -141.4 | - | |
| | Min, Max | -173.5, -141.4 | - | |
| | p-value (within) | NE | NE | NE |
| Visit 5/ Week 4 | n | 253 | 263 | |
| | Mean (SD) | -110.7 (124.33) | -89.9 (100.22) | |
| | Median | -85.4 | -70.0 | |
| | Q1, Q3 | -179.1, -29.9 | -142.6, -27.0 | |
| | Min, Max | -640.0, 339.8 | -466.1, 258.8 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.0366 |
| Visit 6/ Week 8 | n | 256 | 264 | |
| | Mean (SD) | -129.1 (119.19) | -110.4 (108.46) | |
| | Median | -99.7 | -82.5 | |
| | Q1, Q3 | -194.2, -44.0 | -164.2, -34.6 | |
| | Min, Max | -711.2, 167.0 | -526.1, 199.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.0616 |
| Visit 7/ Week 12 | n | 251 | 256 | |
| | Mean (SD) | -137.9 (133.56) | -115.8 (108.66) | |
| | Median | -104.8 | -94.1 | |
| | Q1, Q3 | -213.3, -45.9 | -163.3, -40.1 | |
| | Min, Max | -700.9, 97.1 | -532.8, 163.1 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.0420 |
| Visit 8/ Week 16 | n | 246 | 252 | |
| | Mean (SD) | -129.5 (130.51) | -113.5 (113.57) | |
| | Median | -102.8 | -97.1 | |
| | Q1, Q3 | -195.8, -37.9 | -162.4, -37.0 | |
| | Min, Max | -711.5, 200.3 | -530.9, 278.3 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.1453 |

| | | | | |
|---|---|---|---|---|
| Visit 9/ Week 20 | n | 237 | 249 | |
| | Mean (SD) | -136.1 (133.14) | -121.9 (118.00) | |
| | Median | -100.1 | -99.2 | |
| | Q1, Q3 | -202.8, -48.8 | -181.8, -43.0 | |
| | Min, Max | -695.4, 158.9 | -575.6, 177.2 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.2135 |
| Visit 10/ Week 24 | n | 240 | 243 | |
| | Mean (SD) | -134.7 (134.87) | -118.0 (114.39) | |
| | Median | -104.8 | -95.4 | |
| | Q1, Q3 | -196.8, -46.9 | -179.0, -46.1 | |
| | Min, Max | -632.1, 153.5 | -554.5, 196.1 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.1430 |
| Visit 11/ Week 28 | n | 236 | 241 | |
| | Mean (SD) | -143.0 (135.05) | -123.8 (120.11) | |
| | Median | -113.7 | -101.5 | |
| | Q1, Q3 | -214.6, -48.2 | -179.3, -46.1 | |
| | Min, Max | -676.5, 164.7 | -569.2, 215.3 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.1004 |
| Visit 12/ Week 32 | n | 235 | 239 | |
| | Mean (SD) | -141.1 (140.51) | -122.6 (123.74) | |
| | Median | -109.4 | -101.4 | |
| | Q1, Q3 | -204.5, -46.3 | -183.7, -42.5 | |
| | Min, Max | -684.1, 193.2 | -563.8, 182.4 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.1281 |
| Visit 13/ Week 36 | n | 234 | 237 | |
| | Mean (SD) | -141.6 (139.05) | -119.7 (123.37) | |
| | Median | -109.2 | -101.8 | |
| | Q1, Q3 | -223.9, -37.9 | -178.7, -41.7 | |
| | Min, Max | -706.4, 96.7 | -576.3, 213.0 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.0716 |
| Visit 14/ Week 40 | n | 229 | 227 | |
| | Mean (SD) | -143.5 (140.50) | -125.4 (126.55) | |
| | Median | -112.0 | -101.7 | |
| | Q1, Q3 | -218.7, -40.4 | -189.4, -43.3 | |
| | Min, Max | -695.4, 137.3 | -571.3, 202.6 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.1486 |

| | | | | |
|---|---|---|---|---|
| Visit 15/ Week 44 | n | 224 | 225 | |
| | Mean (SD) | -141.0 (138.96) | -129.9 (130.19) | |
| | Median | -110.8 | -111.7 | |
| | Q1, Q3 | -214.2, -39.3 | -189.4, -43.9 | |
| | Min, Max | -714.3, 149.2 | -562.9, 434.9 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.3826 |
| Visit 16/ Week 48 | n | 223 | 221 | |
| | Mean (SD) | -145.7 (145.58) | -131.3 (130.43) | |
| | Median | -114.3 | -112.8 | |
| | Q1, Q3 | -231.1, -46.6 | -187.2, -47.0 | |
| | Min, Max | -672.2, 153.2 | -584.9, 269.7 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.2726 |
| Visit 17 (EOS)/ Week 52 | n | 228 | 222 | |
| | Mean (SD) | -143.5 (146.49) | -131.1 (128.44) | |
| | Median | -118.0 | -112.0 | |
| | Q1, Q3 | -218.7, -42.7 | -188.9, -45.3 | |
| | Min, Max | -710.3, 247.9 | -584.8, 214.5 | |
| | p-value (within) | <0.0001 | <0.0001 | 0.3425 |

Note 1: n = Number of patients in respective categories.
Note 2: N = Number of patients in respective treatments.
Note 3: p-value (between) has been calculated using independent t-test between two treatments.
Note 4: p-value (within) has been calculated using paired t-test for the comparison of each visit to baseline visit.
Note 5: Change from baseline (CFB) =Post baseline - Baseline.
Note 6: Baseline is defined as visit 2 / Week 0.
Note 7: NE=Not Evaluable
Reference listing: 16.2.6.2

*Table 26: Descriptive statistics for central retinal thickness (FCS) in the study eye measured by SD-OCT (PP set)*

| Visit / Week | Statistics | Intas Ranibizumab (N=260) | Lucentis (N=265) |
|---|---|---|---|
| Baseline/ Week 0 | n | 258 | 265 |
| | Mean (SD) | 432.64 (145.314) | 413.93 (132.905) |
| | Median | 407.32 | 386.47 |
| | Q1, Q3 | 326.21, 523.40 | 317.20, 487.74 |
| | Min, Max | 164.13, 938.68 | 198.62, 877.00 |
| Visit 3/ Week 1 | n | 254 | 255 |
| | Mean (SD) | 352.51 (106.696) | 339.16 (99.502) |
| | Median | 333.55 | 316.72 |
| | Q1, Q3 | 276.36, 408.56 | 270.39, 387.61 |
| | Min, Max | 133.98, 827.84 | 157.19, 802.65 |
| Visit 4/ Week 2 | n | 2 | - |
| | Mean (SD) | 324.81 (25.626) | - |
| | Median | 324.81 | - |
| | Q1, Q3 | 306.69, 342.93 | - |
| | Min, Max | 306.69, 342.93 | - |
| Visit 5/ Week 4 | n | 254 | 263 |
| | Mean (SD) | 323.00 (108.621) | 324.69 (109.276) |
| | Median | 295.36 | 296.20 |
| | Q1, Q3 | 248.41, 366.77 | 245.17, 385.00 |
| | Min, Max | 155.04, 837.16 | 139.28, 778.79 |
| Visit 6/ Week 8 | n | 257 | 264 |
| | Mean (SD) | 303.57 (101.012) | 303.56 (97.543) |
| | Median | 282.61 | 278.13 |
| | Q1, Q3 | 234.81, 343.54 | 236.00, 342.79 |
| | Min, Max | 121.23, 790.67 | 144.68, 709.35 |
| Visit 7/ Week 12 | n | 252 | 256 |
| | Mean (SD) | 293.95 (91.117) | 298.07 (92.173) |
| | Median | 273.74 | 275.79 |
| | Q1, Q3 | 238.29, 329.18 | 238.65, 333.06 |
| | Min, Max | 132.73, 894.54 | 142.78, 718.16 |
| Visit 8/ Week 16 | n | 247 | 252 |
| | Mean (SD) | 302.04 (105.180) | 300.80 (96.089) |
| | Median | 272.98 | 277.92 |
| | Q1, Q3 | 231.80, 346.72 | 236.29, 330.57 |
| | Min, Max | 137.78, 905.93 | 141.56, 733.47 |
| Visit 9/ Week 20 | n | 238 | 249 |
| | Mean (SD) | 292.77 (94.236) | 292.41 (90.482) |
| | Median | 270.43 | 274.75 |
| | Q1, Q3 | 231.37, 326.52 | 236.24, 319.95 |
| | Min, Max | 149.03, 821.73 | 122.31, 701.92 |

| | | | |
|---|---|---|---|
| Visit 10/ Week 24 | n | 241 | 243 |
| | Mean (SD) | 294.74 (92.682) | 294.18 (96.124) |
| | Median | 272.97 | 268.78 |
| | Q1, Q3 | 230.66, 335.49 | 230.10, 323.06 |
| | Min, Max | 131.58, 874.21 | 141.06, 696.77 |
| Visit 11/ Week 28 | n | 237 | 241 |
| | Mean (SD) | 288.66 (84.982) | 291.72 (92.869) |
| | Median | 269.40 | 268.35 |
| | Q1, Q3 | 229.91, 322.63 | 233.52, 318.42 |
| | Min, Max | 142.50, 722.65 | 136.89, 741.21 |
| Visit 12/ Week 32 | n | 236 | 239 |
| | Mean (SD) | 288.71 (88.871) | 294.03 (95.469) |
| | Median | 265.91 | 269.92 |
| | Q1, Q3 | 227.78, 329.25 | 233.77, 330.41 |
| | Min, Max | 143.57, 729.64 | 135.10, 777.70 |
| Visit 13/ Week 36 | n | 235 | 237 |
| | Mean (SD) | 289.78 (87.544) | 294.58 (94.505) |
| | Median | 271.66 | 273.17 |
| | Q1, Q3 | 230.84, 330.41 | 233.68, 330.67 |
| | Min, Max | 140.83, 711.13 | 143.03, 734.21 |
| Visit 14/ Week 40 | n | 230 | 227 |
| | Mean (SD) | 286.27 (79.594) | 290.75 (83.952) |
| | Median | 268.59 | 270.75 |
| | Q1, Q3 | 231.17, 328.26 | 237.15, 321.71 |
| | Min, Max | 133.48, 706.35 | 138.50, 726.03 |
| Visit 15/ Week 44 | n | 225 | 225 |
| | Mean (SD) | 289.83 (86.694) | 286.98 (94.747) |
| | Median | 263.82 | 264.74 |
| | Q1, Q3 | 233.34, 335.03 | 232.05, 311.46 |
| | Min, Max | 134.06, 695.61 | 138.47, 839.74 |
| Visit 16/ Week 48 | n | 224 | 221 |
| | Mean (SD) | 287.70 (81.723) | 283.46 (89.497) |
| | Median | 266.99 | 263.80 |
| | Q1, Q3 | 232.79, 325.58 | 229.90, 309.42 |
| | Min, Max | 146.77, 628.17 | 134.59, 787.82 |
| Visit 17 (EOS)/ Week 52 | n | 229 | 222 |
| | Mean (SD) | 291.22 (88.213) | 283.75 (85.021) |
| | Median | 275.15 | 261.90 |
| | Q1, Q3 | 231.60, 330.60 | 233.09, 315.69 |
| | Min, Max | 138.96, 644.71 | 139.20, 724.75 |

Note 1: n = Number of patients in respective categories.
Note 2: N = Number of patients in respective treatments.
Reference listing: 16.2.6.2

Similar outcomes have been shown for the mITT Set.

**Pre-defined and post-hoc subgroup analyses**

Subgroup analysis by region/country

*Table 27: Region/country wise point estimate and confidence interval for the difference between treatments for mean change in BCVA from baseline to week 8 (PP set)*

| | Intas Ranibizumab (N=260) | | | Lucentis (N=265) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Region/country | n | LS Mean | SE | n | LS Mean | SE | Point Estimate (Difference) | Confidence Interval | Obtained Confidence Interval |
| Europe (n=191) | 94 | 7.2 | 0.71 | 97 | 8.6 | 0.70 | -1.4 | 90% CI | [-3.0, 0.3] |
| | 94 | 7.2 | 0.71 | 97 | 8.6 | 0.70 | -1.4 | 95% CI | [-3.3, 0.6] |
| India (n=334) | 166 | 6.5 | 0.61 | 168 | 6.9 | 0.61 | -0.5 | 90% CI | [-1.9, 1.0] |
| | 166 | 6.5 | 0.61 | 168 | 6.9 | 0.61 | -0.5 | 95% CI | [-2.2, 1.2] |

Note 1: Change from baseline (CFB) =Post baseline - Baseline.
Note 2: Baseline is defined as visit 2 / Week 0.
Note 3: N = Number of patients in respective treatments, n = Number of patients in respective categories.
Note 4: 90% and 95% CI has been calculated by an Analysis of Covariance (ANCOVA) model.
Note 5: LS Mean = Least Square Mean & SE = Standard Error
Reference listing: 16.2.6.1

*Table 28: Region/country wise point estimate and confidence interval for the difference between treatments for mean change in BCVA from baseline to week 8 (mITT set)*

| | Intas Ranibizumab (N=271) | | | Lucentis (N=271) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Region/country | n | LS Mean | SE | n | LS Mean | SE | Point Estimate (Difference) | Confidence Interval | Obtained Confidence Interval |
| Europe (n=191) | 94 | 7.2 | 0.71 | 97 | 8.6 | 0.70 | -1.4 | 90% CI | [-3.0, 0.3] |
| | 94 | 7.2 | 0.71 | 97 | 8.6 | 0.70 | -1.4 | 95% CI | [-3.3, 0.6] |
| India (n=334) | 166 | 6.5 | 0.61 | 168 | 6.9 | 0.61 | -0.5 | 90% CI | [-1.9, 1.0] |
| | 166 | 6.5 | 0.61 | 168 | 6.9 | 0.61 | -0.5 | 95% CI | [-2.2, 1.2] |

Note 1: Change from baseline (CFB) =Post baseline - Baseline.
Note 2: Baseline is defined as visit 2 / Week 0.
Note 3: N = Number of patients in respective treatments, n = Number of patients in respective categories.
Note 4: 90% and 95% CI has been calculated by an Analysis of Covariance (ANCOVA) model.
Note 5: LS Mean = Least Square Mean & SE = Standard Error
Reference listing: 16.2.6.1

Subgroup analysis by baseline BCVA score for the study eye (≤54, >54)

*Table 29: BCVA wise point estimate and confidence interval for the difference between treatments for mean change in BCVA from baseline to week 8 (PP set)*

| | Intas Ranibizumab (N=260) | | | Lucentis (N=265) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| BCVA (≤54/>54) | n | LS Mean | SE | n | LS Mean | SE | Point Estimate (Difference) | Confidence Interval | Obtained Confidence Interval |
| ≤54 (n=237) | 115 | 6.8 | 0.84 | 122 | 6.8 | 0.84 | -0.04 | 90% CI | [-2.0, 1.9] |
| | 115 | 6.8 | 0.84 | 122 | 6.8 | 0.84 | -0.04 | 95% CI | [-2.3, 2.3] |
| >54 (n=288) | 145 | 6.8 | 0.51 | 143 | 8.1 | 0.51 | -1.27 | 90% CI | [-2.5, -0.1] |
| | 145 | 6.8 | 0.51 | 143 | 8.1 | 0.51 | -1.27 | 95% CI | [-2.7, 0.1] |

Note 1: Change from baseline (CFB) =Post baseline - Baseline.
Note 2: Baseline is defined as visit 2 / Week 0.
Note 3: N = Number of patients in respective treatments, n = Number of patients in respective categories.
Note 4: 90% and 95% CI has been calculated by an Analysis of Covariance (ANCOVA) model.
Note 5: LS Mean = Least Square Mean & SE = Standard Error
Reference listing: 16.2.6.1

Source: Final Clinical Study Report, Section 14.2.1 Primary Efficacy Data

*Table 30: BCVA wise point estimate and confidence interval for the difference between treatments for mean change in BCVA from baseline to week 8 (mITT set)*

| | Intas Ranibizumab (N=271) | | | Lucentis (N=271) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| BCVA (≤54/>54) | n | LS Mean | SE | n | LS Mean | SE | Point Estimate (Difference) | Confidence Interval | Obtained Confidence Interval |
| ≤54 (n=237) | 115 | 6.8 | 0.84 | 122 | 6.8 | 0.84 | -0.04 | 90% CI | [-2.0, 1.9] |
| | 115 | 6.8 | 0.84 | 122 | 6.8 | 0.84 | -0.04 | 95% CI | [-2.3, 2.3] |
| >54 (n=288) | 145 | 6.8 | 0.51 | 143 | 8.1 | 0.51 | -1.27 | 90% CI | [-2.5, -0.1] |
| | 145 | 6.8 | 0.51 | 143 | 8.1 | 0.51 | -1.27 | 95% CI | [-2.7, 0.1] |

Note 1: Change from baseline (CFB) =Post baseline - Baseline.
Note 2: Baseline is defined as visit 2 / Week 0.
Note 3: N = Number of patients in respective treatments, n = Number of patients in respective categories.
Note 4: 90% and 95% CI has been calculated by an Analysis of Covariance (ANCOVA) model.
Note 5: LS Mean = Least Square Mean & SE = Standard Error
Reference listing: 16.2.6.1

Source: Final Clinical Study Report, Section 14.2.1 Primary Efficacy Data

Subgroup analysis by Iris Colour (dark or light)

*Table 31: Iris colour wise point estimate and confidence interval for the difference between treatments for mean change in BCVA from baseline to week 8 (PP set)*

| | Intas Ranibizumab (N=260) | | | Lucentis (N=265) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Iris Color | n | LS Mean | SE | n | LS Mean | SE | Point Estimate (Difference) | Confidence Interval | Obtained Confidence Interval |
| Dark Iris (n=355) | 177 | 6.5 | 0.59 | 178 | 6.8 | 0.58 | -0.2 | 90% CI | [-1.6, 1.1] |
| | 177 | 6.5 | 0.59 | 178 | 6.8 | 0.58 | -0.2 | 95% CI | [-1.9, 1.4] |
| Light Iris (n=170) | 83 | 7.2 | 0.75 | 87 | 9.0 | 0.74 | -1.8 | 90% CI | [-3.5, -0.0] |
| | 83 | 7.2 | 0.75 | 87 | 9.0 | 0.74 | -1.8 | 95% CI | [-3.8, 0.3] |

Note 1: Change from baseline (CFB) =Post baseline - Baseline.
Note 2: Baseline is defined as visit 2 / Week 0.
Note 3: N = Number of patients in respective treatments, n = Number of patients in respective categories.
Note 4: 90% and 95% CI has been calculated by an Analysis of Covariance (ANCOVA) model.
Note 5: LS Mean = Least Square Mean & SE = Standard Error
Reference listing: 16.2.6.1

Source: Final Clinical Study Report, Section 14.2.1 Primary Efficacy Data

*Table 32: Iris colour wise point estimate and confidence interval for the difference between treatments for mean change in BCVA from baseline to week 8 (mITT set)*

| | Intas Ranibizumab (N=271) | | | Lucentis (N=271) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Iris Color | n | LS Mean | SE | n | LS Mean | SE | Point Estimate (Difference) | Confidence Interval | Obtained Confidence Interval |
| Dark Iris (n=355) | 177 | 6.5 | 0.59 | 178 | 6.8 | 0.58 | -0.2 | 90% CI | [-1.6, 1.1] |
| | 177 | 6.5 | 0.59 | 178 | 6.8 | 0.58 | -0.2 | 95% CI | [-1.9, 1.4] |
| Light Iris (n=170) | 83 | 7.2 | 0.75 | 87 | 9.0 | 0.74 | -1.8 | 90% CI | [-3.5, -0.0] |
| | 83 | 7.2 | 0.75 | 87 | 9.0 | 0.74 | -1.8 | 95% CI | [-3.8, 0.3] |

Note 1: Change from baseline (CFB) =Post baseline - Baseline.
Note 2: Baseline is defined as visit 2 / Week 0.
Note 3: N = Number of patients in respective treatments, n = Number of patients in respective categories.
Note 4: 90% and 95% CI has been calculated by an Analysis of Covariance (ANCOVA) model.
Note 5: LS Mean = Least Square Mean & SE = Standard Error
Reference listing: 16.2.6.1

Source: Final Clinical Study Report, Section 14.2.1 Primary Efficacy Data

Subgroup analysis by Formulation (PFS and single use vial)

All the subjects in the study were dosed using **single use vials**. Thus, no stratification and subgroup analysis by formulation was conducted.

