EMADOC-1829012207-41728
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Orblid

International non-proprietary name: Bevacizumab

Procedure No. EMEA/H/C/006392/0000

Note

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

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List of abbreviations

Please provide a comprehensive list of all abbreviations used throughout the assessment report (quality, non-clinical, clinical).

AVM	Arteriovenous malformations
CAT	Committee for advanced therapies
CO	Cardiac output
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
ESS	Epistaxis severity score
HHT	Hereditary hemorrhagic telangiectasia
HOCF	High output cardiac failure
NYHA	New York Heart Association
PA	Protocol assistance
PD	Pharmacodynamics
PK	Pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
QoL	Quality of life
RMP	Risk management plan
SAE	Serious adverse event
SOC	System organ class
SmPC	Summary of product characteristics
TEAE	Treatment emergent adverse event
VEGF	Vascular endothelial growth factor

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

1.2. Protocol assistance

Table 1: Scientific advice and protocol assistance

Date	*Topic (quality / non-clinical/ clinical)*	*Reference number / Coordinator(s)*	*Brief summary of the advice*
22 October 2015	Clinical	EMA/CHMP/SAWP/666671 /2015	The Protocol assistance pertained to the following clinical aspects: The dose regimen and design of the BABH study.
22 June 2024	Clinical	EMA/SA/0000133895	The Protocol assistance pertained to the following clinical aspects: The dose regimen and the strength of the available clinical data to assess benefit/risk in the HHT indication.

The applicant has received scientific regarding the following aspects:

- Dose selection: The choice of dose for the treatment of HHT, including discussions on optimal dosing and the lack of dedicated dose-finding studies.
- Endpoints in clinical studies: Discussions on the use of transfusion burden and haemoglobin as endpoints.
- Stratification in clinical studies: Concerning disease characteristics, such as nose bleeds and intestinal bleedings.
- Safety database: The appropriate size of the safety database, considering the incidence of the disease.
- Clinical data: Strength of the existing clinical data, including the feasibility of conducting studies with larger numbers of participants.

1.3. Eligibility to the centralised procedure

The applicant Laboratoires Delbert submitted on 9 July 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for ORBLID (Bevacizumab), through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 July 2023.

The applicant applied for the following indication:

ORBLID is indicated for adult patients with confirmed hereditary hemorrhagic telangiectasia (HHT) presenting

(i) severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnoea despite well-conducted cardiological medical treatment and/or

(ii) a severe hemorrhagic form (epistaxis and/or digestive bleeding) of the disease with dependence on transfusions and/or intravenous iron.

1.4. 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, and 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:	Avastin Concentrate for solution for infusion 100 mg and Avastin Concentrate for solution for infusion 400 mg
Marketing authorisation holder:	Roche registration GmbH
Date of authorisation:	12 January 2005
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/04/300/001 and EU/1/04/300/002

Medicinal product authorised in the European Union/Member States where the application is made for European reference medicinal product:

Product name, strength, pharmaceutical form:	Avastin Concentrate for solution for infusion 100 mg and Avastin Concentrate for solution for infusion 400 mg
Marketing authorisation holder:	Roche registration GmbH
Date of authorisation:	12 January 2005
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/04/300/001 and EU/1/04/300/002

Medicinal product which is or has been authorised in accordance with European Union provisions in force and to which bioequivalence has been demonstrated by appropriate comparability studies:

Product name, strength, pharmaceutical form:	Avastin Concentrate for solution for infusion 100 mg and Avastin Concentrate for solution for infusion 400 mg

Marketing authorisation holder:	Roche registration GmbH
Date of authorisation:	12 January 2005
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/04/300/001 and EU/1/04/300/002

1.5. Information on paediatrics

Not applicable

1.6. Information on orphan market exclusivity

ORBLID was designated as an orphan medicinal product EU/3/14/1390 on 16 December 2014 in the following condition: Treatment of hereditary haemorrhagic telangiectasia.

1.6.1. 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.

1.7. Steps taken for the assessment of the product

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

Rapporteur:	Kristina Dunder
Co-rapporteur:	

The rapporteur and Co-rapporteur appointed by the PRAC were:

PRAC rapporteur:	
PRAC Co-rapporteur:	

The application was received by the EMA on	9 July 2025
The procedure started on	2 October 2025
The CHMP rapporteur's first assessment report was received on	19 December 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	22 December 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	06 January 2026
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	29 January 2026
The applicant submitted the responses to the CHMP consolidated List of Questions on	29 April 2026

2. Introduction

2.1. Therapeutic context

HHT is a rare chronic, progressive vascular disorder with a highly heterogeneous clinical expression, affecting approximately 1 in 5,000 to 10,000 people (Plauchu et al. 1989; Ferry et al. 2020; Al-Samkari 2021; de la Natividad Palomares et al. 2023; Serra et al. 2024). Patients who suffer from recurrent and uncontrolled bleeding leading to iron-deficiency anaemia, and those who develop high cardiac output (HCO) failure due to hepatic arteriovenous malformations (AVMs) are subpopulations of the disease that have a high disease burden.

In the bleeding subgroup, patients may experience daily epistaxis with significant blood volume loss and/or occult gastrointestinal haemorrhages that persist over decades, progressively depleting iron stores and leading to severe anaemia. This chronic condition significantly compromises physical functioning, causes profound fatigue, and often results in long-term dependence on iron supplementation or transfusions.

In the HCO failure subpopulation, AVMs within the liver create abnormal vascular shunts that place a sustained volume load on the heart, leading to high output cardiac failure. Symptoms are often subtle in early stages but evolve into debilitating heart failure, arrhythmias, and ultimately, multi-organ complications. Both groups are associated with considerable morbidity, reduced health-related quality of life, and prolonged healthcare utilization. Their chronic, relapsing nature and resistance to spontaneous resolution contribute to a heavy societal burden, particularly in the absence of therapies that modify the disease course. The severe, life-altering manifestations seen in these subgroups of HHT patients highlight the urgent need for targeted interventions that can address the underlying vascular abnormalities and reduce long-term complications.

Currently, there are no specific therapies approved for HHT which remains a rare disease with a high unmet medical need. For patients with severe bleeding, chronic blood loss due to recurrent epistaxis or gastrointestinal bleeding often leads to iron-deficiency anaemia, necessitating regular intravenous iron supplementation or red blood cell transfusions. While these treatments are essential for correcting anaemia and alleviating symptoms such as fatigue and dyspnoea, they impose a substantial burden.

In patients with HCO related to hepatic AVMs, management currently relies on symptomatic treatment with diuretics, beta-blockers, and other heart failure medications aimed at controlling volume overload and stabilizing cardiac function. However, these interventions do not address the underlying vascular pathology, allowing the disease to progress. Over time, patients may become refractory to medical therapy, ultimately requiring orthotopic liver transplantation (LT)—the only curative option. Still, intrahepatic relapse of HHT lesions is a late but common event after LT.

2.2. Aspects of development

The clinical development of ORBLID includes bioequivalence studies (CSR CT-P16 1.1, CSR CT-P16 1.2, CSR CT-P16 3.1) and three proprietary clinical studies (CSR HHT-PS1, CSR HHT-PS2, CSR HHT-RS1) in patients with severe HHT.

Bevacizumab received orphan designation for the treatment of HHT on December 16, 2014 (EU/3/14/1390) by the Hospices Civils de Lyon (HCL), which was transferred to Delbert Laboratory on December 16, 2022 to take on the remaining of the development.

The applicant has also provided a tabulation of 13 published clinical studies. Two are included in section 5.1 of the SmPC and are assessed in this Clinical AR.

Furthermore, a periodic safety update report (PSUR, module 5, section 5.3.5.2.4) of bevacizumab was performed, with a special focus on HHT patients compared to all patients receiving the drug, mainly in an oncologic context as per the original indication.

2.3. Description of the product

According to the draft SmPC, ORBLID (bevacizumab) is indicated for adult patients with confirmed hereditary haemorrhagic telangiectasia (HHT) presenting with

(i) severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnoea despite well-conducted cardiological medical treatment and/or

(ii) a severe hemorrhagic form (epistaxis and/or digestive bleeding) of the disease with dependence on transfusions and/or intravenous iron.

The proposed treatment protocol consists of two phases. An induction phase 5 mg/kg per infusion, every two weeks for a total of 6 infusions (total duration 12 weeks). Following induction, maintenance infusions should be continued at a minimum dose of 5 mg/kg every two months. The dosing interval between infusions should be tailored based on clinical symptoms such as anaemia, bleeding, elevated cardiac output, or dyspnoea. For patients demonstrating inadequate clinical response, the frequency of administration could be increased.

Bevacizumab binds to vascular endothelial growth factor (VEGF), the key factor in vasculogenesis and angiogenesis, thereby inhibiting the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells.

2.4. Inspection issues

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

No inspection is required.

The review of the manufacturer information in module 1 is within the remit of the EMA Inspection Sector and no issues that would trigger a GMP inspection have been identified by the Rapp CMC team during the assessment of the information in module 3 of the dossier. However, it should be noted that a question has been raised in section S.2.1 that the information in the eAF, flow chart and Module 3 is not aligned, and the relevant documents should be updated. **(OC)**

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

No inspection is required.

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

No inspection is required.

3. Quality aspects

3.1. Introduction

CT-P16 drug substance (bevacizumab) is a recombinant humanised monoclonal IgG1 antibody, that binds with high affinity to human vascular endothelial growth factor A (VEGF-A) and prevents it from interacting with VEGF receptor. Neutralisation of the biological activity of VEGF-A by bevacizumab regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

CT-P16 drug substance has been developed as a proposed biosimilar to the reference product EU approved Avastin, containing bevacizumab as the active ingredient. The chosen formulation including sodium phosphate, trehalose and polysorbate 20 and water for injections is the same as that of Avastin. CT-P16 is produced in two presentations, 400 mg/vial and 100 mg/vial (25 mg/ml, concentrate for solution for infusion), and are the same as that approved for Avastin.

The Applicant is seeking marketing authorization for CT-P16 in accordance with Article 10(4) of Directive 2001/83/EC, but for a novel indication (i.e. hereditary haemorrhagic telangiectasia (HHT)). The reference biological medicinal product Avastin was originally approved in the US in February 2004 and in the EU in January 2005 (EMEA/H/C/000582).

3.2. Active substance

3.2.1. General information

CT-P16 (bevacizumab) is a recombinant, humanised Immunoglobulin G subclass 1 (IgG1) type antibody that binds with high affinity to human vascular endothelial growth factor A (VEGF-A) leading to inhibition of the biological activity of VEGF. VEGF is a secreted factor that regulates angiogenesis. CT-P16 has been developed as biosimilar to bevacizumab, which is the active ingredient of AVASTIN.

Structure of bevacizumab is described by providing the amino acid sequence of heavy and light chains.

The detected oligosaccharides consist mostly of G0F and G1F structures. The molecular weight is 146 306 g/mol and formulae for the light and heavy chains are C1034H1595N273O338S6 and C2229H3409N583O677S16, respectively. Each heavy chain consists of 453 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues. Each heavy chain contains an N-linked oligosaccharide at glycosylation site at N303. All cysteines in the heavy and light chain are involved in either intra- chain or inter-chain disulfide bonding.

Overall, adequate information concerning general information of CT-P16 is included.

3.2.2. Manufacture, process controls and process development

Description of manufacturing process and process controls

Manufacture

The sites responsible for manufacture, testing and release of CT-P16 active substance are provided.

Relevant GMP certifications are available, however some relevant information is missing. The information in the eAF, flow chart and Module 3 is not aligned, and the relevant documents should be updated (**OC**).

Description of manufacturing process and process control

The CT-P16 DS for commercial supply is manufactured using a Chinese hamster ovary (CHO) cell line.

The process setup is a standard monoclonal platform technology. Upstream process consists of several cell expansion steps, harvest, clarification and finally filtration. In the downstream process the clarified harvest is purified using a series of purification steps. Purification includes one virus inactivation step and one virus removal step. Finally, the CT-P16 drug substance is filtered into a DS container.

In general, all steps are adequately described and flow-charts with process controls are provided, including critical input process parameters and critical in-process tests. The active substance manufacturing process has been adequately described.

Control of materials

Information on the source of the cell substrate and analysis of the expression construct to develop the Master Cell Bank is described in satisfactory detail. Chinese hamster cells were used to generate the transfected cell line.

Selection process of production cell line is described adequately.

A common two-tiered cell banking system consisting of a Master Cell Bank (MCB) and Working Cell Bank (WCB), is used. Cell banks are tested for identity, purity and genetic characterization/stability.

Overall, the Cell Banking System, Characterisation and Testing are adequately described. The Applicant has provided method descriptions and qualification summaries for the methods used for testing contamination, determining purity, and characterisation of the expression construct.

Virus safety concerning reagents of animal origin used in the production of CT-P16 bioprocessing stage, are assessed in section Adventitious Agents.

Information on the source of cell substrate, expression construct and cell culture media are described in satisfactory details. Other raw materials are also described. No animal or human derived materials are used. Acceptable in-house specifications are in place for non-compendial raw materials.

Control of critical steps and intermediates

Overall, the approach to defining criticality of parameters and in-process tests is in line with relevant EMA guidelines. Control strategy follows a risk-based approach combined with data from early development and product characterisation studies.