## 5.3.3. Overall discussion and conclusions on clinical efficacy

### *5.3.3.1. Discussion*

The clinical development program consisted of a single double masked, parallel group, randomised, multicentre, global clinical phase 3 study (0504-19, CLARITY) to compare the efficacy and safety of the ranibizumab biosimilar candidate INTP18 with the originator drug Lucentis in patients with neovascular (wet) AMD. An interim clinical study report (version 1.0, dated 11/03/2025, which includes results of 6 months of data (database cutoff: of 16/01/2025) and the final clinical study report

(dated 26/09/2025) were submitted.

The applicant provided a statement that the phase 3 clinical study met the ethical requirements of Directive 2001/20/EC. The clinical trial was performed in accordance with GCP as claimed by the applicant.

**Study design**

**Overall**, the study was adequately designed to demonstrate a possible biosimilarity between INTP18 and Lucentis.

The clinical study was performed in **5 countries**, i.e., India (43 sites) and 4 EU member states: Czech Republic (4 sites), Hungary (5 sites), Latvia (3 sites) and Poland (5 sites).

The **study duration** of 52 weeks was supported already in the initially received advice procedure EMEA/H/SA/4312/1/2019/III (dated: 12/12/2019) and is therefore considered acceptable.

As ranibizumab is known to have a rather long vitreous elimination half-life of approximately 9 days, the **parallel design** is considered appropriate and in line with EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) (Lucentis EPAR, 2007).

Study population

Patients with neovascular age-related macular degeneration (nAMD) were selected to serve as study population for study 0504-19. The applicant did not conduct further clinical studies in other indications approved for Lucentis. This is agreed, because this study population is considered appropriate to demonstrate the similarity in clinical efficacy between INTP18 and the chosen reference product, since nAMD patients are considered a sensitive population to detect potential differences between the treatments and are, therefore, an acceptable study population.

Eligibility of individual study participants for enrollment has been determined during the Screening period (Day -21 to 0). The **key inclusion and exclusion criteria** applied in this process are, overall, considered adequate to recruit a suitable study population for demonstration of biosimilarity between INTP18 and Lucentis. Thus, the selected study population consisted of male and female patients aged ≥50 years, newly diagnosed, treatment naïve patients with active subfoveal CNV lesion secondary to neovascular (wet) age-related macular degeneration in the study eye at screening, with a BCVA of 20/40 to 20/200 (≤73 and ≥34 ETDRS letter score) in the study eye.

The study eye was defined as the eye meeting all of the inclusion criteria and none of the exclusion criteria (i.e., the enrolment criteria). Considering the listed criteria, this is acceptable. It remains, however, unclear which strategy was chosen to designate the study eye, if both eyes met the eligibility criteria. Nevertheless, as the selection of the eye occurred in a masked manner, this lack of information is not further pursued.

Randomisation

Study participants were randomised at a 1:1 ratio to receive either INTP18 or Lucentis via a central randomisation algorithm that was implemented in an interactive web response system (IWRS) by an independent biostatistician before commencement of the study, and randomisation was foreseen to be stratified by baseline BCVA (⩽54 and >54), iris colour (dark iris and light iris), region (India and Europe), and device (PFS and vial, although only the vial was actually used in the study (see later discussion under "Description of trial intervention" ). The randomisation ratio, stratification, and

overall conduct of the implementation of the randomisation scheme are considered adequate**.**

Blinding

Study 0504-19 was double-masked. Participants, investigator staff, and persons performing the assessments remained masked to the identity of the treatment from the time of randomisation until final database lock after study completion. However, the two investigational medicinal products differed in their appearance as the reference product Lucentis was purchased and provided as a labelled vial with unique packaging.

In order to ensure masking nonetheless, investigators were designated as "evaluating investigator" (who was masked to the treatment assignment and performed all the monthly clinical and ancillary assessments during the course of the study) or "injecting investigator" (who was unmasked to the treatment assignment and performed all the intravitreal ranibizumab injections and the post-injection safety assessments. This approach can be accepted, particularly since any remaining concerns regarding systematic bias in this context are mitigated by the fact that this is a multiregional trial with many sites. Of note, a similar dualism of investigators was implemented for study FVF3192 (PIER) that has been conducted for the EU-approved originator Lucentis (Lucentis EPAR, 2007).

To **maintain the blind after interim analysis** at 6 months a separate **unblinded study team** was set up. This unblinded study team was granted access to an unblinded directory and was responsible for the unblinded analysis and reporting of the 6 months results for submission. The study team, which continued to manage the study, did not have access to unblinded information and remained masked to the activities until the 12-month analysis. This approach was accepted during scientific advice procedure EMA/SA/0000086319. Proposed strategy has been implemented in the study protocol accordingly and is therefore considered acceptable. Since the primary efficacy evaluation is set at week 8 and has therefore already been performed, and since all secondary efficacy endpoints evaluated at later time points are considered supportive and purely descriptive in nature (even if a hypothesis test is conducted and a p-value reported), the current analysis is not considered an interim analysis from a methodological standpoint and no concerns regarding the type I error control or similar arise that have to be assessed in conjunction with maintenance of the blind.

Only limited possibility of **unintentional unmasking** of treatment assignment was assumed, as both arms contain the same treatment (i.e., ranibizumab IVT injection). No cases of accidental breaking of the blind and/or emergency unblinding of a participants' intervention during the phase 3 study have been reported, which is acceptable. Of note, the masking of the clinical trial team (i.e. data manager, statistician, trial manager, trial coordinator, medical writer, safety monitor and sponsor's responsible medical officer) was broken on 26/08/2025.

Description of trial intervention

Following randomisation, patients received either INTP18 (i.e., Intas Ranibizumab/Rexatilux) or EU- and US-sourced Lucentis at a dose of 0.5 mg (0.05 mL of a 10 mg/mL solution), planned as a total of 13 monthly IVT injections (every 28 days/4 weeks) given at Visit 2 and Visit 5 to Visit 16 (Week 48, EoT). The trial intervention follows the recommendations for posology and method of administration as outlined in the current version of the product information of Lucentis (Lucentis SmPC, 2024), which is acceptable.

As already lined out in scientific advice EMA/SA/0000086319, the applicant intended a switch from US-sourced Lucentis vials to EU-sourced Lucentis vials due to lack of availability of the US-product.

Thus, the **reference medicinal product** used in the phase 3 trial was EU- or US-sourced Lucentis. For regulatory purposes only the comparison between the proposed biosimilar and EU-Lucentis is relevant. However, in the EMA scientific advice, it was furthermore clarified that "the use of the non-EEA-sourced reference product in comparative clinical trials may be acceptable provided that the non-EEA sourced RMP has been authorised by a regulatory authority that follows similar regulatory and scientific standards as EMA (e.g., ICH countries). Consequently, the use of US-sourced Lucentis is acceptable. However, it is the responsibility of the applicant to demonstrate that the EEA RMP and non-EEA sourced comparator product are comparable at quality level." Comparability of the EEA-sourced and the non-EEA-sourced comparator products has been demonstrated at quality level (refer to section 4. Quality aspects).

Also, a listing of the IMP and RMP batches used in the phase 3 study has been provided. The table allows clear differentiation of INTP18, EU-sourced Lucentis and US-sourced Lucentis batches providing unambiguous identification of the origin of the respective batch. Accordingly, single-use vials for intravitreal injection of 6 INTP18 batches, 3 EU(/UK)-sourced Lucentis batches and 1 US-sourced Lucentis batch have been used for administration of ranibizumab during study 0504-19. The provided listing of batches is considered adequate. The applicant clarified that only the vial presentation was used in study 0504-19. Thus, no further uncertainty arises regarding the type of presentation used for trial intervention.

It has, furthermore, been shown that, in terms of quality attributes, the vial presentation is indeed comparable to the PFS presentation (including, e.g., primary and higher structure, functionality and impurities). However, with reference to the EMA "Guideline on quality documentation for medicinal products when used with a medical device" (EMA/CHMP/QWP/BWP/259165/2019) evidence of suitability for the intended use may be supported by published or other relevant data for identical/similar devices on the market. Relevant data should include bridging data to similar devices, to the same devices used in different patient populations or demonstration of comparability between the device for the proposed biosimilar and the device of the reference product. The applicant has conducted a physical comparability assessment between the PFS devices of INTP18 and RMP Lucentis. The evaluation included overall PFS dimensions, plunger rod, plunger stopper, finger flange, syringe cap, Luer Lock, and dose marking line and demonstrated that the design features and functional attributes are largely similar. Minor differences were observed. However, they were sufficiently justified and were not expected to have impact on the performance of critical tasks during product use, which can be agreed.

Of note, the PFS of Lucentis used for the physical comparability assessment was US-sourced. However, the applicant confirmed that the PFS of US- and EU-approved Lucentis are the same regarding design, functionality and operating principles. In addition, the Notified body opinion report stated that the comparability assessment demonstrated that the products are essentially similar and use within the trained user group is expected to be equivalent.

The applicant, furthermore, clarified that the phase 3 clinical study was only conducted with the vial presentation, which was agreed in the CHMP scientific advice procedure EMA/SA/0000161827 (2024). In this study, DP was administered at the dose of 0.5 mg/mL. However, INTP18 DP vial and DP PFS are identical in terms of the therapeutic dose delivered.

A dose delivery evaluation was performed for the final INTP18 PFS configuration using three DP PFS PPQ batches, evaluating accuracy and precision of delivered dose under representative use conditions. Results confirmed a consistently delivered dose within acceptance criteria. The dose delivery

performance was also evaluated and sufficiently confirmed by the supplier.

The applicant clarified that the INTP18 PFS used in the development phase is identical in design and function to the one intended for commercial use. Thus, comparability between IMP and RMP PFS is considered demonstrated.

Study assessments

All methods used for examination of the visual acuity and morphological/pathophysiological characteristics of the study eye and the fellow eye (the latter only at Screening) were established methods for diagnostic evaluation of age-related macular degeneration (Stahl, 2020; Lim et al., 2025). Furthermore, these methods also have been used in studies conducted for the reference product (Lucentis EPAR, 2007). BCVA by ETDRS and SD-OCT (spectral domain optical coherence tomography) have been performed at monthly visits, which is in line with the scientific advice received. Therefore, assessment of visual acuity, and disease characteristics of nAMD using these methods is considered appropriate.

Overall, the applicant´s development program to demonstrate similarity between INTP18 and Lucentis with respect to efficacy is considered adequate to support this application: study design, study population, inclusion/exclusion criteria, and dose regimen were performed in line with the guidance on similar biological products and were in compliance with scientific advice obtained from the EMA.

**Objective, endpoints and estimands**

To demonstrate therapeutic equivalence between INTP18 and Lucentis the primary efficacy endpoint was chosen to be "the mean change in BCVA in the study eye from baseline to Week 8 using the ETDRS protocol" as recommended by the CHMP (EMEA/H/SA/4312/1/2019/III). The assessment of BCVA using the ETDRS protocol is an established tool for diagnosis of AMD and for monitoring the effectiveness of anti-VEGF therapy. The change from baseline in BCVA is considered a sufficiently sensitive endpoint that allows detection of product-related differences and, thus, is considered acceptable. Moreover, ranibizumab has a steep increase in BCVA during the first 3 months of treatment, thus the timepoint chosen is sensitive to detect differences between the compounds.

To evaluate the potential equivalence between INTP18 and Lucentis an equivalence margin of ±3.4 letters was chosen, following recommendations by the CHMP (EMEA/H/SA/4312/1/2019/III), which is considered acceptable.

The applicant did not use the estimand framework to formulate the primary endpoint analysis and therefore did not discuss any potential intercurrent events and handling strategies. Nevertheless, several sensitivity/supplementary analyses were performed, allowing for an assessment of biosimilar clinical efficacy.

The range of **secondary endpoints** as initially proposed was in general agreed to in the initial scientific advice procedure EMEA/H/SA/4312/1/2019/III. Recommendations to move the first timepoint for evaluation of BCVA and vascular leakage from Week 12 to Week 8 was followed. Evaluation of change from baseline in BCVA was conducted at every visit (with exception of Visit 2a). Fundus fluorescein angiography (FFA) for the evaluation of leakage was scheduled at the Screening Visit and at Week 8, 24, and 52 (EoS), respectively. In addition, the applicant was encouraged to evaluate **CRT** before the efficacy plateau is reached, preferably at Week 4. SD-OCT for FCP/FCS evaluation was, in consequence, scheduled for every visit, except Visit 2a (Week 1) and Visit 4 (Week 2). Thus, timepoints for the evaluation of the secondary endpoints were adjusted as recommended by

the CHMP and are therefore acceptable.

Furthermore, the applicant was recommended to focus on the responder analysis evaluating the proportion of patients that gain ⩾15 letters in BCVA and to explore the gain and loss of ⩾5 and ⩾10 letters. In consequence, the applicant included analysis of the proportion of patients who gained ⩾5, ⩾10 and ⩾15 letters as well as the proportion of patients who lost ⩾5, ⩾10 and ⩾15 letters in the study eye up to 52 weeks. Thus, the CHMP's recommendations have been followed. The respective endpoints are, therefore, considered acceptable.

In summary, the secondary endpoints evaluated are adequately defined to further support biosimilarity assessment. They are overall agreeable, considered adequate to substantiate/support the biosimilarity exercise carried out for INTP18 and Lucentis and in line with the scientific advice received. Anatomic endpoints have been introduced which is endorsed.

Overall, the applicant's development programme to demonstrate efficacy similarity between INTP18 and Lucentis can be considered adequate to support this application in respect to design, study population, inclusion/exclusion criteria, dosing regimen and primary and secondary efficacy endpoints.

**Statistical methods for estimation and sensitivity analysis**

The primary efficacy analysis has been defined as an ANCOVA on the PP set with the mean change in BCVA at week 8 between treatment arms as the dependent variable, and with treatment, baseline BCVA, iris color, and country/region as covariates

The applicant performed the same ANCOVA on the mITT set using LOCF to impute missing values as a supportive analysis. While this approach to imputing missing data is encountered often, it is not considered appropriate since it is based on the unrealistic assumption that the patient outcome remains constant after a dropout. A further supportive analysis using an ANCOVA on the mITT set including all stratification covariates and using multiple imputation and Rubin's rules to combine multiple imputation results was performed. This approach assumes missing data is missing at random (MAR) and is typically preferred.

Further supportive analyses were performed using a MMRM with an unstructured correlation matrix on the mITT and no explicit imputation. The MMRM inherently assumes that missing data is missing at random and utilises all observed longitudinal data for estimation of results, and its usage here is appropriate, although it is noted that the only fixed effects included are baseline BCVA and treatment, it provides little additional information. However, a full tipping point analysis using a similar MMRM (with all the randomisation stratification factors as fixed effects) on the mITT set exploring systemic shifts in potential outcome values of missing data was also performed to support the robustness of the primary analysis results, which is considered more informative.

No concerns are raised regarding the final sample size/power of the trial.

The secondary analyses for the secondary endpoints proposed by the applicant can generally be endorsed. Since no formal error control method was foreseen for the secondary endpoints, all results should be considered purely supportive/descriptive although formal tests are conducted.

The applicant performed and reported subgroup analyses for the primary endpoint by baseline BCVA, iris color, and country/region, which were indeed stratification variables, instead of by age group and country/region, as planned in the SAP. The performed subgroup analyses can be endorsed.

**Results**

Changes in the planned conduct of the study

The original protocol (**Version 1.0**, dated 28/01/2020) was amended 5 times resulting in the final CSP (Version 4.0). Versions 1.0, 2.0 and 3.0 are dated before **study initiation date** (i.e., 01/05/2021). The remaining versions (Versions 3.1, 3.1/CZE-1, 4.0 as presented in scientific advice procedure EMA/SA/0000086319 and 4.0 as submitted for MAA) are dated after the study initiation date. No concerns arise from the first two protocol amendments, implemented before the study was initiated.

Protocol **Version 3.1** (dated 19/05/2021) clarified that PK sampling was only planned in participants from India and not for other countries. Furthermore, regarding baseline characteristics of study participants, it was added that approximately 200 participants are to be recruited from the EU, in addition to the 120 to 150 patients from the US who were already planned in previous versions of the CSP. However, no relevant negative impact on the study results is expected regarding these changes.

With protocol **Version 4.0** (dated 10/02/2022) a section describing the interim analysis was added.

Also, fundus exam with direct ophthalmoscopy was omitted. Only indirect ophthalmoscopy remained as part of Section 8.3.5 Complete Ophthalmic Examination to evaluate the vitreous, retina, macula, choroid, and optic nerve. The following **laboratory investigations** were removed: %Reticulocytes, Alcohol and Drug Screen (amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines), Blood Urea, Bicarbonate, Uric acid, Calcium, Phosphorous, Serum Globulin, A/G Ratio, Lactic Dehydrogenase (LOH), Crystals and cast. The applicant states that this was done considering the risk-benefit analysis based on the current SmPC of Lucentis. While changing methods and parameters while the study has already been initiated can often be problematic, this is not the case for the present application. The changes add value to the dossier and are not considered to negatively impact the main efficacy and safety results.

Overall, these alterations had no profoundly negative influence on the biosimilarity exercise and are therefore acceptable.

Of note, with the submission of the final study data, the applicant provided a protocol erratum note for the latest version of the study protocol (i.e., Version 4.0, dated 10/02/2022). The note corrects the terminology of randomisation, changing the term "dynamic central randomisation" to "central randomisation" as the latter describes the followed method correctly. It remains, however, partially unclear what method was actually used for the stratified randomisation.

Participant flow and numbers analysed

Exactly as pre-defined in the study protocol, 546 patients were randomised into one of the two treatment groups to receive monthly treatment with either INTP18 or Lucentis. Of the 546 randomised patients, 273/546 (50.0%) patients were allocated to the INTP18 treatment group, and 273/546 (50.0%) patients were allocated to the Lucentis treatment group. Thus, allocation to both treatment arms occurred at the planned 1:1 ratio, which is acceptable.

All randomised participants were part of the Safety Set and per definition all participants of the Safety Set received at least one dose of study medication. The number of patients receiving 13 doses was comparable between the two treatment arms (INTP18 vs. Lucentis: 195/273 (71.4%) patients vs. 198/273 (72.5%) patients). Also, the patient numbers receiving less than the planned total of 13

doses was overall comparable between treatment arms. Slightly more patients received 11 doses and slightly less patients received 9 doses in the INTP18 group (INTP18 vs. Lucentis: 11 doses – 10/273 (3.7%) patients vs. 4 (1.5%) patients; 9 doses – 2/273 (0.7%) patients vs. 7/273 (2.6%) patients). However, no concern arises from these numbers, as overall, a similar number of patients has been exposed to IMP or RMP, respectively.

Of note, the Figure 4: Extent of Exposure lists 274 patients for the test arm, although a total of 273 patients was randomised and dosed in the INTP18 arm. The applicant clarified that 274 patients were included for the Test arm in the 'extent of exposure'-table because it represents the actual number of patients who received at least one dose of the Test product. During the study, one patient of the Lucentis arm had a "investigational product related" major protocol deviations reported, as the wrong IMP kit was administered. The patient received the "Test product" (i.e., INTP18) instead of the "Reference product" (i.e., Lucentis) at Visit 10 only, which resulted in an increased count for the test arm.

Slightly more patients of the INTP18 arm completed the study compared to the Lucentis arm (INTP18 vs. Lucentis: 235/273 (86.1%) vs. 226/273 (82.8%) patients). However, the number of patients who completed the study was high and overall comparable between treatment arms, which is acceptable.

In consequence, the number of study discontinuations was lower in the INTP18 arm compared to the Lucentis arm. A total of 38/273 (13.9%) patients in the INTP18 arm and 47/273 (17.2%) patients in the Lucentis arm **discontinued the study**. The main reason for study discontinuation was "withdrawal of consent" (INTP18 vs. Lucentis: 27/273 (9.9%) vs. 38/273 (13.9%) patients), which was higher in the Lucentis group. No concern arises from these numbers. None of the remaining study participants **discontinued treatment**.

The primary analysis was performed using the **Per protocol (PP) set**. Slightly less patients remained in the INTP18 arm (INTP18 vs. Lucentis: 260/273 (95.2%%) vs. 265/273 (97.1%) patients, respectively). However, this difference is minor and does not give reason for concern.

More patients of the INTP18 group have been excluded (INTP18 vs. Lucentis: 9/273 (3.3%) vs. 6/273 (2.2%) patients, respectively) due to a missing Week 8 (Visit 6) evaluation, but not primarily due to major protocol deviations. In consequence, 35 patients with major protocol deviations were nonetheless included in the PP set as the protocol deviations have not been considered to impact the primary efficacy endpoint.

To corroborate evaluation of the efficacy endpoints, additional analysis was performed using the **Modified Intent-To-Treat (mITT) set**. 271/273 (99.3%) patients were part of the mITT set in each treatment arm, which is well balanced. Four patients (2/237 (0.7%) patients of each treatment arm) were excluded from the mITT Set since they did not have a post-baseline efficacy evaluation, which is also balanced and reasonable.

Protocol deviations

A total number of 1646 protocol deviations have been reported for study 0504-19, of which 37 deviations were considered "site level deviations". The latter have not been discussed in detail. Nevertheless, most "site level deviations" were "immunogenicity assessment related" protocol deviations (22), followed by "schedule of activity related" protocol deviations (4). Minor protocol deviations at patient level occurred more often in the INTP18 group than in the Lucentis group (INTP18 vs. Lucentis: 790 vs. 779 deviations). The most frequent minor protocol deviation types were "schedule of activity related" (INTP18 vs. Lucentis: 499 vs. 472 deviations), which seem to refer

mostly to visit window violations or missed visit, according to Listing 16.2.2 Protocol deviations. Those were followed by "post-injection assessment related" and "immunogenicity assessments related" protocol deviations. It remains unclear how many patients were concerned by these deviations. However, as the minor protocol deviations per type and treatment arm overall did occur in comparable numbers in both treatment arms, no concern is raised in this regard.

Patients with major protocol deviations that were considered to impact the primary efficacy endpoint were to be excluded from the PP set, which is in accordance with the definition of the PP set in the latest version of the study protocol (version 4.0, dated 10/02/2022). Minor protocol deviations did not lead to exclusion from any analysis set.

Of the total of 1646 reported protocol deviations, 40 deviations have been categorised as major, which occurred slightly less in the INTP18 arm than in the Lucentis arm (INTP18 vs. Lucentis: 18 vs. 22 major protocol deviations). Overall, the major protocol deviations occurred slightly less frequently in the INTP18 arm than in the Lucentis arm (INTP18 vs. Lucentis: 16/273 (5.9%) vs. 22/273 (8.1%) patients, respectively). 21 patients were excluded from the PP set because Visit 6 was not performed and therefore the BCVA data were not available for the primary efficacy analysis or patient did not complete the study and missed the BCVA assessment at Week 8.

Major protocol deviations were related to "randomisation", "exclusion criteria", "inclusion criteria", "discontinuation of study intervention and participant discontinuation/withdrawal", "schedule of activities", "study intervention", and "treatment of the fellow eye".

Most major protocol deviations (26) were "**randomisation related**" and refer to stratification of the respective patient into the wrong stratum by total BCVA score ($\leqslant$54; >54 letters) or iris color (light; dark) of the study eye at Screening (Visit 1) and failure to correct the strata at Randomisation (Visit 2). This type of major protocol deviation occurred with higher frequency in the INTP18 arm than in the Lucentis arm (INTP18 vs. Lucentis: 8 vs. 18 patients).

The applicant provided a sensitivity analysis for the "Mean change from baseline to week 8 BCVA score", excluding the patients that were incorrectly stratified into the wrong BCVA strata at the baseline visit. The sensitivity analysis showed results consistent with the primary analysis. The least square mean (±SE) of the CfB in BCVA at Week 8 was 6.8 (±0.48) letters for the INTP18 arm vs. 7.5 (±0.48) letters for the Lucentis arm. The difference between treatment arms, as well as the 2-sided 95% CI (i.e., -0.7 letters [-2.0, 0.6]) was still fully contained within the predefined acceptance range of [-3.4, 3.4] letters. Thus, including the patients that were incorrectly stratified into the wrong BCVA/iris color strata at the baseline visit seems to be of minor influence on the results of the primary efficacy analysis.

However, it cannot fully be understood, why the 2 "exclusion criteria related" major protocol deviations were considered not to have any potential influence at the primary efficacy analysis as an elevated blood pressure is associated with lower choroidal blood flow and disturbed vascular homeostasis, contributing to the pathogenesis of AMD. It also remains unclear, in how far the violation of inclusion criteria was handled. Nevertheless, as the remaining "non-randomisation related" major protocol deviations occurred after Visit 6, an influence on the primary efficacy evaluation can be excluded.

Also, most major protocol deviations (with exception to 6 protocol deviations) have already been reported at the time point of the interim analysis. For the interim analysis of efficacy outcomes up to Week 24 those patients were excluded from the PP set. It was shown that results presented for the interim analysis up to Week 24 are consistent with the currently presented results up to Week 24.

Therefore, including the patients with major protocol deviations into the PP set seems to be of minor influence on the overall efficacy outcomes.

Furthermore, the number of major protocol deviations that have not been excluded from the sensitivity analysis was low (14 major protocol deviations) and comparable between treatment arms. Thus, in summary, inclusion of the patients with major protocol deviations into the PP set seems to have little influence on the results and can be accepted.

**Baseline data**

Demographic Data

In general, the demographic characteristics were balanced between treatment arms with exception of age and gender that showed a statistically significant difference ($p \leq 0.05$) between the two arms in the Safety set and in the mITT set, while only age was different in the PP set. Regarding gender, the **proportion of male study participants** in the Safety set was lower in the INTP18 arm vs. the Lucentis arm (INTP18 vs. Lucentis: 137/273 (50.2%) vs. 161/273 (59.0%). Nevertheless, as literature suggests no statistically significant influence of gender on the effectiveness of anti-VEGF therapy, the clinical relevance of this discrepancy appears to be negligible (Gill et al., 2020).

Recruitment of subjects by region was overall balanced between treatment arms, although there were slight differences between treatment arms regarding recruitment per EU country, no concern arises from these small imbalances.

It should be noted that 174 (63.7%) subjects in the Intas Ranibizumab arm were of Asian origin (from India) and 172 (63.9%) subjects in the Lucentis arm. Genetic and environmental factors have been described to influence the progression of the disease and high ethnic variation in the risk for the AMD development has been described. However, the distribution between study treatments is balanced. In addition, the applicant stratified the subjects by their country/region and a subgroup analysis by region/country was conducted.

Also, the applicant intended to ensure that at least 30% of the total number of patients had a light iris, which was achieved overall and per treatment group. This is acceptable.

Baseline Disease Characteristics

Mean (±SD) **total area of leakage from CNV** and **total area of CNV** were comparable between treatment groups at baseline for the PP set. Mean (±SD) **central retinal thickness (CRT) of Foveal Central Point** and of **Foveal Central Subfield** were slightly bigger in the INTP18 group vs. Lucentis group at baseline for the PP set. Comparable baseline characteristics have also been shown for the mITT set.

In summary, baseline disease characteristics were overall balanced between treatment groups.

Overall, reported medical/surgical history, especially regarding ophthalmologic history, seems to be in accordance with an elderly patient population suffering from nAMD.

One participant of the Lucentis arm had a cataract operation in the study eye dated 10/03/2023 and was screened on 29/03/2023. Despite "prior ocular surgery (including cataract) within the previous 3 months from baseline in the study eye" being listed as one of the exclusion criteria preventing study entry, this patient entered the study and is currently listed as ongoing. The first administration of study drug (Lucentis) was done on 19/04/2023, which lies beyond >30 days following cataract surgery

and is in line with pre-defined criteria for study intervention. Though the inclusion of this patient violates predefined exclusion criteria and is not in line with GCP customs, considering the results available inclusion of this 1 patient is not considered to alter the overall conclusion on biosimilar efficacy, therefore this deviation is not further followed on.

No concerns arise, from the **prior medications**. No subject received prohibited medications in advance to the study.

Slightly less patients in the INTP18 treatment arm received any **concomitant medication** compared to the Lucentis arm (INTP18 vs. Lucentis: 212/273 (77.7%) vs. 228/273 (83.5%) patients, respectively). Listed concomitant medication is expected in an elderly patient population. The proportion of patients who received specific concomitant medication (i.e., beta blocking agents, etc.) was roughly comparable between treatment arms but not well balanced. Nevertheless, as these medications, are not considered to have grave impact the overall outcomes of the biosimilarity exercise, no concerns arise in this regard.

However, the use of prohibited medication/therapies may influence efficacy, safety and immunogenicity outcomes and is therefore of interest. The applicant presented a list of patients that have received prohibited medications during study 0504-19. The frequency of administration of prohibited medication was low and comparable between treatment arms (INTP18 vs. Lucentis: 4/273 (1.5%) vs. 3/273 (1.1%) patients). Prohibited medication included treatment with bevacizumab or glucocorticoids (e.g., betamethasone dipropionate, etc.). Furthermore, the applicant provided a sensitivity analysis for the primary efficacy endpoint "mean change in BCVA from baseline to Week 8" (data not shown), excluding the patients who received prohibited medication during the study from the PP set, mITT set or ITT set. It was shown that results were consistent with the primary efficacy analysis including the patients who received prohibited medication during study 0504-19. Thus, no concern arises regarding the influence of prohibited medication administered during the study on the efficacy outcomes.

**Outcomes and estimations**

Primary Efficacy Endpoint - Mean Change in BCVA from Baseline to Week 8

The primary ANCOVA efficacy analysis for the Change from Baseline (CfB) in BCVA to Week 8 was based on the PP set. The least square mean of the CfB in BCVA at Week 8 was slightly higher for the Lucentis arm (INTP18 vs. Lucentis: 7.0 vs. 7.7 letters). The difference between treatment arms, as well as the 2-sided 95% CI (i.e., -0.7 letters [-2.0, 0.6] was however fully contained within the predefined acceptance range of [-3.4, 3.4] letters. Therefore, the primary efficacy endpoint was formally met, thus demonstrating biosimilar efficacy between INTP18 and Lucentis.

Results of the primary analysis were supported by the results of an analysis of the primary endpoint using the mITT set in which missing BCVA values at Week 8 were replaced using LOCF showed comparable results to the PP set, also allowing the conclusion for biosimilar efficacy: again, the least square mean of the CfB in BCVA at Week 8 was slightly lower for the INTP18 arm (INTP18 vs. Lucentis: 7vs. 7.7 letters). The difference between treatment arms, as well as the 2-sided 95% CI (i.e., -0.7 letters [-2.0, 0.6]), was again fully contained within the predefined acceptance range of [-3.4, 3.4] letters.

Supportive MMRM analyses on the mITT set using no explicit imputation of missing values and a supportive ANCOVA on the mITT set using multiple imputation also yielded similar results (LS-mean

difference of -0.8 letters with a 95% CI of [-2.0, 0.5]), and LS-mean difference of -0.8letters with a 95% CI of [-2.0, 0.5], respectively).

A tipping point analysis using an MMRM (with all stratification variables used for randomisation included as fixed effects) on the mITT set confirmed the robustness of the biosimilarity conclusion under MNAR assumptions (unrealistically extreme penalties of -18 and 58 on the INTP18 arm would be required to change the conclusion).

Overall, these results support the bioequivalence of INTP18 to Lucentis in the primary efficacy endpoint.

**Secondary Efficacy Endpoints**

Mean change from baseline in BCVA in the study eye up to 52 weeks using the ETDRS protocol

The **mean change from baseline** in BCVA in the study eye for INTP18 and Lucentis over time was overall slightly lower in the INTP18 vs. Lucentis treatment arm for the PP set. However, from Week 1 up to Week 52, mean change from baseline in BCVA steadily increased over time and reached comparable numbers in both treatment arms. Also, **descriptive statistics** showed comparable BCVA values in the study eye from baseline up to Week 52 and constant improvement for the INTP18 and Lucentis treatment arm for the PP set. Similar outcomes have been shown for the mITT population. Overall, the observed change from baseline in BCVA in the study eye up to 52 weeks was comparable for INTP18 and Lucentis and supports similarity in terms of efficacy for both groups.

Proportion of subjects who **gained** ⩾5, ⩾10 and ⩾15 letters in the study eye using ETDRS protocol up to 52 weeks

The number of patients who gained ⩾5, ⩾10 or ⩾15 letters was higher in the INTP18 arm in some visits and higher in the Lucentis arm in others. However, overall, the number and/or proportion of patients who gained ⩾5, ⩾10 or ⩾15 letters over time rose constantly and comparably in both treatment arms, supporting biosimilarity between INTP18 and Lucentis.

Similar outcomes have been shown for the mITT set.

Proportion of subjects who **lost** ⩾5, ⩾10 and ⩾15 letters in the study eye using ETDRS protocol up to 52 weeks

Furthermore, the results indicated that more patients of the INTP18 arm lost ⩾5, ⩾10 or ⩾15 letters from baseline up to Week 24 compared to the Lucentis arm. The most distinct differences were observed in patients who lost ⩾5 letters at Visit 5/Week 4 (INTP18 vs. Lucentis: 11/260 (4.2%) vs. 4/265 (1.5%) patients, respectively), Visit 6/Week 8 (9/260 (3.5%) vs. 2/265 (0.8%) patients, respectively) and Visit 7/Week 12 (11/260 (4.2%) vs. 4/240 (1.5%) patients, respectively).

However, overall, a rather small proportion of patients was affected by a loss of ⩾5, ⩾10 or ⩾15 letters over time in both treatment arms. Over the first six months of study 0504-19, the values did increase, fluctuating noticeably, especially in the INTP18 group. In addition, starting in Week 16, the values of both treatment groups appeared to converge, resulting in comparable numbers for both treatment arms up to Visit 17 (EoS)/Week 52. Thus, the loss of ⩾5, ⩾10 or ⩾15 letters was shown to be comparable between treatment arms over time, supporting biosimilarity between INTP18 and Lucentis.

Mean change from baseline in the **total area of leakage from CNV** measured by fluorescein

angiography (FA) at Weeks 8 and 52

At baseline "mean total area of leakage from CNV" had been reported for 252/260 (96.9%) patients of the INTP18 arm and 260/265 (98.1%) patients of the Lucentis arm in the PP set. The patient number (n, "number of patients in respective categories") decreased markedly in both treatment arms at Visit 6/Week 8 (INTP18 vs. Lucentis: 205/260 (78.8%) vs. 203/265 (76.6%) patients, respectively) and at Visit 17 (EoS)/Week 52 (67/260 (25.8%) vs. 54/265 (20.4%) patients, respectively).

In addition, the number of patients used to calculate the "mean total area of leakage from CNV" differed from the number of participants used to calculate the "change in total area of leakage from CNV".

For the latter, patient numbers were comparable in both treatment arms at Visit 6/Week 8 (INTP18 vs. Lucentis: 199/260 (76.5%) vs. 199/265 (75.1%) patients, respectively) and higher in the INTP18 arm compared to the Lucentis arm at Visit 17 (EoS)/Week 52 (67/260 (25.8%) vs. 53/265 (20.0%) patients, respectively).

Also, the differences between post-baseline and baseline values of the "mean total area of leakage from CNV" do not match the "change in total area of leakage from CNV" from baseline when calculated as indicated by the applicant (Change from baseline (CFB) = Post baseline – Baseline). The reasons for the differences observed have not been discussed.

Similar outcomes have been shown for the mITT Set.

It was clarified that the decline in patient numbers included in the analysis of "mean total area of leakage from CNV" and "change from baseline in total area of leakage from CNV" was due to the resolution or disappearance of CNV leakage during treatment. As patients experienced complete resolution of leakage, the corresponding value was recorded as blank by the Independent Assessor, which was indicated as "0". As the analysis of mean total area of leakage at each visit included only subjects with an assessable, non-zero leakage area at that specific visit, the number of patients included in the analysis declined over time.