The control strategy was developed by establishing quality target product profile (QTPP) for CT-P16 and critical quality attributes (CQAs). Justification of CQAs is detailed and considered acceptable.

A critical process parameter (CPP) is defined as a process parameter that could affect the critical quality attribute (CQA). Criticality of process parameters was determined using an in-house risk assessment tool. A tabular summary linking process variables to process parameters that could influence CQAs is provided. To define the CPPs, the applicant has performed characterization studies. Justifications for the critical process variables are provided in tabular form.

Manufacturing process development

Manufacturing process development is described and summarized. Description of changes and reasons for changes (justification) with respect to the impact on quality are provided and acceptable.

Critical assessment of the significance of changes has been provided.

Comparability assessment covers all necessary tests to conclude the similarity of the DS before and after the manufacturing changes. The stability profiles for each process batches were also studied and are described in more detail. The change did not have a significant influence on the quality of the product.

Process validation and/or evaluation

Process validation (PV) for CT-P16 drug substance was carried out at commercial scale at the intended production site for CT-P16.

Process validation was performed by evaluation of the ability to control process parameters, ability to meet the acceptance criteria for all in-process tests, and the ability to meet specification for all routine tests.

Overall, the results of PV met acceptance criteria.

Overall, it can be concluded that the process consistency was demonstrated with batches meeting their requirements. Process parameters and in-process tests which have different proposed limit/range for commercial manufacture than applied during process validation are adequately justified.

3.2.3. Characterisation and impurities

Characterisation studies were performed using CT-P16 drug substance (DS) and drug product (DP) batches. DS lots were manufactured using the commercial process. All testing was performed in a side-by-side manner to allow direct comparison of the data from CT-P16 drug substance and drug product. Details of the analytical methods and their qualification are provided.

Characterisation results are summarised in the dossier and includes determination of structure (primary, secondary, and higher-order), charge variants, N-linked glycans, purity, and biological activity. Characterisation studies are further discussed and assessed in Biosimilarity section.

Overall, the performed characterization studies are considered relevant and cover a wide variety of physicochemical and biological characterisation studies. Additionally, based on the provided data the DS and DP are comparable on quality, indicating that the drug product manufacturing process do not compromise the physicochemical quality or biological activities of the final product.

Impurities

The Applicant has identified product-related impurities/substances as well as process-related impurities. Impurities are characterised to the extent possible and their biological activities (product-related impurities) and safety aspects are discussed.

Justification of the identification and classification of the product-related impurities can be agreed.

The presented data for process-related impurities demonstrate that the manufacturing process for commercial production is able to clear process-related impurities to acceptable levels. Risk-based analysis or safety margins are provided for process-related impurities which are acceptable.

Product-related impurities and process-related impurities have been sufficiently identified and characterised. Overall, the performed characterization studies are considered relevant and cover a wide variety of physicochemical and biological characteristics or properties.

Evaluation concerning nitrosamines is provided separately for DS and the Applicant´s conclusions on the potential risk of nitrosamines being negligible, can be agreed on.

3.2.4. Control of active substance

Specifications

The specification for CT-P16 DS at release is provided in a tabular form, including tests for general attributes, safety, identity, glycosylation, purity and impurity, content, and potency. Overall, the

proposed test parameters are considered relevant and cover physicochemical test methods and biological activity.

Justification of specification

The proposed specification includes compendial tests and non-compendial tests. Overall, the proposed test parameters are considered adequate.

The stability specification test items are identical to that employed at drug substance release with the exception of parameters, for which no change is expected.

Historical batch data and justification for each parameter is provided with acceptance limits for individual parameters, which is acceptable.

Analytical procedures

The proposed analytical procedures and corresponding limits are adequate for routine control of the active substance at release and shelf life. They are in line with ICH guidelines and Ph. Eur. System suitability testing and assay acceptance criteria of the methods are described. Key materials and equipment are listed. Representative chromatograms are provided for relevant methods.

Validation of analytical methods

The analytical methods are adequate described for their intended purpose and the implemented system suitability tests and sample acceptance criteria appear suitable to provide adequate control over analytical method performance.

Batch data

Batch analysis data for CT-P16 DS lots from all manufacturing processes is provided in the dossier. The results are within the specifications and confirm consistency of the manufacturing process.

Reference standards

Overall, the reference standards used during the product development for batch release have been adequately described. A two-tiered reference standard system is used for commercial manufacturing including primary reference standard (PRS) and working reference standards (WRS). The WRS is used for routine lot release and stability testing, as well as other quality activities such as investigations and method transfers/validation.

Container closer system

CT-P16 drug substance is filled into pre-sterilised, pyrogen free polycarbonate bottles. Representative certificates of analysis provided by the vendor are provided.

Appropriate specifications for the container are in place.

In summary, the CCS is considered suitable. The available leachable data (studies are ongoing) do not hint at a safety risk; nevertheless, updated leachable data should be provided for intermediate storage and long-term storage and the final study results submitted upon completion of the studies. **(OC)**

3.2.5. Stability

Stability studies have been performed in accordance with ICH guidelines in terms of testing frequency and storage conditions using validated methods

Overall, the presented data support the proposed shelf life in the container closure system defined in Module 3.2.S.6. Only a single issue is raised for an update of the dossier regarding the section on stability of drug product.

Post-approval stability protocol

The applicant commits to continuing the stability testing on the drug substance stored at long-term storage conditions according to the protocols presented in section S.7. The post-approval stability protocol for the drug substance is agreed to.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

CT-P16 drug product is a sterile liquid solution containing 400 mg or 100 mg of CT-P16 active substance. Each vial is designed to deliver a single dose of 400 mg or 100 mg active ingredient in 16 mL or 4 mL of solution at a nominal concentration of 25.0 mg/mL.

The components of a vial of drug product along with their function and grade are presented. The batch formula for each 400 mg and 100 mg of CT-P16 drug product is provided in Section 3.2.P.3.2. The finished product contains the active substance (bevacizumab), sodium phosphate, trehalose, polysorbate 20 and water for injection).

Pharmaceutical development

Formulation development

The formulation development section in P.2.2 describes and justifies the chosen formulation and is found acceptably described. The formulation of CT-P16 (i.e. Orblid) and EU-approved Avastin® is identical.

Formulation studies were conducted to evaluate the impact of changes in five formulation parameters. Quality attributes were evaluated and the respective results indicated robustness of the different formulations in terms of product stability and quality. The quality profile of CT-P16 drug product under the chosen formulation showed comparable profile as Avastin® under the evaluated conditions. Taken together, the chosen formulation is considered suitable.

Manufacturing process development

The CT-P16 drug product manufacturing process development has been described in sufficient detail. The production scale, manufacturing site and details of the material usage from each facility were adequately presented for commercial manufacture of CT-P16 400 mg and 100 mg drug products. Changes were introduced to the manufacturing process for process validation of the commercial manufacture of both 400 mg and 100 mg presentations with modification of in-process controls.

The commercial manufacturing process has been validated. To demonstrate that the change in scale of manufacture of CT-P16 drug product has not adversely impacted product quality, an extensive comparability study has been performed.

Control strategy

For a definition of QTPP, CQAs, CPPs and the adequacy of the control strategy, please refer to section P.3.4 and the respective discussion.

The CPPs and IPCs are provided in section P.3.4 and the specifications in section P.5.1.

Comparability

A summary of the comparability studies undertaken was provided and sufficiently demonstrated the comparability of manufacturing processes of different manufacturing facilities or of each product presentation manufactured with the previous and current process.

Container closure system

The primary container closure system for CT-P16 drug product consists of 20 mL or 4 mL type I borosilicate glass vials, a butyl rubber stopper and a 20 mm flip-off cap. Each CT-P16 drug product vial (20 mL or 4 mL) is packed individually in an outer carton box to prevent exposure to UV light and to protect the vial from any potential physical damage during handling, shipping, and storage. The vials and rubber stopper are compliant with Ph. Eur. Suitability of the material was/is further assessed by leachables and stability studies to evaluate compatibility with drug product. The results of the leachable studies for vial and stopper indicate that no leachables of toxicological concern are present, which is compatible with vial and stopper. A question has been raised to provide the final study report from the leachables study on finished product by July 2026 as well as an intermediate update on the leachables study on finished product. **(OC)**

Nitrosamine risk assessment and elemental impurities

A risk assessment of N-nitrosamine contamination has been performed, and results have been provided in module 1 as well as from links in section P.5.5. It is agreed that the risk of formation and entry of N-nitrosamine impurities is negligible.

A risk assessment of elemental impurities has been performed, and results are provided in section P.5.5. It is agreed that the residual quantity of elemental impurities is very low and all meet the requirements specified in ICH Q3D.

Microbiological attributes

The information on microbiological attributes is found sufficient.

Compatibility

A study was conducted to demonstrate the compatibility of CT-P16 drug product diluted in 0.9% w/v sodium chloride with polypropylene (PP) and polyethylene (PE) infusion bags. The diluted CT-P16 drug product was stored at 2 – 8°C for up to 60 days and subsequently 7 days at 30±2°C/75±5% RH and evaluated for leachables. No leachable substances were detected and no significant change of the studied quality attributes was observed thus indicating in-use stability of the drug product diluted in 0.9% w/v sodium chloride in PP and PE infusion bags at 5±3 °C for 60 days and subsequently at 30±2 °C/75±5 % for 7 days.

From the compatibility results provided in section P.2.6 the applicant concludes that chemical and physical in-use stability has been demonstrated for a period of up to 60 days at 2°C to 8°C after dilution and a period of up to 7 days at temperatures not exceeding 30°C in sodium chloride 9 mg/mL (0.9%) solution for injection. This conclusion is agreed to, and it is in-line with the wording in section 6.3 in the SmPC for Orblid.

"Chemical and physical in-use stability has been demonstrated for a period of up to 60 days at 2°C to 8°C after dilution and a period of up to 7 days at temperatures not exceeding 30°C in sodium chloride 9 mg/mL (0.9%) solution for injection."

3.3.2. Manufacture of the product and process controls

Manufacturers and Batch formula

The information provided on manufacturers and batch formula is considered acceptable.

The review of the manufacturer information in module 1 is within the remit of the EMA Inspections Sector. No issues that would trigger a GMP inspection have been identified by the Rapporteur´s team during the assessment of information in Module 3 of the dossier.

Description of manufacturing process and process controls and control of critical steps and intermediates

Appropriate flow diagrams including (critical) process parameters and (critical) in-process tests, and descriptions for each step of the CT-P16 400 mg and 100 mg drug product manufacturing process are presented in the dossier.

Acceptable ranges are provided for the process parameters and brief flow diagrams are provided for the manufacturing process of drug product.

Overall, the description of the sections for manufacturing process and control of critical steps and intermediates of the drug product manufacturing process for both the 100 mg and 400 mg presentations and relevant manufacturing sites are found adequately and sufficiently described reflecting results from both process characterization and process validation studies.

Process validation and/or evaluation

Process validation at relevant manufacturing sites included consecutive commercial scale PPQ lots of each of the CT-P16 400 mg and 100 mg drug product presentations. Minimum and maximum batch sizes with the sufficient number of lots were considered in the process validation studies. Batch data are provided in section P.5.4 for all commercial scale PPQ batches used for the process validation. Furthermore, stability studies have been initiated and run on these batches as well at long-term (2-8 °C), accelerated and stressed conditions as shown in section P.8.

All commercial scale PPQ lots of each of the CT-P16 400 mg and 100 mg drug product presentations complied with the established validation acceptance criteria for all process validation parameters and in-process controls as well as with the acceptance criteria in the proposed DP specifications document in section P.5.1 and demonstrate consistency in manufacturing.

Hold times/process times have been defined and validated, including both hold conditions and periods. The parameters mentioned have been sufficiently supported and confirmed by hold time and media fill studies in section P.3.5.

In conclusion, the process validation approach of DP manufacturing is found acceptable. Further, the process validation data presented in section P.3.5 demonstrate that the manufacturing process of drug product is robust and performs as intended, giving a drug product which meets the quality requirements when run within the defined operating ranges.

This is found sufficient and acceptable, and no issues are raised for the section on manufacture of drug product.

3.3.3. Control of Finished Product

Product specification

The specifications for routine control at release and shelf-life of CT-P16 drug product are presented.

A comprehensive set of relevant tests is included in the specifications document for the CT-P16 drug product in section P.5.1 covering limits for both release and end-of-shelf life of the various attributes. The CT-P16 drug product is tested using a combination of compendial and non-compendial methods. For compendial test methods, relevant pharmacopoeial references have been given and for non-

compendial test methods, detailed descriptions of the procedures have been provided. Information on test method is provided for all analytical procedures used in the drug product specifications document.

The justification for each test and acceptance criteria have been provided in section P.5.6. The proposed acceptance criteria for all test attributes for Orblid are all found justified and acceptable based on developmental batches of CT-P16 drug product and/or the safe use of the reference medicinal product EU approved Avastin. This is found acceptable.

Analytical procedures

Many tests used for release and stability testing of CT-P16 drug product are also used for release and stability testing of drug substance. Appropriate method descriptions have been provided and the analytical procedures were validated in accordance with ICH Q2 and the compendial methods were verified according to the relevant compendia chapters. Reference standards are the same as for DS.