The same explanation applies to the analyses concerning "mean total area of CNV" and "change in total area of CNV", where declining numbers over time reflect the resolution of CNV, and differences between the two populations result from the requirement to have measurable values at specific visits (for mean area) versus the need for paired baseline and follow-up values (for change from baseline).

Furthermore, the observed difference between the number of patients used to calculate the "mean total area of leakage from CNV" and those used to calculate the "change from baseline in total area of leakage from CNV" was due to missing data at subsequent visits for certain patients.

In summary, the decline in numbers of patients included in the respective analysis and the difference in patient numbers used for the calculation of the mean or the change from baseline values has been clarified sufficiently. No further concern arises from the decline of the patients included in the analysis of "mean total area of (leakage from) CNV" and those used to calculate the "change from baseline in total area of (leakage from) CNV".

This also refers to the total area of CNV.

Overall, presented outcomes for mean change from baseline in the **total area of leakage from CNV** support biosimilarity between INTP18 and Lucentis.

Mean change from baseline in **total area of CNV** measured by FA at Weeks 8 and 52 in the study eye

Regarding **descriptive statistics**, the "number of patients in respective categories" (n) as well as the "mean total area of CNV" declined in a comparable manner in both treatment arms over time, which seem to support similarity regarding efficacy between INTP18 and Lucentis. However, it was not fully clear which patients of the PP set were included in the calculation and why this patient number strongly declines over time. The applicant clarified that due to missing visit data for certain patients, the number of patients included in specific categories (n) may be lower than the total number of patients in the respective treatment group (N).

The observed **change in total area of CNV** was overall comparable between both treatment arms over time. Nevertheless, the differences between post-baseline values and baseline values of the "mean total area of CNV" do not match the "change in total area of CNV" from baseline when calculated as indicated by the applicant (Change from baseline (CFB) = Post baseline – Baseline). The reasons for the differences observed have not been discussed.

Furthermore, regarding the "change in total area of CNV", the patient number was slightly lower in the INTP18 arm vs. the Lucentis arm at Visit 6/Week 8 and Visit 17 (EoS)/Week 52 and slightly higher at Visit 10/Week 24. No concern arises from these differences. Regarding the strong decline of patients included in the analysis of (change in) total area of CNV refer to the section "Mean change from baseline in the **total area of leakage from CNV** measured by fluorescein angiography (FA) at Weeks 8 and 52" above, as the clarification provided applies here as well.

Comparable outcomes have been shown for the mITT set.

Overall, presented outcomes for mean change from baseline in the **total area of CNV** support biosimilarity between INTP18 and Lucentis.

Mean change from baseline in **central retinal thickness** (FCP retinal thickness and FCS retinal thickness) in the study eye measured by SD-OCT up to 52 weeks

**The mean central retinal thickness** (CRT) of the **foveal centre point** (FCP) was slightly larger in the INTP18 group compared to the Lucentis group at baseline. The values decreased in both groups over time and were overall comparable up to Week 52.

The **change from baseline** in CRT of the FCP showed a comparable decline for both treatment arms and, the decline was consistently lower in the Lucentis arm. With the exception of the differences in CRT of the FCP at Visit 5/Week 4, Visit 6/Week 8 and Visit 7/Week 12, where the INTP18 arm showed a significantly greater reduction from baseline compared to the Lucentis arm (INTP18 vs. Lucentis, mean (±SD): -137.7 (± 141.27) µm vs. -101.3 (± 110.57), p-value: 0.0012; -151.9 (± 153.61) vs. -126.2 (± 123.53), p-value: 0.0360; -163.8 (± 159.76) vs. -137.8 (± 123.51), p-value: 0.0406), there was no statistically significant difference between the two treatment arms for mean change in central retinal thickness.

Similar outcomes have been shown for the mITT set.

The results for **mean central retinal thickness** (CRT) of the **foveal central subfield** (FCS) were consistent with those for FCP. The mean foveal central subfield (FCS) at baseline was slightly bigger in the INTP18 group compared to the Lucentis group. The values decreased in both groups over time and were overall comparable up to Week 52.

The **change from baseline** in CRT of the FCS showed a comparable decline for both treatment arms but the decline was consistently lower in the Lucentis arm. With the exception of the difference in CRT of the FCS at Visit 5/Week 4 and Visit 7/Week 12, where the INTP18 arm showed a significantly greater reduction from baseline compared to the Lucentis arm (INTP18 vs. Lucentis, mean (±SD): -110.7 (± 124.33) vs. -89.9 (± 100.22), p-value: 0.0366; -137.9 (± 133.56) vs. -115.8 (± 108.66), respectively), there was no statistically significant difference between the two treatment arms for mean change in central retinal thickness.

Although significant differences between the INTP18 arm and the Lucentis arm have been observed at some timepoints for the **change from baseline** in CRT of the FCP and FCS, also considerably high standard deviations have been reported for these (and all the remaining) timepoints. Hence, the relevance of these differences is rather limited.

Thus, biosimilarity is overall supported as far as retina thickness is concerned.

Furthermore, the "number of patients in respective categories" (n), was overall slightly higher in the INTP18 group compared to the Lucentis group. Due to missing visit data for certain patients, the number of patients included in specific categories (n) may be lower than the total number of patients in the respective treatment group (N). Furthermore, baseline visit data for two patients were missing, which resulted in a lower count for the analysis of change from baseline to CRT of FCP and CRT of FCS.

In addition, the number of patients included in the analysis was lower for the calculation of the "change in CRT from baseline" in comparison to the number of patients for the calculation of the "mean CRT values" at corresponding timepoints, which is due to missing data at certain visits for some patients and prevented calculation of change from baseline and the corresponding mean CRT values at those timepoints. The missing images were either due to missed patient visits or technical errors during image acquisitions.

Similar outcomes have been shown for the mITT set.

In **conclusion**, secondary efficacy analyses support the primary efficacy results.

**Pre-defined and ad hoc important subgroup analyses**

Subgroup analyses have been performed for the primary efficacy endpoint by region/country, by baseline BCVA score for the study eye (⩽54, >54) and by iris colour (dark or light) to determine whether significant differences exist in the primary endpoint results within these subgroups. Note that originally, plans for subgroup analysis by formulation (PFS and single-use vial) and by age group were outlined in the SAP (Version 00, dated 10/02/2022).

**Region/country-wise analysis** showed that the "Mean Change in BCVA from Baseline to Week 8" in the PP set was slightly lower in the INTP18 arm for the subset of patients from **India** (INTP18 vs. Lucentis: 6.5 vs. 6.9 letters). The difference between treatment arms, as well as the 95% CI (i.e., -0.5 letters [-2.2, 1.2]) were fully contained within the predefined acceptance range of [-3.4, 3.4] letters. For the subset of patients from **Europe**, the "Mean Change in BCVA from Baseline to Week 8" was clearly lower in the INTP18 arm (INTP18 vs. Lucentis: 7.2 vs. 8.6letters). However, the difference between treatment arms, as well as the 95% CI (i.e., -1.4 letters [-3.3, 0.6]) were contained within the predefined equivalence margin,

Results by country have been provided with the interim CSR, based on the respective PP set. The

latter has been adapted in the final analysis. Nevertheless, for certain European countries, the effect regarding the lower bound of the 95% CI appears exacerbated. Czech Republic and Latvia had a small sample size and hence a wider CI, however 95% CIs included 0. For Hungary and Poland, the lower limits of 95% CIs were not within the margin of -3.4 letters. While results were not fully within the equivalence range for several subgroups assessed, the individual sample sizes for these are rather small.

Subgroup analysis by **baseline BCVA score** showed comparable LS mean values for the subgroup " BCVA ≤54 letters" . The difference between treatment arms, as well as the 95% CI were contained within the predefined equivalence. This also holds true for the subgroup "BCVA >54 letters".

Subgroup analysis by **iris colour** showed comparable LS mean values for the subgroup "dark iris". The difference between treatment arms, as well as the 95% CI was contained within the predefined equivalence margin. However, for the subgroup "light iris", the LS mean was lower in the INTP18 arm (INTP18 vs. Lucentis: 7.2 vs. 9.0 letters), suggesting a less pronounced effect of INTP18 on VA compared to the reference product. While the estimated difference between treatment arms was contained within the predefined equivalence margin, the lower bound of the 95% CI, clearly fell outside of it (i.e. point estimate -1.8 letters 95% CI [-3.8, 0.3]). Since this subgroup was mostly comprised of European patients, this observation is consistent with the analysis for the European region. In this case, the 95% CI was noticeably asymmetric for patients with light irises. However, it is acknowledged that studies are typically not powered to demonstrate similarity in treatment effect between subgroups and can result in wider CIs crossing the equivalence limits, this discrepancy is not pursued further, and no additional concerns are raised regarding the overall comparability of INTP18 and Lucentis.

#### *5.3.3.2. Conclusions on the clinical efficacy*

In study 0504-19, the efficacy analysis was based on the primary efficacy endpoint "Mean Change in BCVA from Baseline to Week 8". The primary efficacy analysis revealed that the difference between treatment arms, as well as the 95% CI (i.e., -0.7 letters [-2.0, 0.6]) was completely contained within the predefined acceptance range of [-3.4, 3.4] letters, supporting the claim of biosimilarity.

This was further supported by sensitivity analyses and secondary endpoints (Mean change from baseline in BCVA up to 52 weeks; Proportion of subjects who gained ≥5, ≥10 and ≥15 letters; Proportion of subjects who lost ≥5, ≥10 and ≥15 letters; Mean change from baseline in the total area of leakage from CNV; Mean change from baseline in the total area of CNV; Mean change from baseline in central retinal thickness (FCP/FCS)).

In summary, the provided efficacy data support the biosimilarity between INTP18 and Lucentis.

## 5.4. Clinical safety

*Figure 3: Overview of the studies contributing to the safety evaluation of Intas Ranibizumab*

| Study Number | Phase | Status | Study Design | Dosing Regimen | Enrolled / Intas Ranibizumab Dosed | Safety Parameters |
|---|---|---|---|---|---|---|
| 0504-19 | 3 | Completed | Double masked, parallel group, randomised, multicentre, global clinical study to compare efficacy and safety of Intas Ranibizumab with Lucentis in subjects with neovascular (wet) AMD that included a 21-day screening phase, a 48-week double masked intervention phase extending from Day 1 (baseline), and a post-intervention follow up visit (4-weeks after the subject's last dose of study drug to collect any AE/safety assessment since the last study visit). | The subjects were randomised to either Intas Ranibizumab arm or Lucentis arm in a 1:1 ratio:<br>Intas Ranibizumab: 0.5 mg IVT injection every 28 days, a total of 13 doses.<br>Lucentis: 0.5 mg IVT injection every 28 days, a total of 13 doses. | 546 were enrolled<br>273 were dosed | Incidence of AEs and SAEs, laboratory parameters, physical examination, vital signs, ophthalmic examination |

Abbreviations: AE, adverse event; AMD, age-related macular degeneration; ECG, electrocardiogram; IVT, intravitreal; SAE, serious adverse event.

The safety evaluation was based on the safety analysis set that comprised of 546 subjects who received at least one dose of the study drug as of the cutoff date. Unless otherwise specified, all AEs presented are considered to be treatment-emergent AEs (TEAEs). All the 546 randomised subjects received at least one dose of study medication and were included in the safety analysis set: 273 subjects in the Intas Ranibizumab arm and 273 subjects in the Lucentis arm.

### 5.4.1. Safety data collection

Safety considerations associated with the intravitreal route of administration or pharmacology of ranibizumab included endophthalmitis, traumatic complications (i.e., conjunctival haemorrhage, conjunctival oedema, eye irritation, eye pain or ocular foreign body sensation), and post-injection transient increase in IOP. Following the study treatment, participants remained in the clinic for post-injection assessment. The study eye was assessed before injection and then between 5-15 minutes, and 30 (+20) minutes after each IVT injection by the injecting investigator to ensure that the procedure and/or the study medication had not endangered the

health of the eye. The post-injection assessments included gross assessment of vision by finger counting test, measurement of IOP and indirect ophthalmoscopy (to assess the central retinal artery perfusion, presence of retinal detachment, presence of new intraocular haemorrhage(s)).

Complete Ophthalmic Examination

A complete description of standardized procedures and grading scales was outlined in the site operation manual. A complete ophthalmologic examination was done in both eyes at Screening and Week 52/EOS. The ophthalmic exam was done as specified in the schedule of activities and consisted of the following:

• Slit-lamp examination - included evaluation of the lids/lashes, conjunctiva, cornea, iris, lens, and aqueous reaction (cells and flare)

• IOP measurement - a measurement of intraocular pressure was conducted using an applanation tonometer or Tonopen. The same method was used throughout the study for each participant. IOP was measured in the study eye prior to dosing.

• Fundus exam with indirect ophthalmoscopy - included evaluation of the vitreous, retina, macula, choroid, and optic nerve. Dilation for the fundus exam was at the discretion of the Investigator.

• Iris colour: Iris colour was evaluated at screening only, and subjects were stratified based on the colour of their iris (dark iris or light iris).

If study visit assessments and a corresponding treatment occurred on separate days, a repeat ophthalmoscopy was performed as a safety check-up before treatment of the study eye. Results were documented in the source documents but not in the eCRF. If any concern arose, treatment needed to be postponed and a re-evaluation needed to be performed before treatment. Any participant who developed significantly raised IOP (>30 mmHg) or a non-adequately perfused central retinal artery at any time during the study was monitored according to the Investigator's clinical judgment and could undergo additional procedures and measurements of IOP beyond those specified in the protocol. Direct visualization to assess the central retinal artery, presence of retinal detachment, and presence of new intraocular haemorrhage(s) might have been appropriate at the discretion of the investigator and/or based on the results of gross assessment of vision and IOP measurement.

Adverse Events and Serious Adverse Events

Safety assessments consisted of monitoring and recording AEs, including SAEs and non-serious AEs of special interest (AESI), and other protocol-specified tests that were deemed critical to the safety evaluation of the study. AEs were reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study. The investigator and any qualified designees were responsible for detecting, documenting, and recording events that met the definition of an AE or SAE and remained responsible for following up AEs that were serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention. AEs and special reporting situations, whether serious or non-serious, were reported from the start of intervention until 30 days after the last study drug administration or initiation of further treatment of the disease under study, whichever was earlier. Every effort was made to follow all SAEs considered to be related to study intervention until a final outcome could be reported. All AEs were assessed by a masked Investigator.

Adverse Events of Special Interest

An AESI was an event of scientific and medical concern specific to the Sponsor's product or program where ongoing monitoring and rapid communication by the Investigator to the Sponsor was considered appropriate. Depending upon the nature of the event, rapid communication by the Sponsor to other parties might also have been required. AESI for this study included the following:

• AEs resulting from medication error

• Arterial thromboembolic events (ischemic stroke, myocardial infarction, etc.)

• Sight-threatening AEs: An AE was considered to be sight-threatening and had to be reported in an expedited manner if it met one or more of the following criteria:

- Decrease of ≥30 letters in VA score (compared with the last assessment of VA prior to

the most recent assessment) lasting more than 1 hour.

- Decrease in visual acuity to the level of light perception or worse lasting >1 hour

- Surgical intervention (i.e., conventional surgery, vitreous tap, or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.

- Severe intraocular inflammation (i.e., endophthalmitis, 3+ anterior chamber cell/flare or 4+ vitritis).

- Endophthalmitis

- Sustained (>15 minutes) loss of light perception due to elevated IOP OR central retinal artery occlusion; IOP >30 mmHg at/past 60 minutes post-injection OR any elevation of IOP requiring surgical intervention (e.g., paracentesis)

- New retinal tear or detachment

- New vitreous haemorrhage >2+ severity that does not resolve within 14 days of the onset of the event

- Any other AE which in the opinion of the investigator, may require medical intervention to prevent permanent loss of sight. All above-listed sight-threatening AEs were reported as serious events, listing the underlying cause (if known) of the event as the primary event term.

### 5.4.2. Patient exposure

All randomised participants were part of the Safety Set and per definition all participants of the Safety Set received at least one dose of study medication.

*Figure 4: Extent of exposure*

| Product Type | Test Arm (T) | | | | | | | | | | | | | Reference Arm (R) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Exposure | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| Number of Patients (N) | 06 | 05 | 02 | 04 | 05 | 02 | 02 | 03 | 02 | 03 | 10 | 35 | 195 | 03 | 02 | 06 | 03 | 05 | 03 | 03 | 02 | 07 | 04 | 04 | 33 | 198 |

*Exposure means number of doses patients received.
Treatment Specification:
Test Arm (T): Ranibizumab Injection 10 mg/ml Vial
Reference Arm (R): Lucentis®
Source: Study 0504-19 CSR

All the 546 randomised subjects received at least one dose of study medication and were included in the safety analysis set: 273 subjects in the Intas Ranibizumab arm and 273 subjects in the Lucentis arm.

### 5.4.3. Adverse events

Overall, 694 TEAEs were reported by 291 (53.3%) of 546 patients during conduct of the study. The incidence of TEAEs (including ocular TEAEs), study drug related TEAEs, and serious TEAEs was generally similar between the treatment arms:

• TEAEs: 353 TEAEs were reported by 148 (54.2%) of 273 patients from Intas Ranibizumab arm and 341 TEAEs were reported by 143 (52.4 %) of 273 patients from Lucentis® arm.

o Ocular TEAEs: 137 ocular TEAEs (26% patients) were reported in Intas Ranibizumab arm and 122 ocular TEAEs (26.7% patients) were reported in Lucentis® arm.

• Study drug related TEAEs: 44 TEAEs by 29 (10.6%) subjects in Intas Ranibizumab arm versus 42 events by 26 (9.5%) subjects in Lucentis arm.

• Serious TEAEs: 12 TESAEs were reported by 11 patients after receipt of Reference Product-R and 16 TESAEs were reported by 12 patients after receipt of Test Product-T during the study.

Out of the 694 TEAEs, 477 TEAEs were mild, 196 TEAEs were moderate and 21 TEAEs were severe in nature. There were 2 deaths reported in the study (1 death in Intas Ranibizumab arm and 1 death in Lucentis® arm). Two patients in Lucentis arm and no patients in Intas Ranibizumab arm discontinued study due to adverse event. Overall, the AEs reported in Study 0504-19 were generally consistent with the established safety profile of Ranibizumab.

*Table 33: Summary of adverse events*

| TEAEs | Test (T) (N = 273) n (%) e | Reference (R) (N = 273) n (%) e | Total (N = 546) n (%) e |
|---|---|---|---|
| **Severity Grade** | | | |
| Mild AE | 115 (42.1) 237 | 117 (42.9) 240 | 232 (42.5) 477 |
| Moderate AE | 56 (20.5) 106 | 50 (18.3) 90 | 106 (19.4) 196 |
| Severe AE | 8 (2.9) 10 | 10 (3.7) 11 | 18 (3.3) 21 |
| **Relationship to Study Treatment** | | | |
| Certain | 8 (2.9) 8 | 10 (3.7) 17 | 18 (3.3) 25 |
| Probable / Likely | 16 (5.9) 26 | 11 (4.0) 20 | 27 (4.9) 46 |
| Possible | 6 (2.2) 10 | 5 (1.8) 5 | 11 (2.0) 15 |
| Unlikely | 136 (49.8) 306 | 131 (48.0) 297 | 267 (48.9) 603 |
| Conditional /Unclassified | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| Unassessable/Unclassifiable | 2 (0.7) 2 | 2 (0.7) 2 | 4 (0.7) 4 |

| | | | |
|---|---|---|---|
| **Action taken with study treatment** | | | |
| Dose Not Changed | 139 (50.9) 303 | 133 (48.7) 314 | 272 (49.8) 617 |
| Not Applicable | 27 (9.9) 44 | 19 (7.0) 20 | 46 (8.4) 64 |
| Drug Interrupted | 4 (1.5) 5 | 4 (1.5) 5 | 8 (1.5) 10 |
| Drug Withdrawn | 1 (0.4) 1 | 1 (0.4) 2 | 2 (0.4) 3 |
| **Outcome** | | | |
| Converted To SAE | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |
| Change in severity | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| Death | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| Not Yet Recovered | 38 (13.9) 68 | 44 (16.1) 81 | 82 (15.0) 149 |
| Recovered with Sequelae | 3 (1.1) 3 | 3 (1.1) 3 | 6 (1.1) 6 |
| Recovered Without Sequelae | 138 (50.5) 262 | 121 (44.3) 231 | 259 (47.4) 493 |
| Stable | 10 (3.7) 14 | 16 (5.9) 20 | 26 (4.8) 34 |
| Unknown | 2 (0.7) 4 | 2 (0.7) 3 | 4 (0.7) 7 |
| **Total** | 148 (54.2) 353 | 143 (52.4) 341 | 291 (53.3) 694 |

Treatment Specification: Test (T) - Ranibizumab Injection 10 mg/ml Vial; Reference (R) - Lucentis®

N = Number of patients in respective treatments

n = Number of patients in respective categories; e = Number of events

**Note:** Percentages are based on total number of patients in each treatment

*Table 34: Summary of adverse events (Safety Set)*

| | **Intas Ranibizumab (N=273) n (%) e** | **Lucentis (N=273) n (%) e** | **Total (N=546) n (%) e** | **p-value** |
|---|---|---|---|---|
| At least one TEAE | 148 (54.2) 353 | 143 (52.4) 341 | 291 (53.3) 694 | 0.6680 |
| At least one TEAE leading to drug withdrawn | 1 (0.4) 1 | 1 (0.4) 2 | 2 (0.4) 3 | - |
| At least one TESAE | 12 (4.4) 16 | 11 (4.0) 12 | 23 (4.2) 28 | - |
| Seriousness Criteria | | | | - |
| Congenital Anomaly/Birth Defect | 0 (0.0) 0 | 0 (0.0) 0 | 0 (0.0) 0 | - |

| | Intas Ranibizumab (N=273) n (%) e | Lucentis (N=273) n (%) e | Total (N=546) n (%) e | p-value |
|---|---|---|---|---|
| Hospitalization or prolongation of existing hospitalization | 9 (3.3) 12 | 10 (3.7) 10 | 19 (3.5) 22 | - |
| Result in persistent or Significant Disability/incapacity | 0 (0.0) 0 | 0 (0.0) 0 | 0 (0.0) 0 | - |
| Life threatening | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 | - |
| Death | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 | - |
| Other Medically Important Event | 2 (0.7) 2 | 1 (0.4) 1 | 3 (0.5) 3 | - |
| Hospitalization or prolongation of existing hospitalization, other medically important event | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 | - |
| Severity | | | | - |
| Mild | 115 (42.1) 237 | 117 (42.9) 240 | 232 (42.5) 477 | - |
| Moderate | 56 (20.5) 106 | 50 (18.3) 90 | 106 (19.4) 196 | - |
| Severe | 8 (2.9) 10 | 10 (3.7) 11 | 18 (3.3) 21 | - |
| Relationship to Study Treatment | | | | - |
| Related | 29 (10.6) 44 | 26 (9.5) 42 | 55 (10.1) 86 | - |
| Certain | 8 (2.9) 8 | 10 (3.7) 17 | 18 (3.3) 25 | - |
| Probable/Likely | 16 (5.9) 26 | 11 (4.0) 20 | 27 (4.9) 46 | - |
| Possible | 6 (2.2) 10 | 5 (1.8) 5 | 11 (2.0) 15 | - |
| Not-Related | 138 (50.5) 309 | 133 (48.7) 299 | 271 (49.6) 608 | - |
| Unlikely | 136 (49.8) 306 | 131 (48.0) 297 | 267 (48.9) 603 | - |
| Conditional/Unclassified | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 | - |
| Unassessable/Unclassifiable | 2 (0.7) 2 | 2 (0.7) 2 | 4 (0.7) 4 | - |
| Action Taken with Study Treatment | | | | - |
| Dose Increased | 0 (0.0) 0 | 0 (0.0) 0 | 0 (0.0) 0 | - |
| Dose Not Changed | 139 (50.9) 303 | 133 (48.7) 314 | 272 (49.8) 617 | - |
| Dose Reduced | 0 (0.0) 0 | 0 (0.0) 0 | 0 (0.0) 0 | - |
| Drug Interrupted | 4 (1.5) 5 | 4 (1.5) 5 | 8 (1.5) 10 | - |
| Drug Withdrawn | 1 (0.4) 1 | 1 (0.4) 2 | 2 (0.4) 3 | - |
| Not Applicable | 27 (9.9) 44 | 19 (7.0) 20 | 46 (8.4) 64 | - |
| Unknown | 0 (0.0) 0 | 0 (0.0) 0 | 0 (0.0) 0 | - |

| | | | | |
|---|---|---|---|---|
| Outcome | | | | - |
| Death | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 | - |
| Change in severity | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 | - |
| Converted to SAE | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 | - |
| Not yet recovered | 38 (13.9) 68 | 44 (16.1) 81 | 82 (15.0) 149 | - |
| Recovered with sequelae | 3 (1.1) 3 | 3 (1.1) 3 | 6 (1.1) 6 | - |
| | **Intas Ranibizumab (N=273) n (%) e** | **Lucentis (N=273) n (%) e** | **Total (N=546) n (%) e** | **p-value** |
| Recovered without sequelae | 138 (50.5) 262 | 121 (44.3) 231 | 259 (47.4) 493 | - |
| Stable | 10 (3.7) 14 | 16 (5.9) 20 | 26 (4.8) 34 | - |
| Unknown | 2 (0.7) 4 | 2 (0.7) 3 | 4 (0.7) 7 | - |

Abbreviations: e, number of events; N, number of patients in respective treatments; n, number of patients in respective categories; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.
Notes: Percentages were based on the total number of patients in each treatment.
p-value was calculated based on a chi-square test. If any cell had counts less than 5, then the Fisher's exact test was used.
The data cutoff date was 16 Jan 2025.

Common Adverse Events

The most frequently reported treatment emergent adverse events during the study were Conjunctival haemorrhage (6.2 % patients), Urinary tract infection (4.6 % patients), Ocular hyperaemia (4.2 % patients), Nasopharyngitis (3.3 % patients) and Pyrexia (3.1 % patients). Majority of TEAEs were mild or moderate in severity, unlikely to study treatment and recovered without sequelae. The two treatment arms (Intas Ranibizumab and Lucentis®) had similar incidence for treatment-related TEAEs (10.6% and 9.5%). Moreover, both treatment arms (Intas Ranibizumab and Lucentis®) had similar incidence of TESAEs (4.4% and 4%) during the study.

*Figure 5: Adverse events grouped by preferred term*

| System Organ Class | MedDRA (PT) (Version 23.1) | Test Arm (T) (N=273) n (%) e | Reference Arm (R) (N=273) n (%) e | Total (N=546) n (%) e |
|---|---|---|---|---|
| Blood and lymphatic system disorders | Anaemia | 4 (1.5) 4 | 3 (1.1) 3 | 7 (1.3) 7 |
| | Anaemia macrocytic | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Hypochromic anaemia | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Thrombocytopenia | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Thrombocytosis | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| Cardiac disorders | Angina pectoris | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Atrial fibrillation | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Bradycardia | 2 (0.7) 3 | 0 (0.0) 0 | 2 (0.4) 3 |

| System Organ Class | MedDRA (PT) (Version 23.1) | Test Arm (T) (N=273) n (%) e | Reference Arm (R) (N=273) n (%) e | Total (N=546) n (%) e |
|---|---|---|---|---|
| | Cardiac failure | 2 (0.7) 2 | 0 (0.0) 0 | 2 (0.4) 2 |
| | Cardiac failure chronic | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Cardio-respiratory arrest | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Coronary artery disease | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Myocardial infarction | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Myocardial ischaemia | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| Congenital, familial and genetic disorders | Renal fusion anomaly | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| Ear and labyrinth disorders | Deafness | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Deafness neurosensory | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Presbyacusis | 2 (0.7) 2 | 0 (0.0) 0 | 2 (0.4) 2 |
| | Tinnitus | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Vertigo | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| Endocrine disorders | Hyperthyroidism | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Hypothyroidism | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |

| | | | | |
|---|---|---|---|---|
| Eye disorders | Age-related macular degeneration | 2 (0.7) 2 | 0 (0.0) 0 | 2 (0.4) 2 |
| | Blepharitis | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |
| | Cataract | 8 (2.9) 11 | 3 (1.1) 3 | 11 (2.0) 14 |
| | Cataract cortical | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Cataract nuclear | 7 (2.6) 7 | 4 (1.5) 4 | 11 (2.0) 11 |
| | Choroidal neovascularisation | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Conjunctival degeneration | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Conjunctival haemorrhage | 19 (7.0) 23 | 15 (5.5) 20 | 34 (6.2) 43 |
| | Conjunctival hyperaemia | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Conjunctival suffusion | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |
| | Conjunctivitis allergic | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |
| | Cystoid macular oedema | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |

| System Organ Class | MedDRA (PT) (Version 23.1) | Test Arm (T) (N=273) n (%) e | Reference Arm (R) (N=273) n (%) e | Total (N=546) n (%) e |
|---|---|---|---|---|
| | Dry eye | 1 (0.4) 1 | 2 (0.7) 2 | 3 (0.5) 3 |
| | Eye irritation | 1 (0.4) 2 | 0 (0.0) 0 | 1 (0.2) 2 |
| | Eye pain | 2 (0.7) 2 | 5 (1.8) 7 | 7 (1.3) 9 |
| | Eye pruritus | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Eyelid oedema | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Eyelid ptosis | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Flat anterior chamber of eye | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Foreign body sensation in eyes | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Glaucoma | 1 (0.4) 1 | 2 (0.7) 2 | 3 (0.5) 3 |
| | Iridocyclitis | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Iritis | 0 (0.0) 0 | 1 (0.4) 2 | 1 (0.2) 2 |
| | Lacrimation increased | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Lenticular opacities | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Macular degeneration | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Macular oedema | 3 (1.1) 4 | 1 (0.4) 1 | 4 (0.7) 5 |
| | Meibomianitis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Myopic traction maculopathy | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Neovascular age-related macular degeneration | 7 (2.6) 7 | 4 (1.5) 4 | 11 (2.0) 11 |
| | Ocular hyperaemia | 13 (4.8) 17 | 10 (3.7) 11 | 23 (4.2) 28 |
| | Photophobia | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Retinal degeneration | 1 (0.4) 1 | 2 (0.7) 2 | 3 (0.5) 3 |
| | Retinal haemorrhage | 4 (1.5) 5 | 1 (0.4) 1 | 5 (0.9) 6 |
| | Retinal pigment epithelial tear | 2 (0.7) 2 | 1 (0.4) 1 | 3 (0.5) 3 |

| | | | | |
|---|---|---|---|---|
| | Subretinal fluid | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Swelling of eyelid | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |

| System Organ Class | MedDRA (PT) (Version 23.1) | Test Arm (T) (N=273) n (%) e | Reference Arm (R) (N=273) n (%) e | Total (N=546) n (%) e |
|---|---|---|---|---|
| | Vision blurred | 0 (0.0) 0 | 3 (1.1) 3 | 3 (0.5) 3 |
| | Visual acuity reduced | 2 (0.7) 2 | 0 (0.0) 0 | 2 (0.4) 2 |
| | Visual impairment | 2 (0.7) 3 | 4 (1.5) 4 | 6 (1.1) 7 |
| | Vitreoretinal traction syndrome | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Vitreous detachment | 5 (1.8) 7 | 1 (0.4) 1 | 6 (1.1) 8 |
| | Vitreous floaters | 2 (0.7) 2 | 0 (0.0) 0 | 2 (0.4) 2 |
| | Vitritis | 0 (0.0) 0 | 2 (0.7) 3 | 2 (0.4) 3 |
| Gastrointestinal disorders | Abdominal pain | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Abdominal pain upper | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Ascites | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Chronic gastritis | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Constipation | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Diarrhoea | 4 (1.5) 4 | 1 (0.4) 1 | 5 (0.9) 5 |
| | Dyspepsia | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Gastritis | 1 (0.4) 2 | 0 (0.0) 0 | 1 (0.2) 2 |
| | Gastrointestinal obstruction | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Hyperchlorhydria | 3 (1.1) 3 | 1 (0.4) 1 | 4 (0.7) 4 |
| | Inguinal hernia | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Nausea | 2 (0.7) 2 | 1 (0.4) 1 | 3 (0.5) 3 |
| | Toothache | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Umbilical hernia | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Vomiting | 1 (0.4) 1 | 2 (0.7) 2 | 3 (0.5) 3 |

| | | | | |
|---|---|---|---|---|
| General disorders and administration site conditions | Asthenia | 3 (1.1) 3 | 2 (0.7) 2 | 5 (0.9) 5 |
| | Chest pain | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Inflammation | 2 (0.7) 2 | 0 (0.0) 0 | 2 (0.4) 2 |
| | Influenza like illness | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Injection site haemorrhage | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |

| **System Organ Class** | **MedDRA (PT) (Version 23.1)** | **Test Arm (T) (N=273) n (%) e** | **Reference Arm (R) (N=273) n (%) e** | **Total (N=546) n (%) e** |
|---|---|---|---|---|
| | Oedema peripheral | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Pain | 2 (0.7) 2 | 3 (1.1) 3 | 5 (0.9) 5 |
| | Pyrexia | 7 (2.6) 7 | 10 (3.7) 12 | 17 (3.1) 19 |
| | Sensation of foreign body | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Sudden death | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Swelling | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| Hepatobiliary disorders | Cholelithiasis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Hepatic cirrhosis | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Hepatic cyst | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Hepatic steatosis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| Immune system disorders | Drug hypersensitivity | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |

| | | | | |
|---|---|---|---|---|
| Infections and infestations | Bronchitis | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | COVID-19 | 2 (0.7) 2 | 0 (0.0) 0 | 2 (0.4) 2 |
| | COVID-19 pneumonia | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Cellulitis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Conjunctivitis | 4 (1.5) 4 | 7 (2.6) 7 | 11 (2.0) 11 |
| | Conjunctivitis bacterial | 0 (0.0) 0 | 1 (0.4) 2 | 1 (0.2) 2 |
| | Cystitis | 0 (0.0) 0 | 1 (0.4) 6 | 1 (0.2) 6 |
| | Cystitis bacterial | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Dermatophytosis of nail | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Diverticulitis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Ear infection | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Erysipelas | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Gastroenteritis | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Hordeolum | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Influenza | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Laryngitis | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Lower respiratory tract infection | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |

| System Organ Class | MedDRA (PT) (Version 23.1) | Test Arm (T) (N=273) n (%) e | Reference Arm (R) (N=273) n (%) e | Total (N=546) n (%) e |
|---|---|---|---|---|
| | Lyme disease | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Nasopharyngitis | 11 (4.0) 13 | 7 (2.6) 7 | 18 (3.3) 20 |
| | Ophthalmic herpes zoster | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Oral herpes | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Otitis externa | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Otitis media acute | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Periodontitis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Pneumonia | 2 (0.7) 2 | 1 (0.4) 1 | 3 (0.5) 3 |
| | Pulpitis dental | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Rash pustular | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Respiratory tract infection | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |
| | Rhinitis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Tonsillitis | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Typhoid fever | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Upper respiratory tract infection | 5 (1.8) 5 | 4 (1.5) 4 | 9 (1.6) 9 |
| | Urinary tract infection | 14 (5.1) 18 | 11 (4.0) 11 | 25 (4.6) 29 |
| | Vaginal infection | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Varicella | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |

| | | | | |
|---|---|---|---|---|
| Injury, poisoning and procedural complications | Ankle fracture | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Contusion | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Lower limb fracture | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Meniscus injury | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Procedural pain | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Radius fracture | 0 (0.0) 0 | 1 (0.4) 2 | 1 (0.2) 2 |
| | Skin laceration | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Tibia fracture | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| Investigations | Alanine aminotransferase increased | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |

| System Organ Class | MedDRA (PT) (Version 23.1) | Test Arm (T) (N=273) n (%) e | Reference Arm (R) (N=273) n (%) e | Total (N=546) n (%) e |
|---|---|---|---|---|
| | Aspartate aminotransferase increased | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Blood alkaline phosphatase increased | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Blood cholesterol increased | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Blood creatinine increased | 2 (0.7) 2 | 2 (0.7) 2 | 4 (0.7) 4 |
| | Blood lactate dehydrogenase increased | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Blood pressure increased | 5 (1.8) 6 | 5 (1.8) 5 | 10 (1.8) 11 |
| | Blood urea increased | 1 (0.4) 2 | 2 (0.7) 2 | 3 (0.5) 4 |
| | Blood urine present | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Body temperature increased | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Glucose urine present | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Hepatic enzyme increased | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Intraocular pressure increased | 5 (1.8) 9 | 6 (2.2) 11 | 11 (2.0) 20 |

| | | | | |
|---|---|---|---|---|
| Metabolism and nutrition disorders | Diabetes mellitus | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |
| | Dyslipidaemia | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Glucose tolerance impaired | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Gout | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Hypercholesterolaemia | 2 (0.7) 2 | 1 (0.4) 1 | 3 (0.5) 3 |
| | Hyperglycaemia | 7 (2.6) 8 | 9 (3.3) 10 | 16 (2.9) 18 |
| | Hyperlipidaemia | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |
| | Hypertriglyceridaemia | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Hyperuricaemia | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Hypoglycaemia | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Hyponatraemia | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |

| System Organ Class | MedDRA (PT) (Version 23.1) | Test Arm (T) (N=273) n (%) e | Reference Arm (R) (N=273) n (%) e | Total (N=546) n (%) e |
|---|---|---|---|---|
| | Type 1 diabetes mellitus | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Type 2 diabetes mellitus | 1 (0.4) 2 | 1 (0.4) 1 | 2 (0.4) 3 |
| Musculoskeletal and connective tissue disorders | Amplified musculoskeletal pain syndrome | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Ankle deformity | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Arthralgia | 4 (1.5) 4 | 2 (0.7) 2 | 6 (1.1) 6 |
| | Arthritis | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Back pain | 4 (1.5) 5 | 2 (0.7) 2 | 6 (1.1) 7 |
| | Immobilisation syndrome | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Interspinous osteoarthritis | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Joint swelling | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Muscle spasms | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |
| | Myalgia | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Osteoarthritis | 2 (0.7) 2 | 3 (1.1) 4 | 5 (0.9) 6 |
| | Osteoporosis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Pain in extremity | 2 (0.7) 2 | 1 (0.4) 1 | 3 (0.5) 3 |
| | Scoliosis | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Spinal osteoarthritis | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Synovial cyst | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |

| | | | | |
|---|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Basal cell carcinoma | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Breast cancer | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Fibroma | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Haemangioma | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Lipoma | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| Nervous system disorders | Carotid artery stenosis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Cerebral microangiopathy | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Cerebrovascular accident | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Cerebrovascular disorder | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |

| **System Organ Class** | **MedDRA (PT) (Version 23.1)** | **Test Arm (T) (N=273) n (%) e** | **Reference Arm (R) (N=273) n (%) e** | **Total (N=546) n (%) e** |
|---|---|---|---|---|
| | Dizziness | 1 (0.4) 1 | 2 (0.7) 2 | 3 (0.5) 3 |
| | Epilepsy | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Headache | 5 (1.8) 5 | 5 (1.8) 5 | 10 (1.8) 10 |
| | Hypoaesthesia | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |
| | Loss of consciousness | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Monoparesis | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Myoclonus | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Neuropathy peripheral | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Polyneuropathy | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Sciatica | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Subarachnoid haemorrhage | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Transient ischaemic attack | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Vertebrobasilar insufficiency | 0 (0.0) 0 | 1 (0.4) 2 | 1 (0.2) 2 |
| Psychiatric disorders | Anxiety | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |
| | Anxiety disorder | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |

| | | | | |
|---|---|---|---|---|
| Renal and urinary disorders | Azotaemia | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Diabetic nephropathy | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Dysuria | 1 (0.4) 3 | 0 (0.0) 0 | 1 (0.2) 3 |
| | Nephrolithiasis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Proteinuria | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Renal cyst | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Urinary retention | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Urinary tract inflammation | 5 (1.8) 6 | 1 (0.4) 1 | 6 (1.1) 7 |
| Reproductive system and breast disorders | Benign prostatic hyperplasia | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Pelvic pain | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |

| System Organ Class | MedDRA (PT) (Version 23.1) | Test Arm (T) (N=273) n (%) e | Reference Arm (R) (N=273) n (%) e | Total (N=546) n (%) e |
|---|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | Asthma | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Cough | 4 (1.5) 4 | 3 (1.1) 3 | 7 (1.3) 7 |
| | Dyspnoea | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Dyspnoea exertional | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Hiccups | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Obstructive airways disorder | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Oropharyngeal pain | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Pleurisy | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Respiratory disorder | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Rhinitis allergic | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Rhinorrhoea | 4 (1.5) 4 | 2 (0.7) 2 | 6 (1.1) 6 |
| Skin and subcutaneous tissue disorders | Actinic keratosis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Dermatitis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Erythema | 2 (0.7) 2 | 3 (1.1) 5 | 5 (0.9) 7 |
| | Intertrigo | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Pruritus | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Urticaria | 1 (0.4) 2 | 1 (0.4) 1 | 2 (0.4) 3 |

| | | | | |
|---|---|---|---|---|
| Surgical and medical procedures | Bladder catheterisation | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Carpal tunnel decompression | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Cataract operation | 0 (0.0) 0 | 3 (1.1) 3 | 3 (0.5) 3 |
| | Cerumen removal | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Iridotomy | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Ptosis repair | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Skin neoplasm excision | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |
| | Tooth extraction | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| Vascular disorders | Aortic arteriosclerosis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Arteriosclerosis | 0 (0.0) 0 | 2 (0.7) 2 | 2 (0.4) 2 |

| **System Organ Class** | **MedDRA (PT) (Version 23.1)** | **Test Arm (T) (N=273) n (%) e** | **Reference Arm (R) (N=273) n (%) e** | **Total (N=546) n (%) e** |
|---|---|---|---|---|
| | Hypertension | 4 (1.5) 5 | 5 (1.8) 5 | 9 (1.6) 10 |
| | Hypertensive crisis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Hypotension | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Peripheral arterial occlusive disease | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Peripheral artery stenosis | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |

| | | | | |
|---|---|---|---|---|
| Uncoded Events | Bubbles in vitreous body | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Chondropathy left side | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Coronarography | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Elevation of urea and creatinine | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | Immature Senile Cataract NS II-III | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Posterior capsule opacification | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Pronounced weakness after the injection | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Secretions from the eye, OS | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | Tearing | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| | Worsening of Hypertension | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | basalioma excision | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | content remaining in the stomach | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| | displacement of a fragment of the radius and ulna of the left upper limb | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | fracture of the ulna and radius of the left upper limb | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| | low total lymphs ratio | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |

| System Organ Class | MedDRA (PT) (Version 23.1) | Test Arm (T) (N=273) n (%) e | Reference Arm (R) (N=273) n (%) e | Total (N=546) n (%) e |
|---|---|---|---|---|
| TOTAL | | 148 (54.2) 353 | 143 (52.4) 341 | 291 (53.3) 694 |

N = Number of patients in respective treatments

n = Number of patients in respective categories; e = Number of events

Note: Percentages are based on total number of patients in each treatment.

Treatment Specification:

Test Arm (T): Ranibizumab Injection 10 mg/ml Vial

Reference Arm (R): Lucentis®

Summary of adverse events by system organ class and preferred term is presented in Study 0504-19 CSR Table 14.3.2.1.

Source: Study 0504-19 CSR Table 12-1

The most frequently reported treatment emergent adverse events during the study were Conjunctival haemorrhage (6.2 % patients), Urinary tract infection (4.6 % patients), Ocular hyperaemia (4.2 % patients), Nasopharyngitis (3.3 % patients) and Pyrexia (3.1 % patients).

There were 14 TEAEs (Test - 11; Reference - 3) of Cataract, 2 TEAEs (Test – 1; Reference - 1) of Cataract cortical and 11 TEAEs (Test - 7; Reference - 4) of Cataract nuclear observed during the study.

*Figure 6: TEAEs of cataract and its relationship to study treatment*

| | Study Eye (N) | Non-study Eye (N) | Both (N) | Total (N) |
|---|---|---|---|---|
| **PT Term** | | | | |
| Cataract | 08 | 04 | 02 | **14** |
| Cataract cortical | 02 | - | - | **02** |
| Cataract nuclear | 07 | - | 04 | **11** |
| **Relationship to study treatment** | | | | |
| Unlikely | 15 | 04 | 05 | **24** |
| Possible | 01 | - | - | **01** |
| Probable/Likely | - | - | 01 | **01** |
| Unassessable /Unclassifiable | 01 | - | - | **01** |
| **Total** | **17** | **04** | **06** | **27** |

N = Total number of TEAEs reported

The above table indicates that out of total 27 TEAEs of cataract, majority (24 TEAEs) are classified by the applicant as not related to the study treatment. The majority of cataract adverse events were graded as mild to moderate as per severity assessment, with only a single event classified as severe. It is consistent with the natural progression of cataract and does not suggest the acute onset which is usually observed with traumatic or iatrogenic cataract origin. Furthermore, of the 14 cataract events reported in the study, 6 events (~43%) occurred in the non-study eye (four events exclusively in the non-study eye and two events involving both eyes). The occurrence of cataract in untreated eyes strongly supports an age-related or incidental aetiology rather than a treatment- or procedure-related effect.

#### *5.4.3.1. Adverse drug reactions*

Study drug related TEAEs: 44 TEAEs by 29 (10.6%) subjects in Intas Ranibizumab arm versus 42 events by 26 (9.5%) subjects in Lucentis® arm.

There were total 19 patients whose Intra-ocular pressure (IOP) was ≥30 mmHg (13 patients in Lucentis arm and 6 patients in Intas Ranibizumab arm) and 01 patient (Lucentis arm) whose IOP was ≥40 mmHg in the study eye after 30 minutes of study drug injection. Out of these 20 patients, 3 patients in the Lucentis arm (R046 – 32 mmHg, R324 – 30 mmHg and R348 – 36 mmHg) had intra-ocular pressure ≥30 mmHg in study

eye after 60-80 minutes of study drug injection. Furthermore, all these study drug-related TEAEs were previously identified as adverse drug reactions in the published EU SmPC of Lucentis.

### 5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

An AESI was an event of scientific and medical concern specific to the Sponsor's product or program where ongoing monitoring and rapid communication by the Investigator to the Sponsor was considered appropriate. Depending upon the nature of the event, rapid communication by the Sponsor to other parties might also have been required. AESI for this study included the following:

• AEs resulting from medication error

• Arterial thromboembolic events (ischemic stroke, myocardial infarction, etc.)

• Sight-threatening AEs

An AE was considered to be sight-threatening and had to be reported in an expedited manner if it met one or more of the following criteria:

- Decrease of ≥30 letters in VA score (compared with the last assessment of VA prior to the most recent assessment) lasting more than 1 hour.

- Decrease in visual acuity to the level of light perception or worse lasting >1 hour

- Surgical intervention (i.e., conventional surgery, vitreous tap, or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.

- Severe intraocular inflammation (i.e., endophthalmitis, 3+ anterior chamber cell/flare or 4+ vitritis).

- Endophthalmitis

- Sustained (>15 minutes) loss of light perception due to elevated IOP OR central retinal artery occlusion; IOP >30 mmHg at/past 60 minutes post-injection OR any elevation of IOP requiring surgical intervention (e.g., paracentesis)

- New retinal tear or detachment

- New vitreous haemorrhage >2+ severity that does not resolve within 14 days of the onset of the event

- Any other AE which in the opinion of the investigator, may require medical intervention to prevent permanent loss of sight. All above-listed sight-threatening AEs were reported as serious events, listing the underlying cause (if known) of the event as the primary event term.

<u>Severe TEAEs</u>

A total of 8 (2.9%) patients reported 10 severe TEAEs in the Intas Ranibizumab and 10 (3.7%) subjects reported 11 severe TEAEs in the Lucentis arm, however, the incidence of severe TEAEs in both arms was considered low and none of these events was considered as related to the study drug by the investigator, especially considering the age of the included patients. The severe events included in the 2 treatment arms included as below:

• Intas Ranibizumab arm: cerebral arterial infarct, pneumonia, cardiac failure, contusion, nuclear sclerosis, atrial fibrillation, bronchial asthma and myocardial infarction.

- Lucentis arm: otitis externa, pneumonia, hypertension, vertigo, carotid artery stenosis, hypertensive crisis, myocardial infarction, radius fracture, myopic traction maculopathy, and cardio-respiratory arrest.

Deaths

Out of reported 694 TEAEs during the study, the outcome of 02 patient's TEAE was death. Both are not related to the study treatment.

| Patient No. | Preferred Term | Last Treatment administered |
|---|---|---|
| R283 | Sudden Death | T |
| R536 | Cardio-respiratory arrest | R |
| Treatment Specification:<br>T: Test Arm (T): Ranibizumab Injection 10 mg/mL Vial<br>R: Reference Arm (R): Lucentis® | | |

Other Serious Adverse events

There were 28 TESAEs reported by 23 patients during the study. Total 12 TESAEs were reported by 11 patients after receipt of Reference Product-R and 16 TESAEs were reported by 12 patients after receipt of Test Product-T during the study. The causality assessment was judged as unlikely for 26 TESAEs, as possible for 1 TESAE and as certain for 1 TESAE.

*Table 35: Summary of serious adverse events*

| TESAEs | Test (T) (N = 273) n (%) e | Reference (R) (N = 273) n (%) e | Total (N = 546) n (%) e |
|---|---|---|---|
| **Relationship to Study Treatment** | | | |
| Unlikely | 11 (4.0) 15 | 10 (3.7) 11 | 21 (3.8) 26 |
| Possible | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| Certain | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| **Seriousness Criteria** | | | |
| Death | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| Hospitalization or prolongation of existing hospitalization | 9 (3.3) 12 | 10 (3.7) 10 | 19 (3.5) 22 |
| Life threatening | 0 (0.0) 0 | 1 (0.4) 1 | 1 (0.2) 1 |
| Other medically important event | 2 (0.7) 2 | 1 (0.4) 1 | 3 (0.5) 3 |
| Hospitalization or prolongation of existing hospitalization, Other medically important event | 1 (0.4) 1 | 0 (0.0) 0 | 1 (0.2) 1 |
| **Outcome** | | | |
| Death | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| Recovered with sequelae | 1 (0.4) 1 | 1 (0.4) 1 | 2 (0.4) 2 |
| Recovered without sequelae | 9 (3.3) 11 | 7 (2.6) 8 | 16 (2.9) 19 |
| Not yet recovered | 3 (1.1) 3 | 2 (0.7) 2 | 5 (0.9) 5 |
| **Total** | **12 (4.4) 16** | **11 (4.0) 12** | **23 (4.2) 28** |

*Figure 7: Summary of serious adverse events (SAEs)*

| Patient No. | Preferred Term | Last Treatment administered | Severity | Causality | Outcome |
|---|---|---|---|---|---|
| R063 | Cerebrovascular accident | T | Severe | Unlikely | Recovered without sequelae |
| R150 | Lower limb fracture | T | Moderate | Unlikely | Recovered without sequelae |
| R175 | Gastritis | T | Moderate | Unlikely | Recovered without sequelae |
| R175 | Immobilisation syndrome | T | Moderate | Unlikely | Not yet recovered |
| R175 | COVID-19 pneumonia | T | Moderate | Unlikely | Recovered with sequelae |
| R180 | Retinal haemorrhage | T | Moderate | Possible | Not yet recovered |
| R193 | Otitis externa | R | Severe | Unlikely | Recovered with sequelae |
| R216 | Gastrointestinal obstruction | R | Severe | Unlikely | Recovered without sequelae |
| R219 | Pneumonia | R | Severe | Unlikely | Recovered without sequelae |
| R227 | Pneumonia | T | Severe | Unlikely | Recovered without sequelae |
| R227 | Cardiac failure | T | Severe | Unlikely | Recovered without sequelae |
| R261 | Breast cancer | T | Severe | Unlikely | Not yet recovered |
| R265 | Vertigo | R | Severe | Unlikely | Not yet recovered |
| R270 | Blood pressure increased | R | Mild | Unlikely | Not yet recovered |
| R283 | Sudden death | T | Severe | Unlikely | Death |
| R287 | Contusion | T | Severe | Unlikely | Recovered without sequelae |
| R299 | Angina pectoris | T | Moderate | Unlikely | Recovered without sequelae |
| R348 | Intraocular pressure increased | R | Moderate | Certain | Recovered without sequelae |
| R370 | Carotid artery stenosis | R | Severe | Unlikely | Recovered without sequelae |
| R419 | Myocardial infarction | T | Severe | Unlikely | Recovered without sequelae |
| R419 | Atrial fibrillation | T | Severe | Unlikely | Recovered without sequelae |

| Patient No. | Preferred Term | Last Treatment administered | Severity | Causality | Outcome |
|---|---|---|---|---|---|
| R430 | Asthma | T | Severe | Unlikely | Recovered without sequelae |
| R458 | Hypertensive crisis | R | Severe | Unlikely | Recovered without sequelae |
| R467 | Loss of consciousness | R | Moderate | Unlikely | Recovered without sequelae |
| R472 | Myocardial infarction | R | Severe | Unlikely | Recovered without sequelae |
| R472 | Radius fracture | R | Severe | Unlikely | Recovered without sequelae |
| R526 | Gastroenteritis | T | Moderate | Unlikely | Recovered without sequelae |
| R536 | Cardio-respiratory arrest | R | Severe | Unlikely | Death |
| Treatment Specification:<br>Test Arm (T): Ranibizumab Injection 10 mg/ml Vial<br>Reference Arm (R): Lucentis®<br>Source: Study 0504-19 CSR Table 12.5 | | | | | |

Among the serious TEAE events, only 1 serious event of retinal haemorrhage in the Intas Ranibizumab arm and 1 serious event of intraocular pressure increased in the Lucentis arm were considered related to the study drug by the investigator and both events were ocular-related. Other serious TEAEs were unrelated to the study drug. There were no other significant adverse events in the study.

### 5.4.5. Discontinuation due to adverse events

Two patients in Lucentis arm and no patients in Intas Ranibizumab arm discontinued study due to adverse events.

### 5.4.6. Safety in special populations

Not applicable

### 5.4.7. Immunological events

Blood samples will be collected for immunogenicity assessment as secondary endpoint at Day 0 and Week 2, 4, 8, 12, 24, 36 and at 52 / End of study. Serum samples will be screened for antibody binding to Ranibizumab and the titre of confirmed positive samples will be reported. Serum samples will be used to evaluate the immunogenicity of anti-Ranibizumab antibodies. Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period.

The anti-Ranibizumab antibodies will be detected using a validated ELISA based screening assay. All samples deemed positive by the screening assay shall be re-assessed using ELISA based validated confirmatory assay and confirmed positive samples will be submitted for validated ELISA based titre assay and validated neutralizing antibody assay.

Immunogenicity Results

*Figure 8: Patient having immunogenicity positive data (safety set, N=546)*

| Treatments | Test | Results | Day 0 | Week 2 | Week 4 | Week 8 | Week 12 | Week 24 | Week 36 | Week 52 | No. of ADA positive* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Intas Ranibizumab (N=273) | Screening | Potential Positive | 28 | 30 | 29 | 37 | 34 | 43 | 45 | 51 | 111 |
| | Confirmatory | Positive | 7 | 5 | 5 | 7 | 9 | 9 | 14 | 17 | 27 |
| | Neutralizing | Positive | 0 | 1 | 2 | 1 | 3 | 2 | 3 | 7 | 13 |
| | | | | | | | | | | | |
| Lucentis (N=273) | Screening | Potential Positive | 22 | 29 | 26 | 30 | 25 | 30 | 35 | 35 | 105 |
| | Confirmatory | Positive | 5 | 4 | 4 | 4 | 5 | 8 | 8 | 9 | 21 |
| | Neutralizing | Positive | 1 | 0 | 0 | 0 | 1 | 1 | 2 | 1 | 3 |

**(Refer Table No. 14.4.1)**

Note1: N=Number of Patient in respective analysis set, n= Number of patients in respective categories.