In conclusion, the analytical methods chosen to monitor the CT-P16 drug products identity, purity, potency and quantity have been demonstrated to be suitable for their intended purpose.

Batch analyses

Batch analyses data has been provided for CT-P16 drug product batches, for both the 100 mg- and 400 mg-presentations manufactured throughout the development. All batch analysis data complies with the limits in the proposed drug product release specification in place at the time of manufacture and confirm process and product consistency. In conclusion, the batch data provided demonstrate a reproducible manufacturing of CT-P16 drug product.

Impurities of the drug product

Potential process- and product-related impurities are sufficiently addressed in the dossier and no new impurities have been identified in the drug product compared to the ones already identified for the drug substance.

Elemental impurities and nitrosamines

A risk assessment has been performed of elemental impurities for CT-P16 drug product according to ICH Q3D Guideline for Elemental Impurities. It is agreed to the conclusion that elemental impurities do not pose a safety concern for CT-P16 drug product.

Furthermore, a risk assessment has also been performed of N-nitrosamine contamination for CT-P16 drug product and a report provided. Based on the provided risk assessment, it can be agreed to the conclusion that the risk of the presence of nitrosamine impurities is negligible.

This is found sufficient and acceptable, and no issues are raised for the section on control of drug product.

Container closure system

The development of the container closure system has been sufficiently described in section P.2.4. It consists of 20 mL and 4 mL type I borosilicate glass vials and a butyl rubber stopper.

The primary packaging material has been acceptably described and include schematic drawings, dimensions and the quality standards. The vials and stoppers are in compliance with the appropriate Ph. Eur. monographs for primary containers and closures.

The quality of the vial, stopper, and seal is controlled by the manufacturer/supplier, with the test results for each batch provided in the certificate of analysis (CoA) obtained from the supplier.

Manufacturers of primary packaging components are appropriately listed.

3.3.4. Stability of the product

TThe proposed shelf-life for the 400 mg and 100 mg DP presentations is 48 months when stored at the recommended storage condition of 2-8 °C.

All stability results available at long-term storage conditions of 2-8 °C complies with the proposed end-of-shelf-life/stability specifications up to 48 months. Some trends in a few attributes are seen at accelerated storage and stressed conditions while no significant changes were observed for all other tested attributes.

Photostability testing has been performed according to ICH Q1B and showed that the DP should be kept in the outer carton in order to protect from light induced degradation, in line with the wording in section 6.4 in the SmPC.

Compatibility of the drug product with the infusion medium (0.9% sodium chloride) has been studied and satisfactorily demonstrated during the development and in-use stability studies. In-use stability has been studied to simulate in-use conditions and verify the chemical and physical in-use stability of the diluted drug product as well as to confirm the compatibility with the material of the infusion bags as specified in section 6.6 in the SmPC. The proposed shelf-life for diluted CT-P16 drug product in 100 mL polyolefin (PP and PE) bag containing 0.9 % sodium chloride is 60 days at 5 ± 3ºC and subsequently for 7 days at 30 ± 2 °C / 75 ± 5 % RH. The statement in section 6.6 in the SmPC *"No incompatibilities between ORBLID and polyolefine bags or infusion sets have been observed"* is agreed to.

Post-approval stability protocol

The applicant commits to continuing the stability testing on the drug product stored at long-term storage conditions according to the protocols presented in section P.8. The post-approval stability protocol for CT-P16 DP is agreed to.

Proposed shelf-life and storage conditions

The proposed shelf-life of 48 months is found acceptable for the 100 mg and 400 mg presentations of CT-P16 DP when stored in the commercial container protected from light at the recommended storage conditions of 5 ± 3ºC. In addition, the proposed shelf-life for diluted CT-P16 DP in 100 mL polyolefin (PP and PE) bag containing 0.9 % sodium chloride is 60 days at 5 ± 3ºC and subsequently for 7 days at 30 ± 2 °C / 75 ± 5 % RH is found acceptable as well. However, an update of the stability data should be provided as few time points have been reached which are not provided. **(OC)**

This is found sufficient and acceptable, and only a single issue is raised for an update of the dossier regarding the section on stability of drug product.

3.3.5. Biosimilarity exercise

General strategy for biosimilarity assessment

CT-P16 has been developed as a proposed biosimilar candidate to the reference medicinal product (RMP) EU-approved Avastin containing bevacizumab as active ingredient. The RMP for this MAA is EU-approved Avastin.

The Applicant presents a 2-way biosimilarity study between CT-P16 and EU-approved Avastin.

Several independent CT-P16 DP batches and several EU-approved Avastin batches were included in the similarity study and the batches cover an appropriate range of expiration dates and product ages. All samples were stored under prescribed conditions. The DP material used in the analytical biosimilarity

studies is considered representative of the commercial material. The similarity analyses were performed side-by-side (as possible) using a qualified in-house reference standard.

The approach and methodology of the analytical similarity assessment is sufficiently described and overall acceptable. The similarity assessment is well presented in the dossier and figures and tables summarising the individual results as well as chromatographs, spectra, etc. have been included.

Comparability of the 100 mg/vial and 400 mg/vial presentations of CT-P16 have been sufficiently demonstrated, see assessor´s comments in section P.2.3.

The Applicant used a statistical analysis to evaluate similarity of biological functions of CT-P16 and EU-Avastin based on comparability ranges of mean ± 3 SD of the RMP. This approach is considered reasonable although not fully aligned with the current guidance (EMA/CHMP/BWP/247713/2012; EMA/CHMP/138502/2017). However, since the applicant also provides graphical and tabular presentations of individual analytical results and side-by-side comparisons for both CT-P16 and Avastin, this enables an assessment independent of the defined quality ranges of each attribute. From the graphical presentations, it was also concluded that the quality ranges were acceptably defined and differences have been highlighted and discussed.

Additional mechanism of action studies was performed using several lots each of CT-P16 and EU-Avastin. These data were evaluated in a descriptive manner without using comparability ranges.

The selected set of orthogonal state-of-the-art analytical methods is considered comprehensive and relevant, covering primary and higher order structure, post-translational modifications, size and charge variants, aggregates, protein concentration, as well as Fab- or Fc-mediated biological functions, and is also judged as adequate to address the relevant quality attributes of bevacizumab. The descriptions and qualification data that have been provided for the analytical methods used for the analytical comparability exercise are considered sufficient.

In conclusion, the information provided on the general approach to assess analytical similarity is found sufficient and acceptable.

Primary structure and post-translational modifications

The primary structure was analysed on CT-P16 and EU-approved Avastin by intact mass (LC-MS), sequence coverage by peptide mapping (LC-MS) and C- and N-terminal amino acid sequences by peptide mapping (MS-MS). CT-P16 and Avastin were shown to have similar intact mass and same amino acid sequence with a 100% sequence coverage as well as the same N-terminal and C-terminal sequences.

The analysis of the post-translational modifications of the light and heavy chains of CT-P16 and Avastin were evaluated by peptide mapping (LC-MS). CT-P16 and EU-approved Avastin contain the same post-translational modifications but with some minor quantitative differences These observed differences noted are rather minor and appropriately discussed and sufficiently justified as not expected to have adverse impact on clinical performance.

The data support the claim of similarity of primary structure between CT-P16 and EU-approved Avastin. This is found sufficient and acceptable.

Charge heterogeneity

IEC-HPLC and icIEF have been applied to compare batches of the biosimilar candidate CT-P16 DP and EU-approved Avastin with respect to charge related variants.

Isoelectric point (pI) of charge variants in CT-P16 and EU-approved Avastin was determined by isoelectric focusing (icIEF). The icIEF electropherograms show a similar pattern in all samples at large with only some minor differences noted that was sufficiently justified as not clinically significant.

Several charge variant peaks were detected by IEC-HPLC in both CT-P16 and EU-approved Avastin and no other peaks/new charge variants were detected. Some minor differences between CT-P16 and EU-approved Avastin were noted in the relative proportion of the charge variants. Based on the results of glycation study and supported by results from the peak characterisation study as well as peptide mapping (LC-MA) and nrCE-SDS, it can be agreed that the slight differences observed in charge variant profiles are unlikely to affect safety and efficacy and are clinically insignificant. In addition, all variants are biologically active.

In conclusion, similar charge variants profiles have at large been demonstrated for batches of CT-P16 DP compared to EU-approved Avastin. Only some minor differences are noted in acidic and basic variants, but they have all been sufficiently justified as not clinically meaningful. This is found sufficient and acceptable.

Glycation and glycosylation

Glycation of CT-P16 and EU-approved Avastin was analysed by LC-MS, N-linked glycan profiles determined by HILIC-UPLC-FLD and the type and amount of N-glycans attached to peptides evaluated by peptide mapping (LC-MS).

Glycated LC and HC were detected in all CT-P16 and Avastin samples but slightly different levels of glycation of both the LC and HC were shown in CT-P16. The Applicant justifies that the difference in the glycation levels is not likely to have an adverse effect on efficacy as none of the glycation sites are located in either epitope binding or Fc receptor binding regions. This is also supported by the biological activity study results.

The oligosaccharide profile appears comparable for CT-P16 and EU-approved Avastin. The small differences in individual fucosylated glycan species are highly unlikely to be of clinical relevance as the MoA of bevacizumab is not mediated by Fc effector functions (ADCC, CDC).

Since ADCC and CDC are not relevant MoAs for bevacizumab, comparison of the overall N-linked glycan profile is regarded as appropriate for elucidation of similarity. Based on the reported results on glycan profile, CT-P16 and EU-approved Avastin are considered similar. This is found sufficient and acceptable.

Size heterogeneity

Several complementary and orthogonal analytical tests have been applied to compare batches of the biosimilar candidate CT-P16 and the RMP EU-approved Avastin with respect to size related variants including assessments of HMWs, LMWs, HC+LC and NGHC. Size heterogeneity has been evaluated by SEC-HPLC (diluted and neat), SEC-MALS, AUC and CE-SDS (reduced and non-reduced). the biosimilar candidate CT-P16 and the RMP EU-approved Avastin are primarily monomers and similar in their size heterogeneity. A different level of HMW and NGHC is found in CT-P16 but are considered as desirable quality characteristics and as such positive for the biosimilar candidate, the difference in the amount of HMW species and NGHC levels is judged as rather small and not considered as clinically relevant. This conclusion is also supported by the similar biological activities of the two products as shown below. This is found sufficient and acceptable.

Higher order structure

Circular dichroism (CD, near and far UV-spectra), differential scanning calorimetry (DSC), DTNB method/Ellman assay and LC-MS peptide mapping have been applied to study higher order structure, thermal stability, free thiols and disulphide bonds in batches of CT-P16 and EU-approved Avastin.

The secondary and tertiary structures of CT-P16 were determined to be highly similar to Avastin as analysed by near and far UV CD spectra. Similar thermal stability and conformation were also demonstrated by DSC. Furthermore, the same disulphide bond linkages in CT-P16 and Avastin has been demonstrated by LC-MS peptide mapping while some minor differences were noted in the level of free thiol groups in CT-P16 as compared to Avastin as determined by the DTNB method/Ellman's assay.

This is found sufficient and acceptable.

Content

CT-P16 and EU-approved Avastin are highly similar in protein concentration as analysed by UV-absorbance at 280 nm. The extinction coefficient has been determined experimentally.

This is considered sufficient to ensure the desired dose.

This is found sufficient and acceptable.

Biological activity

A large and comprehensive panel of biological assays have been applied in the biosimilarity exercise to compare batches of the biosimilar candidate CT-P16 to the RMP EU-approved Avastin with respect to functional activities and biological binding testing.

This comparison covered assessment of both Fab-related biological activity and Fc-related biological properties. Furthermore, it can also be noted that several additional MoA studies were performed to further support the similar functionality of CT-P16 and EU-approved Avastin.

In conclusion, the similarity assessment CT-P16 and EU-approved Avastin showed highly similar biological activity of both the Fab and Fc-based functionality.

This is found sufficient and acceptable.

Forced degradation stability

A set of relevant tests and attributes, covering physicochemical and biological activities, have been included in the studies to compare batches of the biosimilar candidate CT-P16 to the RMP EU-approved Avastin with respect to comparative forced degradation stability.

All the changes observed during the comparative forced degradation stability study occurred in both CT-P16 and Avastin at a comparable rate and degree. No specific degradation variants were detected that were only found in either CT-P16 or in Avastin. Hence, the presented stress stability data supports the claim for biosimilarity. Furthermore, additional comparative stability data are presented under section P.8 as well and these data also show comparable stability profiles under accelerated and stress conditions and give further support to the similarity claim.

This is found sufficient and acceptable.

Analytical method description and qualification

Qualified state-of-the-art physicochemical and biological methods have been used in the similarity assessment.

Appropriate descriptions of the analytical methods used for biosimilarity studies have been provided.

The qualification results of the assays have been summarised and the corresponding reports provided.

This is found sufficient and acceptable.

Concluding comments on the biosimilarity section

The applicant has provided a 2-way biosimilarity study between the biosimilar candidate CT-P16 and the RMP EU-approved Avastin, evaluating relevant quality attributes by a panel of state-of-the-art and standard analytical methods.

Several independent CT-P16 DP batches representative of the commercial scale and Several EU-approved Avastin batches are included in the similarity study. The batches reflect an appropriate range of expiration dates and product ages. The DP material used in the analytical biosimilarity studies is considered representative of the commercial process. The similarity analyses have been performed side-by-side using a qualified in-house reference standard. The overall approaches used for the establishment of the biosimilarity assessment criteria are considered acceptable.