Note 2: * The count of unique post dose ADA positive patients (i.e. at least one time-point positive after dosing) for confirmatory and neutralizing assay, the count of unique ADA positive patients including pre-dose data for screening assay.

Over the 52-week treatment period, Intas Ranibizumab demonstrated a higher incidence of immunogenicity compared to Lucentis. Confirmatory positive responders were 27 with Intas Ranibizumab and 21 in Lucentis. Additionally, neutralizing antibody responses were 13 with Intas Ranibizumab and 3 in Lucentis.

Over the 52-week treatment period, both Intas Ranibizumab and Lucentis exhibited low to moderate immunogenicity titres. For Intas Ranibizumab, the proportion of patients with titres in the range of 1 < Titre $\leqslant$ 100 increased progressively, peaking at Week 36 (4.8%) and remaining elevated at Week 52 (3.7%). Notably, a small number of patients (1.1%) developed high titres (>100) at Week 52. In comparison, Lucentis showed lower percentages of moderate titres throughout the study and only isolated occurrences of high titres at Week 24 and Week 36 (0.4% each).

*Figure 9: Comparison of immunogenicity data with efficacy and pharmacokinetic (safety set, N=546)*

| Treatment | ADA status | CFB in BCVA Score at week 52 | | $C_{max}$ (pg/mL) | | |
|---|---|---|---|---|---|---|
| | | n | Mean ± SD | n | Dose | Mean ± SD |
| Intas Ranibizumab (N=273) | Without ADA Confirmatory Positive (N=244) | 211 | 11.0 ± 10.79 | 19 | 1 | 3533.590 ± 2720.4537 |
| | | | | | 7 | 3347.973 ± 2510.0065 |
| | With ADA Confirmatory Positive (N=27) | 27 | 14.2 ± 12.03 | 3 | 1 | 4780.569 ± 1053.6214 |
| | | | | | 7 | 2575.849 ± 1253.3012 |
| Lucentis (N=273) | Without ADA Confirmatory Positive (N=251) | 212 | 12.2 ± 11.56 | 23 | 1 | 3165.873 ± 2286.3846 |
| | | | | | 7 | 2860.3799 ± 1921.1516 |
| | With ADA Confirmatory Positive (N=21) | 21 | 9.8 ± 7.92 | 3 | 1 | 5644.952 ± 2912.2503 |
| | | | | | 7 | 7689.582 ± 3577.1365[€] |

[€] n=2

Note: Immunogenicity data of R213 (Intas Ranibizumab), R395 (Intas Ranibizumab) and R504 (Lucentis) are not received.

The relationship between immunogenicity and clinical efficacy was assessed by comparing the mean change from baseline BCVA at week 52 and pharmacokinetic (i.e. Cmax) across treatment arms and ADA status.

In the Intas Ranibizumab arm, ADA-positive patients showed a slightly higher mean improvement in BCVA compared to ADA-negative patients. Cmax values were higher in ADA-positive patients at dose 1 but lower at dose 7 compared to ADA-negative patients at dose 1 and dose 7. This suggests that although ADA-positive patients initially exhibited elevated systemic exposure, the reduced Cmax observed at later dosing indicates that immunogenicity may have progressively influenced pharmacokinetic behaviour over time. In the Lucentis arm, ADA-positive patients demonstrated slightly lower BCVA improvement than ADA-negative patients. However, Cmax values were higher in ADA-positive patients at both dose 1 and dose 7 compared to ADA-negative patients for dose 1 and dose 7 in the presence of anti-drug antibodies.

Overall, these findings show that no clear association can be established between ADA positivity, efficacy and pharmacokinetics.

## 5.4.8. Safety related to drug-drug interactions and other interactions

Not applicable

## 5.4.9. Vital signs and laboratory findings

No clinically significant increase or significant decrease in mean values over time is expected for any of the laboratory parameters in either of the treatment arms.

Overall, there were minimal changes in the vital sign parameters (including systolic blood pressure, diastolic blood pressure, respiratory rate, heart rate, and body temperature) across visits in the treatment arms with no clinically relevant differences observed between the 2 treatment arms.

## 5.4.10. Post-marketing experience

Not applicable

## 5.4.11. Overall discussion and conclusions on clinical safety

#### *5.4.11.1. Discussion*

The safety assessment of the Rexatilux biosimilar candidate INTP18 was conducted by taking into account the known safety profile of the reference product Lucentis. This is line with the overall concept of comparable safety evaluation for a similar biological medicinal product and thus acceptable.

The clinical safety assessment of INTP18 is based on one phase 3 study (Study 0504-19), a randomised, double-masked, parallel group, multicentre study to compare efficacy and safety of INTP18 in comparison with Lucentis in patients with neovascular (wet) age-related Macular Degeneration (AMD).

The Safety Analysis Set is defined as all randomly assigned patients who received at least 1 full or partial dose of study drug in Study Period of 12 months.

Vital signs, ophthalmologic examinations and adverse events were assessed at every visit of the study, and laboratory tests, physical examination and immunogenicity were assessed less frequently, but throughout the study duration of 52 weeks, which is considered appropriate.

The total safety database for INTP18 in this application consists of 546 patients with (wet) AMD who were exposed to INTP18 or Lucentis (EU) at a dose of 0.5 mg per IVT injection every 4 weeks for 48 weeks (total 13 doses). The chosen posology of IVT injection every 4 weeks until week 48 is considered sensitive from a safety perspective.

The safety profile of Lucentis is well established and the safety database of 546 patients treated for up to 48 weeks with INTP18 is considered sufficient for the general evaluation of safety and immunogenicity of INTPP18 in comparison to the reference product. A follow up of 52 weeks from time of randomisation is considered a relevant time period to assess comparative safety and immunogenicity. The overall design of the study No. 0504-19 is adequate to assess biosimilarity between Intas Ranibizumab and Lucentis in terms of safety/immunogenicity.

The applicant applied for the same indications as approved for the reference product Lucentis in adults:

treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME), proliferative diabetic retinopathy (PDR), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) and visual impairment due to choroidal neovascularisation (CNV), but not for the treatment of paediatric patients with ROP.

The overall number [proportion] of patients who experienced at least 1 TEAE in Study 0504-19 was 148 [54.2%] and 143 [52.4%] patients in the INTP18 and Lucentis groups. The number of patients in the safety data set is deemed adequate for assessment of comparable safety of Intas Ranibizumab with Lucentis in terms of biosimilarity.

TEAEs

148 (54.2%) subjects in the Intas Ranibizumab arm reported a total of 353 TEAEs and 143 (52,4%) subjects in the Lucentis arm reported a total of 341 TEAEs. Majority of the TEAEs were mild and moderate in severity.

TEAEs considered related to the study drug

The number [proportion] of patients who experienced at least 1 TEAE that was considered to be related to the investigational product was 29 [10.6%] and 26 [9.5%] patients in the INTP18 and Lucentis groups, respectively.

According to the applicant, all the certain TEAEs were ocular TEAEs in the study eye, i.e., conjunctival haemorrhage (19 patients [7.0%] in Intas Ranibizumab arm versus 15 [5.5%] patients in Lucentis arm), retinal pigment epithelial tear (2 patients [0.7%] in Intas Ranibizumab arm versus 1 [0.4%] patients in Lucentis arm), vitreous floaters (2 patients [0.7%] in Intas Ranibizumab arm versus 0 patients in Lucentis arm) and intraocular pressure increased (5 patients [1.8%] in Intas Ranibizumab arm versus 6 [2.2%] patients in Lucentis arm).

Ocular TEAEs

Eye disorders were reported in numerically slightly more patients 95 (34.7%) in Intas Ranibizumab as compared to 77 patients (28.2%) in Lucentis arm. The most commonly reported eye disorders were conjunctival haemorrhage (19 patients [7.0%] in Intas Ranibizumab arm versus 15 [5.5%] patients in Lucentis arm), ocular hyperaemia (13 patients [4.8%] in Ranibizumab arm versus 10 patients [3.7%] in Lucentis arm, cataract (8 patients [2.9%] in Intas Ranibizumab arm versus 3 [1.1%] patient in Lucentis arm), cataract nuclear (7 patients [2.6%] in Intas Ranibizumab arm versus 4 [1.5%] patient in Lucentis arm), vitreous detachment (5 patients [1.8%] in Intas Ranibizumab arm versus 1 [0.4%] patient in Lucentis arm), intraocular pressure increased (13 patients in Intas Ranibizumab arm versus 6 patients in Lucentis arm). These are in line with the known safety profile of ranibizumab.

In the Lucentis SmPC, it is mentioned that in adults transient intraocular pressure increase have been seen within 60 minutes of injection of ranibizumab.

Nevertheless, the frequency of cataracts was higher in the Intas Ranibizumab group with 11 subjects vs 3 subjects in the Lucentis Reference group. The applicant classified the majority of these cataracts as unlikely to be related to the investigational product and it was concluded that these events were age-related rather than iatrogenic or traumatic in origin. (Iatrogenic traumatic cataract is included in the SmPC as less frequently reported but serious adverse reaction upon Ranibizumab treatment) The majority of cataract adverse events were graded as mild to moderate as per severity assessment, with only a single event classified as severe. It is consistent with the natural progression of cataract and does not suggest the acute

onset which is usually observed with traumatic or iatrogenic cataract origin. Furthermore, of the 14 cataract events reported in the study, 6 events (~43%) occurred in the non-study eye (four events exclusively in the non-study eye and two events involving both eyes). The occurrence of cataract in untreated eyes strongly supports an age-related or incidental aetiology rather than a treatment- or procedure-related effect.

Non-ocular TEAEs

The most commonly reported non-ocular TEAEs were urinary tract infections (14 patients [5.1%] in Intas Ranibizumab arm versus 11 [4.0%] patients in Lucentis arm), nasopharyngitis (11 patients [4.0%] in Intas Ranibizumab arm versus 7 [2.6%] patients in Lucentis arm), pyrexia (7 patients [2.6%] in Intas Ranibizumab arm versus 10 [3.7%] patient in Lucentis arm), headache (5 patients [1.8%] in Intas Ranibizumab arm versus 5 [1.8%] patients in Lucentis arm) and urinary tract inflammation (5 patients [1.8%] in Intas Ranibizumab arm versus 1 [0.4%] patient in Lucentis arm). Except urinary tract inflammation, occurrence of which was higher in Intas Ranibizumab arm as compared to Lucentis arm, the frequency of other very common Lucentis ADRs was comparable between treatment groups.

Majority of the TEAEs were mild (115 [42.1%] in Intas Ranibizumab arm and 117 [42.9%] in Lucentis arm) and moderate (56 [20.5%] in Intas Ranibizumab arm and 50 [18.3%] in Lucentis arm). 10 severe events were reported in 8 (2.9%) subjects in Intas Ranibizumab arm and 11 severe events in 10 (3.7%) subjects in Lucentis arm. The incidence of severe TEAEs in both arms was considered low and none of the severe TEAEs were considered related to the study drugs by the investigator.

No clinically significant differences between treatment arms were observed in haematology, biochemistry, urinalysis results, and vital signs. Overall, Intas Ranibizumab and Lucentis were well tolerated, and their safety profiles were similar with no significant safety concerns observed.

Severe TEAEs

A total of 8 (2.9%) patients reported 10 severe TEAEs in the Intas Ranibizumab and 10 (3.7%) subjects reported 11 severe TEAEs in the Lucentis arm, however, the incidence of severe TEAEs in both arms was considered low and none of these events was considered as related to the study drug by the investigator, especially considering the age of the included patients.

There was 1 serious ocular TEAE of retinal haemorrhage reported in 1 (0.4%) subject in the Intas Ranibizumab arm and 1 serious TEAE of intraocular pressure increased reported in 1 (0.4%) subject in the Lucentis arm.

The severe events included in the 2 treatment arms included as below:

• Intas Ranibizumab arm: cerebral arterial infarct, pneumonia, cardiac failure, contusion, nuclear sclerosis, atrial fibrillation, bronchial asthma and myocardial infarction.

• Lucentis arm: otitis externa, pneumonia, hypertension, vertigo, carotid artery stenosis, hypertensive crisis, myocardial infarction, radius fracture, myopic traction maculopathy, and cardio-respiratory arrest.

Other Serious adverse Events

There were 28 TESAEs reported by 23 patients during the study. Total 12 TESAEs were reported by 11 patients after receipt of Reference Product-R and 16 TESAEs were reported by 12 patients after receipt of Test Product-T during the study. The causality assessment was judged as unlikely for 26 TESAEs, as possible for 1 TESAE and as certain for 1 TESAE.

There are no new safety signals observed and no new pattern of serious adverse events were reported.

It should be noted that for intraocular anti-VEGF treatments, concerns were raised on potential adverse effects resulting from the systemic suppression of these treatments. These particularly relate to cardiovascular and arterial thromboembolic effects, renal and gastrointestinal effects and wound-healing complications. With ranibizumab, systemic VEGF-inhibiting activity is expected to be low, when compared to other VEGF inhibitors such as bevacizumab or aflibercept. A low frequency of cardiac disorders throughout the study was reported with no significant difference between the treatment groups.

Deaths

There were 2 deaths reported, one in the Intas Ranibizumab treatment group and one in the reference treatment group. Both are not considered related to the study treatment.

Discontinuations

Two patients in Lucentis arm and no patients in Intas Ranibizumab arm discontinued study due to adverse events.

Immunogenicity

Over the 52-week treatment period, Intas Ranibizumab demonstrated a higher incidence of immunogenicity compared to Lucentis. Confirmatory positive responders were 27 with Intas Ranibizumab and 21 in Lucentis. Additionally, neutralizing antibody responses were 13 with Intas Ranibizumab and 3 in Lucentis. Over the 52-week treatment period, both Intas Ranibizumab and Lucentis exhibited low to moderate immunogenicity titres.

The relationship between immunogenicity and clinical efficacy was assessed by comparing the mean change from baseline BCVA at week 52 and pharmacokinetic (i.e. Cmax) across treatment arms and ADA status.

• In the Intas Ranibizumab arm, ADA-positive patients showed a slightly higher mean improvement in BCVA compared to ADA-negative patients. Cmax values were higher in ADA-positive patients at dose 1 but lower at dose 7 compared to ADA-negative patients at dose 1 and dose 7. This suggests that although ADA-positive patients initially exhibited elevated systemic exposure, the reduced Cmax observed at later dosing indicates that immunogenicity may have progressively influenced pharmacokinetic behaviour over time.

• In the Lucentis arm, ADA-positive patients demonstrated slightly lower BCVA improvement than ADA-negative patients. However, Cmax values were higher in ADA-positive patients at both dose 1 and dose 7 compared to ADA-negative patients for dose 1 and dose 7 in the presence of anti-drug antibodies.

Overall, these findings show that no clear association can be established between ADA positivity, efficacy and pharmacokinetics.

There was no apparent impact of ADA+ status on clinical safety. Given the contradictory outcomes and the overall low number of ADA+ subjects in the trial, it is not feasible to ascribe clinical significance to these observations.

In general, Intas Ranibizumab shows higher immunogenicity positive patients across all visits compared to Lucentis. As per Lucentis (ranibizumab injection) for intravitreal injection (SmPC), antibodies to Lucentis were detected in 1% to 9% patients following 6 to 24 months treatment. Intas Ranibizumab shows a stronger and more progressive immunogenic response compared to Lucentis. However, there was not an obvious relationship between ADA positivity and safety, though this cannot be completely ruled out.

#### 5.4.11.1.1. Overall assessment of available safety data

The safety profile of Lucentis is well established and the safety database of 546 patients treated for up to 48 weeks with INTP18 is considered sufficient for the general evaluation of safety and immunogenicity of INTPP18 in comparison to the reference product. There were no significant differences in frequency of either adverse events, drug related adverse events, deaths and discontinuation by treatment groups. However, the frequency of cataract was higher in the Intas Ranibizumab group compared to the Lucentis Reference group. The majority of cataract adverse events were graded as mild to moderate as per severity assessment, with only a single event classified as severe. It is consistent with the natural progression of cataract and does not suggest the acute onset which is usually observed with traumatic or iatrogenic cataract origin. Furthermore, of the 14 cataract events reported in the study, 6 events (~43%) occurred in the non-study eye (four events exclusively in the non-study eye and two events involving both eyes). The occurrence of cataract in untreated eyes strongly supports an age-related or incidental aetiology rather than a treatment- or procedure-related effect. The majority of cataract adverse events were graded as mild to moderate as per severity assessment, with only a single event classified as severe.

In general, Intas Ranibizumab shows higher immunogenicity positive patients across all visits compared to Lucentis. Therefore, Intas Ranibizumab shows a stronger and more progressive immunogenic response compared to Lucentis. Hence, immunogenicity response of Intas Ranibizumab is comparable with literature data. Furthermore, there was not an obvious relationship between ADA positivity and safety, though this cannot be completely ruled out.

#### *5.4.11.2. Conclusions on clinical safety*

The safety profile established in the Intas Ranibizumab clinical development program is consistent with the known safety profile of Lucentis. Therefore, Rexatilux is **approvable** from a safety perspective.

# 6. Risk management plan

## *6.1. Safety specification*

### 6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

*Table 36:* Summary of safety concerns in the proposed RMP

| ***Summary of safety concerns*** | |
|---|---|
| ***Important identified risks*** | Infectious endophthalmitis<br>Intraocular inflammation<br>Retinal detachment and retinal tear<br>Intraocular pressure increase |
| ***Important potential risks*** | None |
| ***Missing information*** | None |

### 6.1.2. Discussion on proposed safety specification

The applicant proposed a summary of safety concerns as shown above.

The proposed summary of safety concerns is in line with the reference product's (Lucentis (ranibizumab)) latest approved RMP version 22.0 (date of final sign-off: 12 Oct 2022).

The important potential risk "Neurodevelopmental impairment (ROP)" is not included in the summary of safety concerns as it is only relevant for the ROP indication, which is accepted.

No additional safety concerns other than those reported for Lucentis were identified during the development of this biosimilar.

The summary of safety concerns is accepted.

## *6.2. Pharmacovigilance plan*

### 6.2.1. Proposed pharmacovigilance plan

The applicant considers routine pharmacovigilance activities to be sufficient to monitor the safety concerns. The proposed routine pharmacovigilance activity beyond adverse reactions reporting and signal detection is the use of specific adverse reaction follow-up questionnaires to collect data to help further characterise and/or closely monitor the safety concerns of "infectious endophthalmitis"

The applicant did not propose any additional pharmacovigilance activities.