The analytical biosimilarity studies of CT-P16 and Avastin included comparisons of primary and higher order structures, post-translational modifications, glycation, glycosylation, charge heterogeneity, purity/impurity, content, biological activity of Fab and Fc related functions, and comparative forced degradation studies.

CT-P16 is considered to be highly similar to EU-approved Avastin with respect to the presented physicochemical and biological characterisations. Some minor analytical differences are noted but these have all been sufficiently justified by the applicant to have no clinical impact.

In conclusion, the provided data in the analytical similarity study between CT-P16 and EU-approved Avastin demonstrates a high degree of similarity in support of the biosimilarity claim. This is found sufficient and acceptable, and no issues are raised on the Biosimilarity section.

3.3.6. Post approval change management protocol(s)

Not applicable.

3.3.7. Adventitious agents

Adventitious agents

The virus testing is in compliance with ICH Q5A (R2). The results of viral testing performed as part of cell line qualification demonstrate that CT-P16 MCB and WCB are free of adventitious and endogenous viral agents. These results also indicate that no viral contamination occurred during cell line development and cell banking MCB and WCB testing is reviewed as part of the drug substance control, as well as the control of raw materials.
Viral clearance studies were performed with a suitable panel of model viruses on qualified small-scale models. The total process clearance determined by summation of orthogonal removal/inactivation methods indicates a sufficient log reduction of model viruses. The safety margin over the estimated retroviral burden per Retrovirus-like particles in unprocessed bulk is considered satisfactory.

The TSE risk associated with the raw materials used during the development of the production cell line has been presented in the dossier. No materials of animal origin are used during manufacture of CT-P16 drug product. On the basis of presented information, it can be concluded that there is minimal risk of contamination by TSE in the final product.

3.3.8. GMO

Not applicable.

3.4. Discussion and conclusions on quality aspects

Information on development, manufacture and control of drug substance and drug product has been presented in a mostly satisfactory way. The presented documentation indicates that the drug substance and drug product are manufactured in well-controlled and validated processes. However, some information is lacking in the dossier for example on the manufacture and certain leachables and stability studies.

The applicant has evaluated the similarity between the biosimilar candidate CT-P16 to EU-approved Avastin in a comprehensive comparability program.

In general, CT-P16 is considered to be similar to the EU-approved Avastin at the quality level. Some minor differences are noted but the applicant justifies these as being not clinically meaningful which is agreed to.

From the quality perspective, the Other Concerns as detailed in the List of Questions should be appropriately addressed before a final conclusion on similarity can be drawn and, eventually, a positive CHMP opinion be granted.

3.4.1. Recommendation(s) for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

The submitted non-clinical program includes a battery of comparative *in vitro* primary pharmacodynamic (PD) studies (same as included under the biosimilarity studies) of CT-P16 and the Reference Medicinal Product (RMP) EU-Avastin, and a 4-week repeat-dose toxicity study in cynomolgus monkeys including toxicokinetic (TK) and immunogenicity assessment.

The repeat-dose toxicity study in cynomolgus monkeys including TK and immunogenicity assessment (Study No. 8342524) and the bioassays to quantify bevacizumab and anti-drug antibodies in monkey serum were performed in compliance GLP.

4.2. Analytical methods

Methods were adequately validated for quantification of CT-P16 and EU-Avastin and anti-CT-P16 and anti-Avastin antibody in cynomolgus monkey serum, and for formulation analysis of CT-P16 and EU Avastin.

Similar sensitivity was demonstrated in drug tolerance for CT-P16 and Avastin.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

A number of *in vitro* biological assays have been performed as part of the biosimilarity exercise. The results of these assays and the assessment of the biosimilarity claim are presented in section 4.2.6.

Literature studies on the effects of anti-VEGF treatments in various animal disease models have also been provided.

The HHT models studied include mouse models with targeted mutations in the genes *Eng* and *Alk1*, which have been implicated in HHT1 and HHT2 disease, respectively. These models have been used to investigate the potential of anti-VEGF treatments in mitigating the symptoms of HHT.

Several anti-VEGF therapies have been tested in these models, including anti-VEGF-A antibody (G6.31), anti-VEGFR2 antibody (DC101) and small molecule VEGFR2 inhibitors (SU5416 and AV951). The antibody G6.31 is reported to be a potent inhibitor of mouse VEGF-A with an EC_{50} of 0.6 nM. For DC101, and the VEGFR2 inhibitors, no information on the potency and/or specificity have been provided although it seems clear from the data that treatment-related effects have been noted.

The anti-VEGF-A antibody (G6.31) has been shown to reduce tissue VEGF levels, colonic inflammation, and angiogenesis in adult *Eng+/-* mice with DSS-induced colonic inflammation (Ardelean et al, 2014b). G6.31 was also shown to prevent or cease the progression of dermal AVM development in adult *Alk1-iKOe* mice with wound- or VEGF-induced dermal AVMs, and to ameliorate internal bleeding in the GI tract, lungs, and heart (Han et al 2014). Finally, in adult *Eng+/-* and *Alk1+/-* mice, G6.31 normalized microvessel density and secondary right ventricular hypertrophy in the lungs (Ardelean et al, 2014a).

The anti-VEGFR2 antibody (DC101) has been shown to abrogate AVM formation in the pelvic region and attenuate the progression to high-output heart failure in adult *Eng-iKOe* mice (Tual-Chalot et al, 2020), and to prevent excessive angiogenesis and the formation of multiple telangiectases (small AVMs) in adult *Alk1+/-* mice infected with *Mycoplasma pulmonis* (Thalgott et al, 2018).

The small molecule VEGFR2 inhibitors SU5416 and tivozanib have been shown to reduce the frequency and severity of retinal AVMs in neonatal Eng-iKOe pups (SU5416) (Jin et al, 2017), and to prevent progression of dorsal aorta and posterior cardinal vein phenotypes in embryonic Eng-mutant zebrafish embryos (tivozanib) (Snodgrass et al, 2021).

Altogether the results of the literature studies in animal models of HHT1 and HHT2 indicate that anti-angiogenetic strategies targeting the VEGF pathway may have beneficial effects in HHT patients.

4.3.1.2. Secondary pharmacodynamics

No secondary pharmacodynamic studies have been performed and are not required.

4.3.1.3. Safety pharmacology

No safety pharmacology studies have been performed and are not required.

4.3.1.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed and are not required.

4.3.2. Pharmacokinetics

Comparative toxicokinetic analysis was performed as part of repeat-dose toxicity study for CT-P16 and EU-Avastin in cynomolgus monkeys using two doses of 10 and 50 mg/kg (Study No. 8342524).

4.3.2.1. Absorption

Comparative TK measurements were incorporated in the 4-week repeat-dose study with CT-P16 and EU-Avastin in cynomolgus monkeys, see section 5.4.6.

4.3.2.2. Distribution

No distribution studies have been performed and are not required.

4.3.2.3. Metabolism

No metabolism studies have been performed and are not required.

4.3.2.4. Excretion

No *excretion* studies have been performed and are not required.

4.3.2.5. Pharmacokinetic drug interactions

Not applicable

4.3.2.6. Other pharmacokinetic studies

Not applicable

4.4. Toxicology

4.4.1. Single-dose toxicity

No single dose toxicity studies were conducted and are not required.

4.4.2. Repeat-dose toxicity

A GLP-compliant 4-week repeat-dose toxicity study in cynomolgus monkeys with TK assessment was designed to support the safety of the CT-P16 (Study No. 8342524). Doses of CT-P16 and EU-Avastin 10 mg/kg and 50 mg/kg were administered via intravenous (IV) bolus twice a week (eight doses) for 4 weeks.

The study was conducted with CT-P16 DP lot 16P12B01 manufactured from Process A drug substance (DS). The comparability studies for both the DS (Process A) and the PD from commercial manufacturing process demonstrated that process changes have not had an adverse impact on the product quality.

CT-P16 and EU-Avastin were well tolerated at dose levels up to maximum dose used, 50 mg/kg twice weekly for 4 weeks in cynomolgus monkeys. No test-article-related mortality or effects on vital signs (body temperature and respiration rates), ophthalmic parameters, blood pressure, immunophenotyping, organ weight, growth plate evaluation and clinical (haematology, coagulation, clinical chemistry, urinalysis) and anatomic (macroscopic and microscopic observation) pathology was noted. Minor test-article related changes were noted.

Altogether, there were no toxicologically significant differences between CT-P16 or EU-Avastin group animals, including the injection site findings.

4.4.3. Genotoxicity

No genotoxicity or mutagenicity studies were performed and are not required.

4.4.4. Carcinogenicity

No carcinogenicity studies were performed and are not required.

4.4.5. Developmental and reproductive toxicity

No reproductive and developmental studies were performed and are not required.

4.4.6. Toxicokinetics

The exposure was similar between CT-P16 and EU-Avastin at dose levels of 10 and 50 mg/kg twice weekly in cynomolgus monkeys. These results revealed no significant differences between CT P16 and EU-Avastin in their toxicokinetic characteristics.

CT-P16 or EU-Avastin did not trigger formation of anti-drug antibodies.

4.4.7. Local tolerance

There were no toxicologically significant differences noted in the local tolerance of CT-P16 or Avastin in the 4-week repeat-dose study cynomolgus monkeys as examined by macroscopic observation and histopathological assessments of local (injection site).

4.4.8. Other toxicity studies

Not applicable

4.4.9. Ecotoxicity/environmental risk assessment

An ERA has been provided, consisting of a justification for not submitting ERA studies. CT-P16 is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

CHMP's position:

Orblid is a monoclonal antibody targeting VEGF, authorised as Avastin® in the EU since 2005 for several oncology indications at doses ranging from 5–10 mg/kg every 2 weeks to 15 mg/kg every 3 weeks, administered intravenously and used chronically. The proposed indication is HHT, a non-oncology, non-S9 setting, at a regimen of 5 mg/kg every 2 weeks for 12 weeks, followed by 5 mg/kg every 8 weeks as maintenance.

The non-clinical package comprises the historical development programme supporting the approved oncology indications, three additional bioanalytical methods validation, and a new GLP 28-day toxicology and toxicokinetic study in cynomolgus monkeys. No additional pharmacology, safety pharmacology, genotoxicity, carcinogenicity or reproductive and developmental toxicity studies were performed which is considered acceptable.

Pharmacology

The similarity assessment CT-P16 and EU-approved Avastin showed highly similar biological activity of both the Fab and Fc-based functionality, see further section 4.2.5.

The mechanism of action (VEGF inhibition) is well characterised and unchanged from the authorised oncology indications. The rationale for clinical benefit in HHT relies on the established role of pathological angiogenesis in telangiectasias and AVMs and is adequately supported by literature data. Although bevacizumab has not been tested in murine HHT models due to its limited affinity for mouse VEGF-A, VEGF pathway inhibition has been explored extensively using surrogate anti-VEGF agents and anti-VEGFR2 inhibitors.

The HHT models studied include mouse models with targeted mutations in the genes *Eng* and *Alk1*, which have been implicated in HHT1 and HHT2 disease, respectively. As complete loss of *Eng* or *Alk1* leads to death at mid-gestation of cardiovascular and angiogenic defects, the first mouse models of HHT1 and HHT2 were based on *Eng+/−* and *Alk1+/−* mice. The models survive until adulthood but are reported to have a milder and less penetrant phenotype than that of the human disease. In addition, it is reported that additional angiogenic triggers, such as inflammation, are required to develop HHT-like lesions in these heterozygous models. More recent models include mice with inducible EC-specific gene deletion of either gene in post-natal or adult life. Some of these models have a short life-span (a few weeks) following gene deletion and die due to severe haemorrhages. Overall, these mouse models have HHT-like vascular lesions including AVMs during angiogenesis. In general, the *in vivo* studies were short in duration.

The tested anti-VEGF therapies include anti-VEGFA antibody (G6.31), anti-VEGFR2 antibody (DC101) and small molecule VEGFR2 inhibitors (SU5416 and AV951). The antibody G6.31 is reported to be a potent inhibitor of mouse VEGFA with an EC_{50} of 0.6 nM. For DC101, and the VEGFR2 inhibitors, no information on the potency and/or specificity have been provided although it seems clear from the data that treatment-related effects have been noted.

The anti-VEGF-A antibody (G6.31) has been shown to reduce tissue VEGF levels, colonic inflammation, and angiogenesis in adult *Eng+/-* mice with DSS-induced colonic inflammation (Ardelean et al, 2014b). G6.31 was also shown to prevent or cease the progression of dermal AVM development in adult *Alk1-iKOe* mice with wound- or VEGF-induced dermal AVMs, and to ameliorate internal bleeding in the GI tract, lungs, and heart (Han et al 2014). Finally, in adult *Eng+/-* and *Alk1+/-* mice, G6.31 normalized microvessel density and secondary right ventricular hypertrophy in the lungs (Ardelean et al, 2014a).

The anti-VEGFR2 antibody (DC101) has been shown to abrogate AVM formation in the pelvic region and attenuate the progression to high-output heart failure in adult *Eng-iKOe* mice (Tual-Chalot et al, 2020), and to prevent excessive angiogenesis and the formation of multiple telangiectases (small AVMs) in adult *Alk1+/-* mice infected with *Mycoplasma pulmonis* (Thalgott et al, 2018).

The small molecule VEGFR2 inhibitors SU5416 and tivozanib have been shown to reduce the frequency and severity of retinal AVMs in neonatal *Eng-iKOe* pups (SU5416) (Jin et al, 2017), and to prevent progression of dorsal aorta and posterior cardinal vein phenotypes in embryonic Eng-mutant zebrafish embryos (tivozanib) (Snodgrass et al, 2021).

Altogether the results of the literature studies in animal models of HHT1 and HHT2 indicate that anti-angiogenetic strategies targeting the VEGF pathway may have beneficial effects in HHT patients.

No studies of secondary pharmacology of bevacizumab were conducted. This is agreed.

No dedicated new safety pharmacology studies were conducted. This is acceptable as ICH S6(R1) allows assessment of cardiovascular, respiratory and CNS parameters within repeat-dose toxicology studies for monoclonal antibodies. Safety pharmacology endpoints were included in the new 28-day cynomolgus study (ECG, blood pressure, respiratory parameters, temperature) and in historical toxicology studies. No new safety concerns were identified.

Pharmacokinetics

The PK profile of the antibody is well known from the authorised product. For the new indication, no additional ADME studies were performed, in line with ICH S6(R1), which does not require extensive ADME investigations for monoclonal antibodies. Bioanalytical methods for TK assessment were validated. Cross-reactivity and tissue binding have been previously characterised and remain applicable.

Toxicology

A GLP-compliant comparative 4-week repeat-dose toxicity study including toxicokinetics, for CT-P16 and EU-Avastin in cynomolgus monkeys using two doses of 10 and 50 mg/kg was performed.

Methods were adequately validated for quantification of CT-P16 and EU-Avastin and anti-CT-P16 and anti-Avastin antibody in cynomolgus monkey serum, and for formulation analysis of CT-P16 and EU Avastin.

CT-P16 and EU-Avastin were well tolerated at dose levels up to maximum dose used, 50 mg/kg twice weekly for 4 weeks in cynomolgus monkeys. No test-article-related mortality or effects on vital signs (body temperature and respiration rates), ophthalmic parameters, blood pressure, immunophenotyping, organ weight, growth plate evaluation and clinical (haematology, coagulation, clinical chemistry, urinalysis) and anatomic (macroscopic and microscopic observation) pathology was noted. were noted with exception of minor changes (in increased incidence, fecal abnormalities and in ECG measurements, and increases of neutrophil and white blood cell counts) were noted. The results of the study in cynomolgus monkeys did not reveal notable differences in effects between the CT-P16 and Avastin in their toxicological profiles.

Exposures (C_{max} and AUC_{0-72h}) to CT-P16 and EU-Avastin increased dose-proportionally and were similar for CT-P16 and EU-Avastin. Sex differences in concentrations were less than 2-fold. The relative values (CT-P16/EU-Avastin) for C_{max} and AUC_{0-72h} for 10 mg/kg/day dose were 104% and 106% on Day 1, respectively, and 110% and 105% on Day 26, respectively. For the dose of 50 mg/kg/day, the relative values were 101% and 102% on Day 1, respectively, and 98% and 110% on Day 26, respectively.

CT-P16 or EU-Avastin did not trigger formation of anti-drug antibodies.

In vivo studies of toxicity are not considered necessary to substantiate a claim of biosimilarity. This is in accordance with the guidance contained in Guideline on similar biological medicinal products containing monoclonal antibodies–nonclinical and clinical issues EMA/CHMP/BMWP/403543/2010, which states that *in vivo* toxicity studies are generally not required to support marketing authorisation of such products.

No genotoxicity or mutagenicity, carcinogenicity or reproductive and developmental studies were performed and are not required.

There were no toxicologically significant differences noted in the local tolerance of CT-P16 or Avastin in the 4-week repeat-dose study cynomolgus monkeys as examined by macroscopic observation and histopathological assessments of local (injection site).

As outlined in this AR, CT-P16 is considered biosimilar to Avastin. Important differences between Orblid and Avastin include the indication, dosing regimen and target population. HHT is generally a more benign condition than cancer, and the treatment duration in HHT populations may extend over longer periods than is typical in oncology indications. It is also noted that no maximum recommended dose is provided in SmPC section 4.2 (**see SmPC comment**). The non-clinical safety profile of bevacizumab is already well characterised based on data from the reference product, including repeat-dose toxicity studies in cynomolgus monkeys of up to 26 weeks and reproductive and developmental toxicity studies in rabbits. In addition, a GLP-compliant 4-week repeat-dose toxicity study with CT-P16 and EU-Avastin, including comparative toxicokinetics did not reveal new safety concerns. Therefore, it is agreed that no new non-clinical studies seem necessary, but the Applicant is asked to justify that the exposure achieved in the monkey studies sufficiently covers the proposed clinical dosing regimen, treatment duration, and target populations for HHT (**OC**).

An ERA has been provided, consisting of a justification for not submitting ERA studies. CT-P16 is a monoclonal antibody and classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment.

SmPC sections 4.6 and 5.3. for CT-P16 and EU-Avastin are identical.

4.5.2. Conclusions

CHMP's position:

Overall, the provided non-clinical study package seems sufficient. One OC has been raised that should be addressed by the Applicant.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

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

5.1.2. Tabular overview of clinical trials

Table 2: Tabular overview of main clinical studies

Study	*Study design*	*Treatment*	*Subject population*	*Study objectives and primary endpoint*	Number of subjects total and per group randomised (treated)/completed study
Pivotal PK study (CT-P16)	Phase I, randomized, double-blind, three-arm, parallel group, single dose study	CT-P16, US-Avastin or EU-Avastin: 5 mg/kg, a single IV infusion of study drug for 90 minutes (±15 minutes)	healthy male subjects	Primary: To demonstrate the similarity of PK in terms of AUC0-inf, AUC0-last , Cmax of CT-P16, EU-Avastin and US-Avastin Secondary: - To assess the additional PK parameters - To evaluate safety and immunogenicity of CT-P16, EU-Avastin and US-Avastin	Randomized: 144 - CT-P16: 47 - EU Avastin: 49 - US Avastin: 48
Supportive Japanese PK study (CT-P16)	Phase I, randomized, double-blind, parallel group, single-dose study to compare the PK and safety of CT-P16 and EU-Avastin	CT-P16 or EU-Avastin: 5 mg/kg, a single IV infusion of study drug for 90 minutes (±15 minutes)	Healthy Japanese male subjects	Primary: To demonstrate the similarity of the PK in terms of AUC0-inf, AUC0-last , Cmax of CT-P16 and EU Avastin in healthy Japanese male subjects Secondary: To assess the	Randomized: 46 - CT-P16: 22 - EU Avastin: 24

Study	Study design	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
				additional PK parameters To evaluate safety and immunogenicity of CT-P16 and EU Avastin	
Therapeutic similarity study (CT-P16 3.1)	Ph III, double-blind, randomized, active controlled, parallel group study to compare efficacy and safety of CT-P16 and EU-Avastin.	CT-P16 or EU- Avastin: Induction 15 mg/kg IV of study drug every 3 weeks for 6 cycles, coadministered with paclitaxel and carboplatin (at least for 4 cycles) Maintenance Monotherapy of study drug every 3 weeks until progressive disease or intolerable toxicity occurrence	Male or female patients with metastatic or recurrent nsNSCLC (first-line treatment)	Primary: To demonstrate CT-P16 is similar to EU- Avastin in terms of efficacy as determined by ORR during the Induction Study Period Secondary: - To evaluate additional efficacy parameters - To evaluate the PK profile (Ctrough) - To evaluate the safety profile including immunogenicity To evaluate quality of life	Randomized: 689 - CT-P16: 342 - EU Avastin: 347
Pivotal Safety, efficacy, PK in HHT patients with symptomatic hAVM and	Phase II monocentric / non-comparative	Avastin® 5 mg/kg, every 14 days for a total of 6 injections	confirmed HHT with severe liver involvement and high	Primary: Reduction of cardiac index at 3 months of treatment. Secondary: improvement in	25 pts included / 24 completed. All treated with bevacizumab

Study	*Study design*	*Treatment*	*Subject population*	*Study objectives and primary endpoint*	**Number of subjects total and per group randomised (treated)/completed study**
cardiac repercussion (HTT-PS1/Metafore)			cardiac index related to HHT	NYHA class; reduction of cardiac index at 6 months of treatment; reduction of epistaxis duration; reduction of telangiectasias; improvement of Hb levels; reduction in number of RBC transfusions; quality of life improvement.	
Safety, efficacy, PK in severe hemorrhagic HHT patients requiring transfusions (HHT-PS2 /BABH)	Phase II double-blind multicenter randomized, placebo-controlled (1:1)	Avastin® 5 mg/kg every 14 days with a total of 6 injections	confirmed HHT with need for at least 4 RBC units transfused in the 3 months before study.	Primary: number of patients with a >50% decrease in the cumulative number of RBC units transfused in a 3-month period after treatment compared to before treatment. Secondary: improvement of Hb levels; reduction in the number of RBC units transfused ; quality of life improvement.	24 pts randomized (12 bevacizumab, 12 placebo), 21 completed
Safety, efficacy, PK in HHT	Retrospective analysis of CIROCO	Most patients had an induction with	Confirmed HHT patients	Primary: descriptive analysis of	237 pts treated with bevacizumab

Study	Study design	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
patients (HHT-RS1/ Cobevaro)	database (Registry-based study)	bevacizumab 5 mg/kg every 14 days for 4 to 6 infusions. Maintenance schemes differ and are analyzed as variables.		bevacizumab's real-world use in HHT patients. Secondary: Nature and frequency of adverse events, Evolution of clinical parameters (number of transfusions, iron supplementation, hemoglobin levels, cardiac index), Clinical profile of patients treated	

5.2. Clinical pharmacology

The clinical pharmacology dossier for the biosimilar Orblid (CT-P16), to support biosimilarity to Avastin, includes two Phase 1 clinical studies, CT-P16 1.1 and CT-P16 1.2, which were conducted in healthy male subjects, and one Phase 3 clinical study, CT-P16 3.1, which was conducted in patients with metastatic or recurrent non-squamous non-small cell lung cancer (nsNSCLC).

In addition, three studies have been provided for the use of (mainly) Avastin in the Hereditary Hemorrhagic Telangiectasia (HHT), HHT-PS1/Metafore, HHT-PS2/BABH, and HHT-RS1/CoBevaRo, with supportive PK data though sparse PK sampling, popPK and PK/PD modelling.

5.2.1. Methods

Bioanalytical Methods

Pharmacokinetics

Quantification of bevacizumab in human serum a meso-scale discovery-electrochemiluminescence (MSD-ECL) based method was used in the pharmacokinetics studies to quantify bevacizumab (CT-P16, EU-Avastin and US-Avastin) concentrations in healthy human serum (clinical study CT-P16 1.2) and in human serum samples from the patients with nsNSCLC (clinical study CT-P16 3.1). An Enzyme-Linked Immunosorbent Assay (ELISA) based method was used for the quantification of bevacizumab concentrations in healthy human serum samples collected in the clinical study CT-P16 1.1. Both methods were, in principle, validated according to ICH M10 Bioanalytical method validation guideline.

HHT studies

The bioanalytical method applied during the clinical development of bevacizumab in HHT is an ELISA designed to measure human serum levels of the drug substance Avastin and its biosimilars. This method was utilised in studies HHT-PS1/Metafore, HHT-PS2/BABH, and HHT-RS1/CoBevaRo, with the latter also including other biosimilars. The development and validation of this ELISA method are attributed to Université François Rabelais & CHRU, Tours, France, and were published in a scientific paper Ternant et al., 2010.

Overall, the bioanalytical method for measuring bevacizumab in serum of HHT was not completely validated according to the ICH M10 Bioanalytical method validation guideline, however, the validation appears overall adequate, and issues are not further pursued.

No within-study bioanalysis reports for the studies in HHT patients could be found in the dossier, therefore the performance in these studies could not be assessed. The Applicant is asked to provide within-study bioanalysis reports, if available, for the proprietary studies in HHT, mainly PS1/Metafore study, and if possible, HHT-PS2/BABH and HHT-RS1/CoBevaRo (**OC**).

PD biomarkers

BMP9 and VEGF concentrations was evaluated by ELISA in HHT-PS1/Metafore. Detailed descriptions of the bioanalytical analysis of BMP9 and VEGF could not be located in the dossier, nor pre-validation and in-study validation of these methods. Since these biomarkers are not considered essential for the overall efficacy or PK/PD assessment, this issue is not further pursued.

Immunogenicity

Detection of ADA and NAb in human serum A three-tiered approach comprising of screening, confirmation and titer was used for detection of antidrug antibodies. Two ECL based methods (validated either by PPD laboratory or BDS) were utilised for the detection of ADAs against ORBLID, EU-Avastin and US-Avastin and two ECL based methods (validated either by PPD laboratory or BDS) were utilised for the detection of NAbs against bevacizumab in healthy and diseased human serum. In general, the method validation followed current guidance.

Immunogenicity was not studied in HHT patients.