### 6.2.2. Discussion on the pharmacovigilance plan

#### *6.2.2.1. Routine pharmacovigilance activities*

The applicant considers routine pharmacovigilance activities to be sufficient to monitor the safety concerns. This is endorsed.

In line with routine pharmacovigilance activities for the originator Lucentis (ranibizumab), 'Follow up of case reports' is required as other forms of routine pharmacovigilance activity and has been added by the applicant. The subsection 'Other forms of routine pharmacovigilance activities' of section III.1. has been aligned with the originator.

#### *6.2.2.2. Additional pharmacovigilance activities*

No additional pharmacovigilance activities are proposed by the applicant. This is endorsed.

## *6.3. Plans for post-authorisation efficacy studies*

There are no post-authorisation efficacy studies proposed.

## *6.4. Risk minimisation measures*

### 6.4.1. Proposed risk minimisation measures

*Table 37: Planned routine risk minimisation measures by safety concern*

| **Safety concern** | **Routine risk minimisation activities** |
|---|---|
| Infectious endophthalmitis | Routine risk communication:<br>• SmPC Sections 4.2, 4.3, 4.4, 4.8, 6.6.<br>• PL Sections 2, 3, 4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Recommendation to minimize the potential to develop infectious endophthalmitis associated with an intravitreal injection is included in SmPC section 6.6.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Pack size: one vial or one PFS for single use only.<br>• Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. |
| Intraocular inflammation | Routine risk communication:<br>• SmPC Sections 4.3, 4.4.<br>• PL Sections 2, 4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• None.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Pack size: one vial or one PFS for one injection. |

| | |
|---|---|
| | • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. |
| Retinal detachment and retinal tear | Routine risk communication:<br>• SmPC Sections 4.4, 4.8.<br>• PL Sections 2, 4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• None.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Pack size: one vial or one PFS for single use only.<br>• Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. |
| Intraocular pressure increase | Routine risk communication:<br>• SmPC Sections 4.4, 4.8, 4.9.<br>• PL Sections 2, 4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Recommendation for monitoring and managing both intraocular pressure and the perfusion of the optic nerve head is included in SmPC section 4.4.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Pack size: one vial or one PFS for single use only.<br>• Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. |

In addition, the applicant has proposed the following additional risk minimisation measures:

In line with the reference product Lucentis (ranibizumab), an educational plan for adult patients for the indications nAMD, CNV, DME, RVO, and PDR is proposed by the applicant. Patient information booklets are developed by the applicant to ensure that patients are adequately informed about the potential to develop IOP increase, intraocular inflammation, retinal detachment and retinal tear, and infectious endophthalmitis after an intravitreal injection of ranibizumab.

The booklets which are also available as audio-file and/or 'in spoken form in audio-CD format', are provided to the physician for distribution to the patient after Rexatilux has been prescribed for them.

Rationale for the additional risk minimization activity:

This additional risk minimization measure is aligned with that of reference product.

The patient information booklets aim to provide adequate patient education on key signs and symptoms of potential adverse reactions and when to seek urgent attention from their physician, ensuring rapid identification and treatment of these events.

## 6.4.2. Discussion on the risk minimisation measures

#### *6.4.2.1. Routine risk minimisation measures*

The proposed routine risk minimisation measures are agreed since the safety concern 'Neurodevelopmental impairment (ROP)' and its RMMM have been removed.

#### *6.4.2.2. Additional risk minimisation measures*

The additional risk minimisation measure proposed is in line with the reference product and is endorsed. It is agreed on the need for information for patients, i.e. educational material directed to the patient, and it is considered vital that the patient receives adequate information on key signs and symptoms and guidance on when to seek medical attention. The patient information booklets are also available as audio-file and/or 'in spoken form in audio-CD format'.

No HCP-material is considered necessary because intravitreal administration has become part of standard practice for ophthalmologists and is part of standard ophthalmology training. HCP material was removed for Lucentis in 2018. The recommendations provided in the SmPC are considered sufficient to minimize the risks.

## *6.5. RMP summary and RMP annexes overall conclusion*

The RMP Part VI and the RMP Annexes are considered acceptable.

## *6.6. Overall conclusion on the Risk Management Plan*

The CHMP and PRAC consider 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 Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

# 7. Pharmacovigilance

## *7.1. Pharmacovigilance system*

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

## *7.2. Periodic safety update reports (PSURs) submission requirements*

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.

# 8. Product information

## *8.1. User consultation*

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Lucentis and Osvryti. The bridging reports submitted by the applicant have been found acceptable.

## *8.2. Additional monitoring*

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rexatilux is included in the additional monitoring list since:

- it is a biological product that is not covered by the previous category* and authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

* As outlined in Good Pharmacovigilance Practise (GVP) Module X - Additional monitoring, section X.C.1.1. Criteria for including a medicinal product in the additional monitoring list - Mandatory scope, the *previous category* refer to medicinal products authorised in the EU that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

# 9. Biosimilarity assessment

## *9.1. Comparability exercise and indications claimed*

Rexatilux (also referred to as Intas Ranibizumab and INTP18) is developed as a biosimilar to the reference product Lucentis. The administration route (intravitreal), posology, and indications are according to the reference product as described in the Lucentis SmPC.

The marketing authorization is **claimed** for

- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

**Quality data**

A comprehensive analytical similarity study was performed by the applicant in order to demonstrate biosimilarity at the quality level between the INTP18 biosimilar and reference medicinal product (RMP).

The number of batches included into the biosimilarity assessment is considered to be appropriate. US Lucentis has been included into the comparability study in order to bridge between the EU and US Lucentis, as US Lucentis has been used in clinical trials. The selected INTP18 FP batches are representative for the commercial FP.

Based on quality attributes criticality ranking approach, an approach which is in principle supported, an evaluation plan has been designed. The resulting criticality ranking of the quality attributes is not fully endorsed. Nevertheless, considering the results of the individual batches in the comparability exercise as well as the number of batches included for each quality attribute, the ranking of the quality attributes does not have an impact on the similarity conclusion.

A methodological approach was applied for the definition of the acceptance criteria set for the biosimilarity exercise and has been provided. Based on the results observed no impact on the overall conclusion on biosimilarity is expected as the overall conclusion on biosimilarity is based on the measured values and results provided.

Concerning the analytical methods and quality attributes, it is acknowledged that the recommendations given by the CHMP in the Scientific Advice from 2019 and 2024 (procedure number EMEA/H/SA/4312/1/2019/III and EMA/SA/0000161827) have been taken into account. Thus, a broad and state-of-the-art testing panel of analytical and functional tests have been applied for the biosimilarity evaluation of the primary and higher order structure, functional characteristics, particulates and aggregates and product related variants. Sufficient orthogonal methods have been used in order to determine potential differences in the quality attributes. In detail, the analytical methods used in the biosimilarity exercise are in line with the recommendation given in the EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)

(EMA/CHMP/BWP/247713/2012). All test methods applied at the biosimilarity study have been validated or qualified appropriately.

As recommended in the EMA guideline, forced degradation profiles have also been compared between INTP18 FP and EU and US Lucentis.

**Non-clinical data**

The applicant provided an extensive *in-vitro* functional similarity/comparability program on non-clinical aspects of INTP18. Results of analytical similarity studies conducted to demonstrate biosimilarity between INTP18 and EU- and US-Lucentis are subject of the assessment of Quality aspects and discussed in Quality sections of this assessment report.

**Clinical data**

The clinical developmental program comprises one pivotal clinical study.

The pivotal Phase 3 study 0504-19 (CLARITY) was a multiple dose (0.5 mg per IVT injection every 4 weeks), double-masked, parallel group, randomised (1:1), multicentre, clinical study for a duration of up to 52 weeks to compare efficacy and safety of INTP18 (i.e., Rexatilux or Intas Ranibizumab) with the reference product EU-/US-Lucentis in 546 patients (273 in each treatment arm) with neovascular (wet) age-related macular degeneration (nAMD).

PK was planned to be evaluated in a subset of 50 patients (25 patients of each treatment arm) of study 0504-19. Safety and immunogenicity were evaluated as secondary objectives. PD aspects have been added as secondary endpoints.

Three Scientific Advices were sought from EMA (EMA/CHMP/SAWP/648227/2019, EMA/SA/0000086319, EMA/SA/0000161827), most of the recommendations were implemented.

## *9.2. Results supporting biosimilarity*

**Quality aspects**

For all quality attributes tested in biosimilarity exercise, the following is provided, where applicable: actual results for each batch analysed, min-max for INTP18 and Lucentis, spectra / chromatogram overlays, scatter plots.

Results presented demonstrate high degree of comparability to EU Lucentis for all quality attributes. Most of the results are within the pre-defined biosimilarity range.

**Non-clinical aspects**

In regard of the assessment of the *in-vitro* functional similarity/comparability program in support of the demonstration of biosimilarity of INTP18 to the RMP reference is made to the Quality sections of this report.

**Clinical aspects**

Efficacy

*Primary endpoint*: The least square mean of the **change from baseline in BCVA at Week 8** was slightly lower for the INTP18 arm (INTP18 vs. Lucentis: 7.0 vs. 7.7 letters). The difference between treatment arms, as well as the 95% CI (-0.7 letters [-2.0, 0.6]) was contained within the predefined acceptance range of [-3.4,

3.4] letters.

Supportive MMRM analyses on the mITT set using no explicit imputation of missing values and a supportive ANCOVA on the mITT set with multiple imputation also yielded similar results (LS-mean difference of -0.8 letters with a 95% CI of [-2.0, 0.5]), and LS-mean difference of -0.8letters with a 95% CI of [-2.0, 0.5], respectively). A tipping point analysis performed using an MMRM on the mITT set supported the robustness of the biosimilarity conclusion under MNAR assumptions. Overall, the results presented support the bioequivalence of INTP18 to Lucentis in the primary efficacy endpoint.

Secondary endpoints: The **mean change from baseline** in BCVA in the study eye for INTP18 and Lucentis **over time** was overall slightly lower in the INTP18 vs. Lucentis treatment arm for the PP set. However, from Week 1 up to Week 52, mean change from baseline in BCVA steadily increased over time and reached comparable numbers in both treatment arms.

Overall, the number and/or proportion of patients of the PP set who **gained ⩾5, ⩾10 or ⩾15 letters** over time rose constantly and comparably in both treatment arms.

Also, the **loss of ⩾5, ⩾10 or ⩾15 letters** was shown to be comparable between treatment arms over time, supporting biosimilarity between INTP18 and Lucentis.

Overall, the observed **change in total area of CNV** (mm2) in the PP set declined in a comparable manner in both treatment arms over time. Overall, the observed **change in total area of CNV** (mm2) was comparable between both treatment arms over time.

**Mean central retinal thickness** (CRT) of the **foveal centre point** (FCP) was slightly bigger in the INTP18 group compared to the Lucentis group at baseline for the PP set. The values decreased in both groups over time and were overall comparable up to Week 52. The **change from baseline** in CRT of the FCP showed a comparable decline for both treatment arms. The results for **mean central retinal thickness** (CRT) of the **foveal central subfield** (FCS) were consistent with those for FCP.

Similar outcomes have been shown for the mITT set.

Safety

The clinical safety assessment of INTP18 is based on one phase 3 study (Study 0504-19), a randomised, double-masked, parallel group, multicentre study to compare efficacy and safety of INTP18 in comparison with Lucentis in patients with neovascular (wet) AMD for 52 weeks.

Overall, 694 TEAEs were reported by 291 (53.3%) of 546 patients during conduct of the study. The incidence of TEAEs (including ocular TEAEs), study drug related TEAEs, and serious TEAEs was generally similar between the treatment arms. 353 TEAEs were reported by 148 (54.2%) of 273 patients from Intas Ranibizumab arm and 341 TEAEs were reported by 143 (52.4 %) of 273 patients from Lucentis arm.

Ocular TEAEs: 137 ocular TEAEs (26% patients) were reported in Intas Ranibizumab arm and 122 ocular TEAEs (26.7% patients) were reported in Lucentis arm. Study drug related TEAEs: 44 TEAEs by 29 (10.6%) subjects in Intas Ranibizumab arm versus 42 events by 26 (9.5%) subjects in Lucentis arm.

Out of the 694 TEAEs, 477 TEAEs were mild, 196 TEAEs were moderate and 21 TEAEs were severe in nature.

The most frequently reported ocular TEAE in the study eye was conjunctival haemorrhage during the entire study (19 [7.0%] and 15 [5.5%]) patients, respectively. In general, the frequency of ocular adverse events was low and there were no significant differences in frequency of ocular adverse events by treatment groups (except cataract, see 10.3). The most frequently (≥5% subjects in either of the treatment arms) reported

TEAEs by SOC included eye disorders, infections and infestations, and metabolism and nutrition disorders. No differences between treatment groups were observed.

No clinically significant differences between treatment arms were observed in haematology, biochemistry, urinalysis results, and vital signs from baseline through Week 52. Overall, Intas Ranibizumab and Lucentis were well tolerated, and their safety profiles were similar with no significant safety concerns observed.

A total of 11 (4.0%) subjects in the Intas Ranibizumab arm had 12 serious TEAEs and 12 (25.8%) subjects in the Lucentis arm had 16 serious TEAEs. There were no notable differences in the incidence of serious adverse events between the treatment groups throughout the study. In general, there were no new safety signals observed or new pattern of serious adverse events reported.

It should be noted that for intraocular anti-VEGF treatments, concerns were raised on potential adverse effects resulting from the systemic suppression of these treatments. These particularly relate to cardiovascular and arterial thromboembolic effects, renal and gastrointestinal effects and wound-healing complications. With ranibizumab, systemic VEGF-inhibiting activity is expected to be low, when compared to other VEGF inhibitors such as bevacizumab or aflibercept. However, based on the fact that no PK data are included so far the non-ocular safety profile and the evaluation of the mentioned class effects seems of particular interest for the present procedure. A low number of cardiac disorders throughout the study was reported with no significant difference between the treatment groups.

There were 2 deaths reported in the study (1 death in Intas Ranibizumab arm and 1 death in Lucentis arm). Two patients in Lucentis arm and no patients in Intas Ranibizumab arm discontinued study due to adverse event. It is acknowledged, that the number of discontinuation and deaths is very low. Further for the phase 3 study it is acknowledged that most frequent reported AEs are in line with the AEs reported for the reference product.

## *9.3. Uncertainties and limitations about biosimilarity*

**Quality aspects**

There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity.

**Non-clinical aspects**

In regard of the assessment of the in-*vitro* functional similarity/comparability program in support of the demonstration of biosimilarity of INTP18 to the RMP reference, there are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity.

**Clinical aspects**

PK/PD

No dedicated (comparative) clinical pharmacodynamic studies have been performed as part of the clinical biosimilarity exercise for INTP18.

Efficacy

The method used for generating the (stratified) central randomisation scheme that was implemented via the interactive web response system was not unequivocally stated. The resulting scheme appears

to have a low randomness component.

**Minor protocol deviations** that were considered "site level deviations" have not been discussed in detail. Thus, the nature of these minor protocol deviations is not fully clear. It remains, furthermore, unclear how many patients were concerned by minor protocol deviations. The frequency of occurrence of the minor protocol deviations per type can therefore not be compared between treatment arms.

Regarding **major protocol deviations**, it cannot fully be understood, why the 2 "exclusion criteria related" major protocol deviations were considered not to have any potential influence at the primary efficacy analysis as an elevated blood pressure is associated with lower choroidal blood flow and disturbed vascular homeostasis, contributing to the pathogenesis of AMD. It also remains unclear, in how far the violation of inclusion criteria was handled.

In addition, for the subgroup "light iris", VA was lower for the INTP18 arm compared to the reference product. While the difference between treatment arms was contained within the predefined equivalence margin, the lower bound of the 95% CI, clearly fell outside of it.

Safety

The applicant addressed the concern regarding cataract frequency accordingly. The frequency was higher in the Intas Ranibizumab group with 11 subjects vs 3 subjects in the Lucentis Reference group. The applicant classified the majority of cataracts as unlikely to be related to the investigational product and it was concluded that these events were age-related rather than iatrogenic or traumatic in origin.

The majority of cataract adverse events were graded as mild to moderate as per severity assessment, with only a single event classified as severe. It is consistent with the natural progression of cataract and does not suggest the acute onset which is usually observed with traumatic or iatrogenic cataract origin. Furthermore, of the 14 cataract events reported in the study, 6 events (~43%) occurred in the non-study eye (four events exclusively in the non-study eye and two events involving both eyes). The occurrence of cataract in untreated eyes strongly supports an age-related or incidental aetiology rather than a treatment- or procedure-related effect.

In general, Intas Ranibizumab shows higher immunogenicity positive patients across all visits compared to Lucentis. Therefore, Intas Ranibizumab shows a stronger and more progressive immunogenic response compared to Lucentis. However, there was not an obvious relationship between ADA positivity and safety, though this cannot be completely ruled out.

## *9.4. Discussion on biosimilarity*

### *Quality*

Quality results presented indicate high degree of similarity between Rexatilux and reference product Lucentis.

### Non-clinical aspects

Regarding biosimilarity assessment of Rexatilux to the reference product Lucentis, reference is made to the Quality sections of this report as the assessment of biosimilarity of INTP18 and Lucentis was primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted.

**Clinical aspects**

The pivotal comparative efficacy and safety study in neovascular AMD patients evaluating the proposed biosimilar INTP18 and EU-/US-Lucentis is overall adequately designed. Biosimilarity was demonstrated as the primary efficacy endpoint *Mean Change in BCVA from Baseline to Week 8* in the PP set was met. Results were supported by sensitivity analyses and outcomes obtained in the mITT set. Additional analyses investigating the treatment effect over time were overall consistent between treatment arms.

Overall, the safety data from the clinical trial appear consistent with the established safety profile of the reference product Lucentis. Rexatilux is **approvable** from a safety perspective.

## *9.5. Extrapolation of safety and efficacy*

The applicant applied for all adult indications granted for the reference product Lucentis (DME, PDR, RVO, and CNV) for the proposed ranibizumab biosimilar INTP18. Ranibizumab is a humanised recombinant monoclonal antibody fragment that binds to the VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165) with high affinity. Thereby ranibizumab prevents binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2 and suppresses neovascularization as well as vascular leakage. The mode of action of ranibizumab is considered to be the same across all approved indications of Lucentis. The biological activities related to the mode of action have been comprehensively evaluated in the analytical similarity exercise.

Therefore, in view of the demonstrated biosimilarity of ranibizumab INTP18 to the ranibizumab reference medicinal product Lucentis, extrapolation to other indications of the reference product than wet AMD is considered acceptable.

## *9.6. Additional considerations*

Not applicable

## *9.7. Conclusions on biosimilarity and benefit risk balance*

In conclusion, based on the review and totality of the submitted data, Rexatilux is considered biosimilar to Lucentis and a benefit/risk balance comparable to the reference product can be concluded.