Pharmacokinetic data analysis

Study CT-P16 1.1 (pivotal PK study):

The PK parameters were calculated from the serum concentration-actual time profiles. The non-compartmental analysis was performed using Phoenix WinNonlin version 6.3 (Certara US, Inc., Princeton, NJ).

Study CT-P16 1.2 (supportive Japanese PK study):

The PK parameters were calculated from the serum concentration-actual time profiles. The noncompartmental analysis using Phoenix WinNonlin Version 8.0 (Certara L.P., Princeton, New Jersey USA) was performed.

Study CT-P16 3.1 (comparative efficacy and safety study):

The PK parameter was presented in a listing by treatment group.

PK data in the target population

PK data in the target population were collected using sparse PK sampling and analysed using population pharmacokinetic (PopPK) modelling in Studies Study HHT-PS1/Metafore (see Section

2.2.2.1.), Study HHT-PS2/BABH (see Section 2.2.2.1.) and Study HHT-RS1/CoBevaRo (see Section 2.4.).

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The pharmacokinetics of bevacizumab are well known from Avastin, and studies have been submitted to establish PK biosimilarity between CT-P16 (Orblid) and EU-Avastin. PK in the target population, HHT, is mainly descriptive. PKPD analyses of several PD endpoints have been submitted.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population pharmacokinetics

Population pharmacokinetic (PopPK) modelling was used to describe PK in the target population. Two PopPK analyses were conducted, for each of the two target populations consisting of HHT patients with severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnea despite well-conducted cardiological medical treatment (Study Metafore) and HHT patients with a severe hemorrhagic form (epistaxis and/or digestive bleeding) of the disease with dependence on transfusions and/or intravenous iron (Study BABH).

Study HHT-PS1 / Metafore

The blood samples for PK analysis of bevacizumab were to be drawn at predose, 2h, 5h and 24h after the first dose as well as at predose and 2h post-dose for all other administrations. A total of 317 serum concentration measurements were available from 25 patients.

Baseline characteristic of patients is presented in Table 3 below.

Table 3:Characteristics of the patients at baseline

	No. (%)	Mean (SD)	Median (Range)
Patients	25 (100)		
Age (year)		57.44 (8.6)	59 (35-68)
Sex			
Female	24 (96)		
Male	1 (4)		
Cardiac index (L/min/m^2)	24	5.01 (0.67)	5.05 (4.1-6.2)
Duration of epistaxis (min/month)	25 (100)	221 (239.7)	179 (0-947)

Table copied from Azzopardi et al 2015 https://doi.org/10.1080/19420862.2015.1022693

The pharmacokinetics of bevacizumab is accurately described by a two-compartment model with linear elimination.

The final model parameters are shown in Table 4.

Table 4: Estimated pharmacokinetic and pharmacokinetic-pharmacodynamic parameters

Parameter (unit)	Value	r.s.e.(%)	CV%
V_1 (L)	3.51	7	34%
k_{10} (1/day)	0.0572	6	26%
k_{12} (1/day)	0.195	17	-
k_{21} (1/day)	0.284	18	39%
CK_{e0} (1/day)	0.0321	13	46%
Cl_0 (L/min/m^2)	4.93	3	12%
Cl_{min} (L/min/m^2)	3.92	4	15%
CC_{50} (mg/L)	3.72	52	-
Ek_{e0} (1/day)	0.0116	23	146%
EC_{50} (mg/L)	5.48	7	-
λ_0 (-)	0.518	26	207%
b_{BVZ}	0.126	5	-
b_{Cl}	0.0573	14	-

Table copied from Azzopardi et al 2015 https://doi.org/10.1080/19420862.2015.1022693

None of the covariates tested (age, weight, body surface area or body mass index) explained the inter-subject variability of the estimated pharmacokinetic or PK-PD parameters.

Study HHT-PS2 / BABH

The blood samples for PK analysis of bevacizumab were to be drawn at predose and 2h post-dose following the first dose as well as at predose for all other administrations.

The baseline characteristics of the patients are shown in Table 5.

Table 5: Characteristics of the patients at baseline

Variable	Modality	All	Placebo group *n* (%)	Bevacizumab group *n* (%)	*p*
Number	*n*	24	12	12	
Age (years)	Median (min–max)	60 (42–80)	68 (42–75)	59.5 (50–80)	0.50
	Mean (SD)	61.21 (10.81)	62.5 (12.89)	59.92 (8.64)	
Females	*n* (%)	10 (41.7)	6 (50)	4 (33.3)	0.68
Mutated gene	*n* (%)				0.64
ALK1		17 (70.8)	8 (66.7)	9 (75)	
ENG		5 (20.8)	2 (16.7)	3 (25)	
Ongoing		2 (8.3)	2 (16.7)	0	
Parameters on inclusion					
Nasal surgery	*n* (%)	19 (79.2)	11 (91.7)	8 (66.7)	0.32
Nasal septum perforation	*n* (%)	8 (34.8)	5 (45.5)	3 (25)	0.40
Digestive bleeding					
No	*n* (%)	14 (58.3)	4 (33.3)	10 (83.3)	
Yes	*n* (%)	10 (41.7)	8 (66.7)	2 (16.7)	0.04
Hemoglobin level	Mean ± SD	86.09 (14.66)	84 (13.6)	88 (15.91)	0.32
(g/L)	Median (min–max)	91 (54–104)	86 (54–104)	94.5 (56–104)	
Ferritin level (ng/mL)	Mean ± SD	66.96 (117.89)	61.82 (92.97)	71.67 (141.02)	0.50
	Median (min–max)	25 (4–515)	15 (5–302)	30.5 (4–515)	
Systolic blood pressure (mmHg)	Mean ± SD	125.25 (19.54)	123.25 (23.86)	127.25 (14.84)	0.88
	Median (min–max)	127.5 (85–158)	127.5 (85–158)	125.5 (103–149)	
Diastolic blood pressure (mmHg)	Mean ± SD	68 (12.63)	66.83 (13)	69.17 (12.71)	0.60
	Median (min–max)	64.5 (47–91)	62.5 (48–88)	69.5 (47–91)	

Note: *p* is the value for the exact Mann–Whitney test or Fisher's exact test.

For PK, a two-compartment model with first-order transfer and elimination rate constants provided the best results (Table 6).

Table 6: Parameter estimates

Parameter	Unit	Base model	
		Estimate	RSE%
V_1	L	3.8	6.2
CL	L/day	0.28	11
V_2	L	3.0	37
Q	L/day	0.31	20
k_{in}	U/day	0.11	14
ke_0	day^{-1}	$3.1\ 10^{-4}$	31
C_{e50}	mg/L	2.3	29
ω_{V1}	–	0.18	33
ω_{CL}	–	0.31	25
ω_{V2}	–	1.0	34
ω_{kin}	–	0.64	16
σ_{prop_PK}	–	0.12	14
$\sigma_{add\_PK\text{-}PD}$	–	2.9	3.9

Legends: V 1 and V 2 are central and peripheral volumes of distribution; CL and Q are systemic and intercompartment clearances; k in is RBC unit infusion rate constant; k e0 is biophase turnover rate constant, Ce50 is bevacizumab biophase concentration leading to 50% decrease in k in; ω is interindividual standard deviation, σprop is proportional error, σadd is additive residual error and RSE is relative standard error.

The model satisfactorily described bevacizumab concentrations.

5.2.2.3. Absorption

Not applicable.

5.2.2.4. Bioavailability

Orblid is administered by intravenous (IV) infusion, its bioavailability is 100%.

5.2.2.5. Biosimilarity

Study CT-P16 1.1

The study was conducted at three centres in Republic of Korea between 01st Aug 2017 and 17th Jan 2018. The bioanalytical analyses were performed at Biologics Development Services, LLC US between 9th Oct 2017 and 28th Mar 2018.

The study was a phase I, randomised (the number of subjects with body weight < 70 kg and ≥ 70 kg was balanced among the 3 treatment groups), double-blind, 3-arm, parallel group, single-dose study in adult healthy Asian male subjects. Subjects received single dose (i.e. 5 mg /kg) of either CT-P16, EU-Avastin or US-Avastin by IV infusion for 90 minutes (± 5 minutes) on Day 1. Blood samples were collected for measurement of serum concentrations of bevacizumab from all subjects at the following time points: pre-dose, immediately end-of-infusion (EOI), 1 h after EOI, 4 h after start of infusion (SOI), 8 h after SOI and 12 h after SOI, days 2, 3, 4, 8, 15, 29, 43, 57, 71, 85 and 99.

Pharmacokinetic results

The PK population consisted of 141 subjects (n = 46 in CT-P16 group, n =47 in the EU-Avastin group and n = 48 in the US-Avastin group). The 90% CIs for the geometric mean ratios of AUC0-inf, AUC0-last, and Cmax were entirely contained within the predefined bioequivalence margin of 80% to 125%, indicating bioequivalence for CT-P16, EU-approved Avastin, and US-licensed Avastin. Following single IV infusion over 90 minutes (± 5 minutes) of either 5 mg/kg CT-P16, EU-approved Avastin, or US-licensed Avastin, the overall shape of mean serum concentration-versus-time profile for bevacizumab was similar among CT-P16, EU-approved Avastin and US-licensed Avastin (see Figure 1 below). Mean serum concentrations for bevacizumab at each time point were similar for 3 treatment groups.

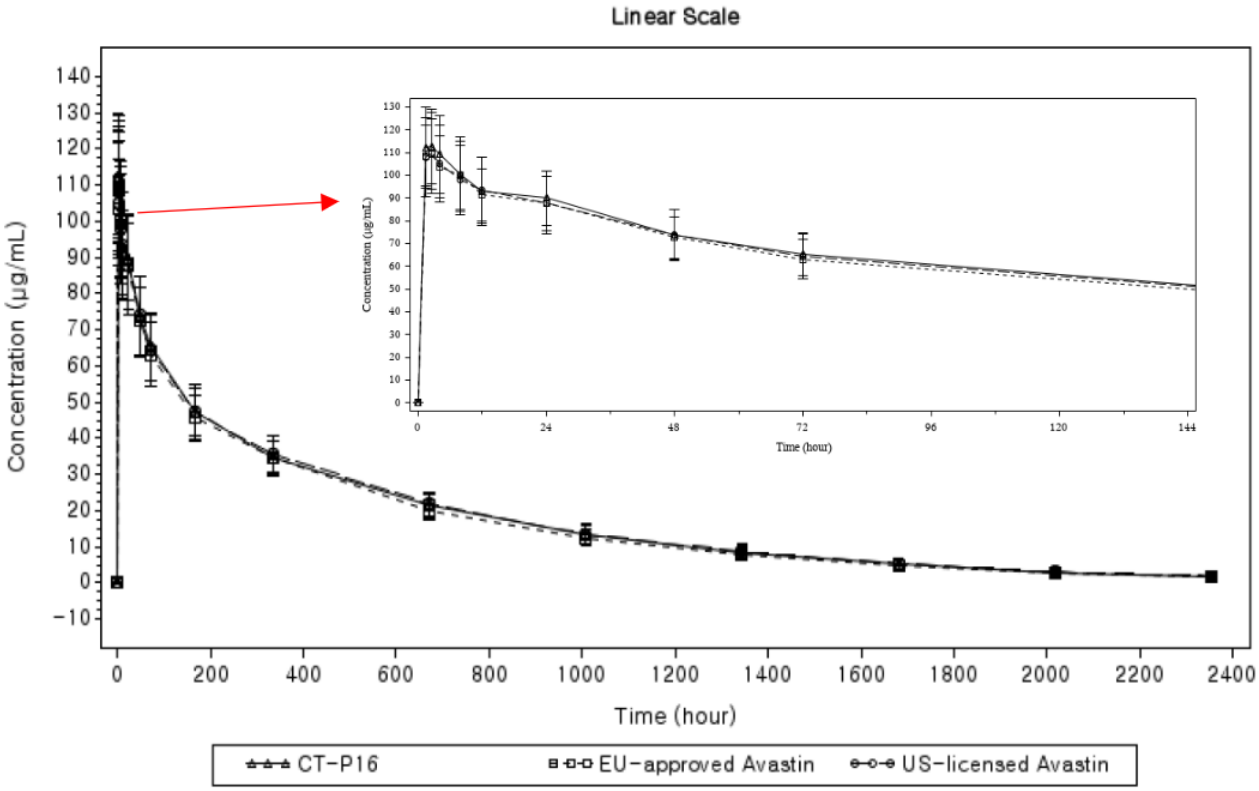


Figure 1: Mean (± SD) serum concentrations of CT-P16, EU-Avastin and US-Avastin versus time in study CT-P16 1.1 (PK population)

Table 7: Summary of primary serum PK parameters for bevacizumab in study CT-P16 1.1 (PK population)

PK Parameter (unit)	Statistic	CT-P16 N = 46	EU-approved Avastin N = 47	US-licensed Avastin N = 48
$AUC_{0\text{-inf}}$ (h·µg/mL)	n	45	46	46
	Mean ± SD	42034.90 ± 6070.668	40413.44 ± 5012.778	43017.95 ± 5782.951
	CV	14.44	12.40	13.44
	GM	41608.53	40095.88	42621.36
	Median	41281.82	40294.19	42898.41
	Min, Max	30241.1, 54111.9	27362.5, 50941.1	28786.0, 54525.9
$AUC_{0\text{-last}}$ (h·µg/mL)	n	45	47	44
	Mean ± SD	41142.81 ± 5694.184	39411.98 ± 4649.319	41804.05 ± 5463.814
	CV	13.84	11.80	13.07
	GM	40757.85	39133.03	41440.57
	Median	40795.51	39445.89	41781.24
	Min, Max	30123.7, 52541.9	27156.6, 49635.7	27938.7, 53737.3
C_{max} (µg/mL)	n	46	47	48
	Mean ± SD	117.22 ± 17.756	114.06 ± 15.391	113.09 ± 17.402
	CV	15.15	13.49	15.39
	GM	115.96	113.05	111.77
	Median	116.00	111.00	112.00
	Min, Max	83.6, 173.0	83.2, 148.0	72.6, 155.0

Abbreviations: $AUC_{0\text{-inf}}$ = area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-last}}$ = area under the concentration-time curve from time zero to the last quantifiable concentration; C_{max} = maximum serum concentration; CV = coefficient of variation; EMA = European Medicines Agency; EU = European Union; GM = geometric mean; λ_z = Terminal elimination rate constant; Max = maximum; Min = minimum; PK = pharmacokinetic; SD = standard deviation; US = United States.

Table 8: Statistical analysis of serum PK parameters for bevacizumab (ANCOVA) study CT-P16 1.1 (PK population)

	Geometric LS Means											
	CT-P16 N = 46		EU-approved Avastin N = 47		US-licensed Avastin N = 48		CT-P16 /EU-approved Avastin		CT-P16 /US-licensed Avastin		EU-approved Avastin /US-licensed Avastin	
PK Parameters (unit)	n	Results	n	Results	n	Results	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
$AUC_{0\text{-inf}}$ (h·µg/mL)	45	41608.92	46	40054.33	46	42593.20	103.88	[99.04,108.96]	97.69	[93.14, 102.46]	94.04	[89.68, 98.61]
$AUC_{0\text{-last}}$ (h·µg/mL)	45	40746.44	47	39058.63	44	41400.01	104.32	[99.70, 109.15]	98.42	[93.99, 103.06]	94.34	[90.14, 98.74]
C_{max} (µg/mL)	46	116.01	47	112.65	48	111.53	102.98	[98.22, 107.97]	104.02	[99.24, 109.03]	101.01	[96.39, 105.85]

Abbreviations: ANCOVA = analysis of covariance; $AUC_{0\text{-inf}}$ = area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-last}}$ = area under the concentration-time curve from time zero to the last quantifiable concentration; CI = confidence interval; C_{max} = maximum serum concentration; EMA = European Medicines Agency; EU = European Union; λ_z = Terminal elimination rate constant; LS = least squares; PK = pharmacokinetic; US = United States.

Note: Ratio of geometric means was calculated by backed transforming difference of LS means calculated using an ANCOVA model with treatment as a fixed effect and body weight (< 70 kg versus ≥ 70 kg) assessed on Day -1 and study site as covariates.

Immunogenicity

Overall 7 subjects (5.0%) were reported at least 1 positive anti-drug antibody (ADA) test result after bevacizumab administration; 2 subjects (4.3%), 2 subjects (4.3%) and 3 subjects (6.3%) in the CT-P16, EU-approved Avastin, and US-licensed Avastin treatment groups, respectively. However, none of subjects were had positive neutralizing antibody (NAb) results.

Study CT-P16 1.2

This study was conducted at one centre Anaheim Clinical Trials, LLC USA between 31st Jul and 22nd Dec 2020. Bioanalytical analyses were performed at PPD® Bioanalytical Lab USA between 29th Oct 2020 and 28th Jan 2021.

This study was a phase I, a single-centre, randomised, double-blind, parallel group, prospective single-dose study. Subjects received a single IV infusion (5 mg/kg; 90 minutes ±5 minutes) of CT-P16 or EU-Avastin according to the randomly assigned treatment groups on Day 1. Blood samples were collected for measurement of serum concentrations of bevacizumab from all subjects at the following time points: pre-dose, immediately end-of-infusion (EOI), 1 h after EOI, 4 h after start of infusion (SOI), 8 h after SOI and 12 h after SOI, days 2, 3, 4, 8, 15, 29, 43, 57, 71, 85 and 99.

Pharmacokinetic results

The PK population consisted of 45 subjects (n = 22 subjects in the CT-P16 group and n = 23 subjects in the EU-Avastin group).

The 90% CIs of ratios of geometric LS means of Cmax, AUC0-last, and AUC0-inf were entirely contained within the predefined equivalence margin of 80% to 125% which indicated that bevacizumab exposures from CT-P16 were similar to those from EU-Avastin (see Table 9).

Table 9: Statistical analysis of primary PK parameters (ANCOVA) in study CT-P16 1.2 (PK population)

Comparison	PK Parameter (unit)	Geometric LS Means[a] Test (N=22) n	Test (N=22) Result	Reference (N=23) n	Reference (N=23) Result	%Ratio (Test/Reference)[a]	90% CI[a]
CT-P16 (Test) vs EU-approved Avastin (Reference)	$AUC_{0\text{-}inf}$ (h•µg/mL)	22	37120.07	23	37810.47	98.17	(90.74, 106.22)
	$AUC_{0\text{-}last}$ (h•µg/mL)	22	36404.72	23	36820.05	98.87	(91.65, 106.67)
	C_{max} (µg/mL)	22	112.03	23	100.86	111.08	(100.37, 122.93)

Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration versus time curve from time zero extrapolated to infinity; $AUC_{0\text{-}last}$, area under the concentration-time curve from time zero to the time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum serum concentration; EU, European Union; LS, least squares; PK, pharmacokinetic.

An analysis of covariance was performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and body weight (< 70 kg vs ≥70 kg) assessed on Day 1 as a covariate.

(a) The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

A statistical outlier was identified using the IQR method and robust regression method, which resulted in the detection of an unusual Cmax value in one subject in the EU-Avastin group. Therefore, a sensitivity analysis was performed on the primary PK endpoints with data excluding the observed outlier. It should also be noted that the subject had an unusual profile shape that resembled more like subcutaneous administration and not an IV administration which aligns with the outlier analysis results. Statistical analysis excluding the Cmax outlier value of the subject was performed and the 90% CIs of the %ratio of geometric LS mean were within the equivalence interval (80% to 125%) supporting the same outcome as in previous analysis; i.e., no notable differences in Cmax between CT-P16 and EU-Avastin.

Immunogenicity

No subject had a positive anti-drug antibody (ADA) test result at baseline (Day 1 pre-dose). After bevacizumab administration, no subject had a positive ADA test result on any day (Days 15, 43, 71, and 99) in either treatment group.

Study CT-P16 3.1

The primary objective was to compare efficacy and safety of CT-P16 in nsNSCLC patients. The secondary objective of this study was to evaluate the PK of CT-P16 compared with EU-Avastin in terms of C_{trough}.

Patients received 15 mg/kg study drug dose every 3 weeks. PK samples were collected on Day 1 of each cycle (prior to the beginning of the study drug administration [-3 days as window were allowed]) in the induction study period, on Day 1 (-3 days as window were allowed) of cycle 1, and every 3 cycles (end of Cycle 3, Cycle 6, and Cycle 9, etc.) in the maintenance study period and EOT visit. In patients whose dose was delayed from the planned schedule, serum samples were obtained on Day 22 of the last cycle (-3 days as window were allowed).

Pharmacokinetic results

A total of 650 patients (327 patients and 323 patients in the CT-P16 and EU-Avastin treatment groups, respectively) were included in the PK population. Thirty-seven patients who did not have post-treatment PK results were excluded from PK population and 2 patients who received the incorrect treatment during the induction study period were excluded from the PK population. The mean (standard deviation) Ctrough at each cycle in the induction period was generally similar for the CT-P16 and EU-Avastin treatment groups in the PK population.

Table 10: Mean (SD) trough serum concentrations of bevacizumab (µg/L) in study CT-P16 3.1 (PK population)

Visit		CT-P16 (N=327)		EU-approved Avastin (N=323)
Induction Cycle 1	n=318	50426.3 (39847.34)	n=316	52515.7 (32356.13)
Induction Cycle 2	n=302	73127.7 (35883.59)	n=287	81533.7 (52567.34)
Induction Cycle 3	n=283	93100.6 (50495.29)	n=269	95878.8 (53977.69)
Induction Cycle 4	n=268	96445.2 (45597.95)	n=254	101583.1 (46275.62)
Induction Cycle 5	n=252	108957.3 (55135.16)	n=238	108512.5 (49823.61)
Induction Cycle 6	n=246	116188.2 (58735.47)	n=228	114849.6 (56309.70)

Abbreviation: PK, pharmacokinetic.

Immunogenicity

ADA incidence was below 5% at each time point, hence, the majority of patients had negative ADA test results. In general, the proportion of patients with positive ADA and NAb results at any time during the study period was similar in the CT-P16 and EU-approved Avastin treatment groups. Post-treatment ADA was 21.4% and 23.3% for CT-P16 and EU-Avastin, respectively. For, nAb, the percentages were 9.5% and 10.0%, respectively.

Impact of ADA on PK

Data from Study CT-P16 3.1 was further analysed to determine whether there is any correlation between immunogenicity and clinical outcome. In the subjects with negative ADA status, the mean serum concentrations are slightly higher in the EU-Avastin group at induction cycles 2 and 4 than in the CT-P16 group and at induction cycles 1 and 6 the mean serum concentration is slightly higher in

the CT-P16 group than in the EU-Avastin group. However, the number of ADA-positive patients was small in the study, and a definite conclusion could not be drawn on the impact of ADA on PK of bevacizumab. Correlation between immunogenicity and efficacy or safety has not been established.

5.2.2.6. Distribution

Following a single-dose of 5 mg/kg in healthy male subjects (clinical study CT-P16 1.1), the geometric mean of Vz for CT-P16 was 5.25 L, for EU-Avastin 5.46 L. In the supportive clinical PK study (i.e. CT-P16 1.2), the geometric mean for Vz was 5.9 L and for EU-Avastin 6.1 L.

In Study HHT-PS1 / Metafore, including HHT patients with severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnea despite well-conducted cardiological medical treatment, the central volume of distribution was estimated to 3.51 L L (%CV=34%).

In Study HHT-PS2 / BABH, including HHT patients with a severe hemorrhagic form (epistaxis and/or digestive bleeding) of the disease with dependence on transfusions and/or intravenous iron, the volume of distribution was estimated to 3.8 L (%CV=18%).

5.2.2.7. Metabolism

Metabolism of bevacizumab is similar to endogenous IgG i.e. primarily via proteolytic catabolism throughout the body, including endothelial cells, and does not rely primarily on elimination through the kidneys and liver. Binding of the IgG to the FcRn receptor results in protection from cellular metabolism and the long terminal half-life.

There is no new data on the metabolism of bevacizumab in HHT patients.

5.2.2.8. Elimination

Study CT-P16 1.1
The geometric mean CL of CT-P16 was 0.008 L/h and for EU-Avastin 0.009 L/h. The mean half-lives varied from 17 days to 19 days, in line with that reported in the Avastin SmPC.

HHT
Half-life

The elimination half-life ($t_{1/2}$) in study HHT-PS2/BABH, was 422.22 ± 84.2 h, i.e. 17.6 days. In HHT-RS1/Cobevaro, elimination half-life was estimated to 575.40 ± 372.76, i.e., 24.0 days.

The elimination in the target population was estimated using PopPK modelling; In Study HHT-PS1 / Metafore, including HHT patients with severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnea despite well-conducted cardiological medical treatment, the terminal elimination half-life was estimated to 21.5 days. In Study HHT-PS2 / BABH, including HHT patients with a severe hemorrhagic form (epistaxis and/or digestive bleeding) of the disease with dependence on transfusions and/or intravenous iron, the terminal elimination half-life was estimated to 20.5 days.

Overall, the half-life of bevacizumab in HHT patients ranged from 17.6 to 24.0 days and seem similar to oncology patients, where distribution half-life of bevacizumab was 1.4 days and the elimination half-life was 19.9 days for males (for females 20.6 days), respectively (Lu et al., 2008).

There are discrepancies in the SmPC regarding distribution half-life stated as 1.6 days in HHT referencing Azzopardi et al 2015, but the table states 1.4 days referencing Dupuis-Girod et al 2012. Lu et al 2008 states that $t_{1/2\,\beta}$ (i.e. elimination half-life) is 19.9 (17.9, 22.5) and not 21.5 days in oncology indications. See overall SmPC comment on section 5.2 (**LoQ SmPC comment**)

Clearance

The clearance (L/h) was estimated to 0.01367 ± 0.00457, i.e. 0.328 L/day in HHT patients in the study HHT-PS2/BABH. In the registry-based study HHT-RS1/Cobevaro, clearance was estimated to 0.0121 ± 0.00286 L/h, i.e 0.290 L/day. Typical clearance in oncology patients were 0.207 L/day for a typical female, and 0.262 L/day for a typical male according to Lu, et al 2008.

Clearance was in a similar range in HHT patients compared with oncology patients.

5.2.2.9. Dose proportionality and time dependency

Based on the Avastin SmPC, PK of bevacizumab is linear over a dose range of 1 mg/kg to 10 mg/kg.

5.2.2.10. Pharmacokinetics in the target population

PK in the target population was described using PopPK modelling as described in Section 2.1.

The MAH has provided reports of three studies bevacizumab in HHT patients: HHT-PS1/Metafore, HHT-PS2/BABH, and HHT-RS1/Cobevaro. These studies evaluated the efficacy and safety of bevacizumab in HHT patients and provided supportive PK data.

Study HHT-PS1/Metafore

Study HHT-PS1/Metafore was a phase 2, open-label, single-arm trial that investigated the efficacy, safety, and pharmacokinetics (PK) of bevacizumab (Avastin) in patients with HHT and severe liver involvement. In the study, subjects were administered bevacizumab intravenously at a dose of 5 mg/kg every 14 days for 3 months, followed by a 12-month follow-up period. A total of 25 patients received treatment and were included in the analysis.

The blood samples for PK analysis of bevacizumab were taken pre-dose and 2h, 5h and 24h after dose for the first administration, and pre-dose and 2h post-dose for all following administrations.

One patient received only 2 infusions of bevacizumab. A total of 317 bevacizumab serum concentration and 96 CI measurements were available.

A popPK model was developed, and PK parameters were predicted by a two- compartment model with linear elimination.

Pharmacokinetic results

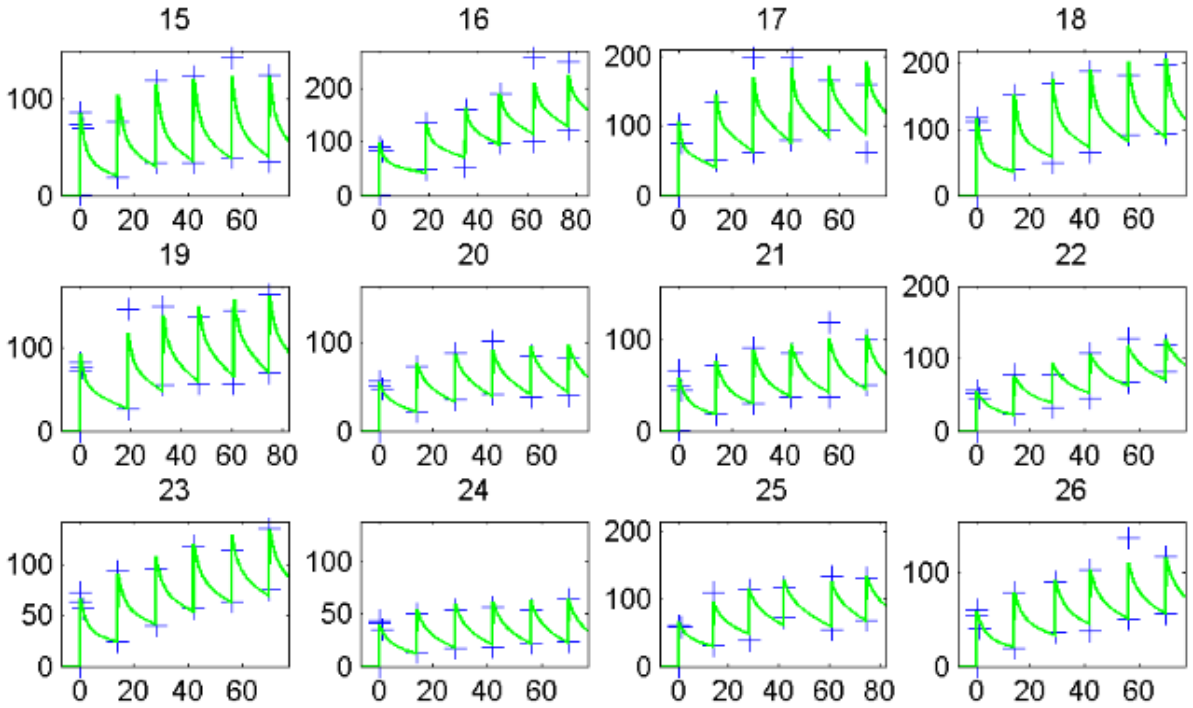


Figure 2: Concentration of bevacizumab over time for 12 patients. The blue crosses represent the observed concentrations. The green curves represent the individual concentrations predicted by a two- compartment model with linear elimination

Study HHT-PS2/BABH

Study HHT-PS2/BABH was a randomized, double-blind, placebo-controlled Phase 2 trial that assessed the efficacy, safety, tolerability, and PK of bevacizumab (Avastin) administered intravenously at a dose of 5 mg/kg every 14 days for 10 weeks, consisting of a total of 6 injections. The study consisted of 24 patients, with n=12 receiving bevacizumab.

The blood samples for PK analysis of bevacizumab were taken pre-dose and 2h post dose for the first administration, and pre-dose for the subsequent administrations.

For patients 122, 208, and 213, the treatment was extended due to delays in administration, however it is not stated exactly when treatments were given. Subject 318 and 405 had their treatment stopped after 3 and 4 administrations, respectively.

Table 11: Details on missed administrations in the BABH study

Details of the administrations not carried out

Identifier for the Study	Group	V1 - Administration	v1_report	V2 - D14 : Administration	v2_report	V3 - D28 : Administration	v3_report	V4 - D42 : Administration	v4_report	V5 - D56 : Administration	v5_report	V6 - D70 : Administration	v6_report	V7 - Month 3: Consultation HHT	V8 - Month 6
[redacted]	Beva	Yes	.	No	Yes	Yes	.	Yes	.	Yes	.	Yes	.	Yes	Yes
	Placebo	Yes	.	Yes	.	No	Yes	Yes	.	Yes	.	Yes	.	Yes	Yes
	Beva	Yes	.	Yes	.	No	Yes	Yes	.	Yes	.	Yes	.	Yes	Yes
	Placebo	Yes	.	Yes	.	Yes	.	Yes	.	Yes	.	Yes	.	No	Yes
	Beva	Yes	.	Yes	.	Yes	.	No	.	No	.	No	.	Yes	No
	Beva	Yes	.	Yes	.	Yes	.	Yes	.	No	.	No	.	Yes	Yes

The 2 patients with non-postponed visits are 1 patient who left because of non-compliance (318) and one patient whose treatment was stopped (405)

PK results

PK parameters for n=12 subjects receiving bevacizumab administered every 14 days. Concentration day 14 (C14) and concentration 3 months (CM3) after the first administrations are observed values, other parameters are estimated based on pop-PK modelling (except for subject 122 who had a missing value at day 14, and C14 was estimated based on the popPK model).

A two-compartment model with first-order transfer and elimination rate constants were used.

Table 12: PK parameters for the subjects receiving bevacizumab in HHT-PS2/BABH study

Patient	CL (L/day)	$t_{1/2}\beta$ (day)	C_{14} (mg/L)	C_{M3} (mg/L)	AUC_{14} (day*mg/L)	AUC_{M3} (day*mg/L)	AUC_{M6} (day*mg/L)
[redacted]	0,397	15,44	16,32	22,23	499	4411	4891
	0,390	13,46	15,46	20,55	602	4977	5365
	0,345	15,09	35,42	37,24	852	7578	8363
	0,399	16,19	20,51	31,04	616	5731	6432
	0,332	15,73	24,45	30,77	642	5882	6557
	0,547	13,05	15,88	17,81	540	4482	4809
	0,219	23,29	***33,65***	101,93	782	5941	10556
	0,217	18,31	38,00	117,73	973	8376	10950
	0,183	22,68	25,18	54,86	659	7240	8910
	0,352	19,36	***25,07***	11,91	635	3571	3891
	0,180	21,89	37,41	81,02	938	10364	12751
	0,381	16,62	17,79	7,49	503	3381	3557

CL = individual elimination clearance of bevacizumab
$t_{1/2}\beta$ = individual terminal elimination half-life
C14 and *CM3* = residual concentrations of bevacizumab at D14 and M3 (D92). The values in italics are the concentrations predicted by the model. The others (C14 only) are the concentrations measured using the ELISA technique.
AUC14 = cumulative area under the curve between D0 and D14 for evaluation of early exposure.
AUCM3 = cumulative area under the curve between D0 and M3 (V7), first evaluation date.
AUCM6 = cumulative area under the curve between D0 and M6 (V7), second evaluation date.

The mean (SD) $t_{1/2}$ in study BABH, was 422.22 ± 84.2 h, i.e. 17.6 days and mean clearance (L/h) 0.01367 ± 0.00457. In addition, the mean(SD) AUC for 0-3months and 0-6months were reported as; AUC0-M3: 143868 ± 49842.07 AUC0-M6: 174064 ± 72370.69.

Study HHT-RS1 / Cobevaro

This study utilized a registry-based approach, collecting data on all patients who received bevacizumab for the treatment of HHT up to December 31, 2023, from the CIROCO data warehouse. The routine monitoring of serum trough concentrations of bevacizumab has been integrated into the therapeutic management of HHT patients treated with bevacizumab in France, although not systematically. A total of 520 bevacizumab trough concentration measurements from 123 patients between 2010 and 2023 were analysed, 73% of patients had 5 or less trough concentrations measured, with a maximum of 18 measurements in a single patient.

The average trough concentration was 18.0 mg/L, with a median of 13.4 mg/L. The maximum concentration measured was 89.3 mg/L and 1st and 3rq quantiles 3.4 mg/L and 28.6 mg/L, respectively.

The limited data did not allow for the development of new PK and PKPD models, it was used to externally validate models that had been previously established using clinical trial data.

5.2.2.11. Special populations

Impaired renal function
According to the Avastin SmPC, PK of bevacizumab has not been investigated in patients with impaired renal function. No study is required in the context of this biosimilar application.

Impaired hepatic function
According to the Avastin SmPC, PK of bevacizumab has not been investigated in patients with impaired hepatic function. No study is required in the context of this biosimilar application.

Gender
Specific differences in regard to PK and gender have not been studied for the HHT population.

Ethic factors
In the Avastin SmPC, there exist no data related to the ethinicty/race vs PK. Consequently, no such data are needed in the Orblid SmPC.

Weight
According to Avastin SmPC, children, adolescents, and adults (based on a population PK model), exposure tends to be lower with decreasing body weight. The effects of body weight have not been specifically studied in the HHT population.

Elderly

Table 13: Age ranges studied in the elderly population

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials			

The Applicant should provide data for the above summary table on number of elderly subjects in the different age categories studied in clinical trials of HHT (**OC**).

5.2.2.12. Pharmacokinetic interaction studies

No formal interaction studies were performed and no interaction studies are needed.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Bevacizumab binds to vascular endothelial growth factor (VEGF), the key factor in vasculogenesis and angiogenesis, thereby inhibiting the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. The general pharmacological action of bevacizumab is well-described, and the substance has been used clinically for oncological indications since 2004 when AVASTIN was approved.

No specific clinical pharmacology studies have been performed concerning the HHT indication.

Hereditary Haemorrhagic Telangiectasia (HHT) results from mutations in genes involved in the transforming growth factor-β (TGF-β) signalling pathway, primarily affecting the ENG (endoglin) or ACVRL1 (activin receptor-like kinase 1) genes (Fernández-L et al. 2006; David et al. 2007; McDonald et al. 2015). Through an over-activation of this signalling pathway, these mutations cause an angiogenic imbalance caused by an over-expression of VEGF, leading to the development of abnormal blood vessels and arteriovenous malformations (AVMs) in the skin, mucous membranes, and vital organs such as the lungs, liver, and brain (Frigerio et al. 2016; EASL Clinical Practice Guidelines 2016; Karlsson et Cherif 2018; Bodilsen 2020). These AVMs lack the normal capillary bed between arteries and veins, resulting in direct high-flow connections that predispose the vessels to rupture and bleeding. The clinical manifestations of HHT stem directly from the location of these vascular anomalies.

Based on the overexpression of VEGF in HHT, clinicians started to use bevacizumab off-label in this disease, with the first case-report found in PubMed going back to 2008 (Flieger et al. 2006) reporting its successful use in a patient with hepatic involvement associated with HCO. From then, bevacizumab has been increasingly used off-label in the treatment of severe bleeding manifestations and cardiac involvement associated with hepatic AVMs and investigated through clinical trials (Dupuis-Girod et al. 2012, 2023, 2025) and retrospective studies.

5.2.3.2. Primary and secondary pharmacology

No specific clinical pharmacology studies have been performed concerning the HHT indication. No secondary pharmacology studies were performed and are not required.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

No pharmacology drug interaction studies were performed and are not required.

5.2.3.4. Genetic differences in PD response

In the BABH study, the Cobevaro registry and the Inhibit-Bleed registry, the identified mutations were mainly located to the ACVRL1 and ENG genes, which are the most commonly affected genes causing HHT. No information on genetics is available from the Metafore study. No conclusions on possible genetic differences in the PD response can be drawn from the limited studies. Mutations in the SMAD4

and GDF2 genes occur less frequently, and robust clinical data on the response in these genotypes will be more difficult to obtain. Since there is data indicating an altered VEGF signalling also in these genotypes, there is no obvious basis for expecting a different outcome.

5.2.3.5. Immunological events

Immunogenicity was studied in the clinical development program for CT-P16 and the studies have been previously assessed in the MAA concerning the oncologic indications. No immunogenicity data in the target population (HTT) has however been submitted.

The immunogenicity assessment of CT-P16 in the clinical program was done with clinical results of 141 healthy subjects in Study CT-P16 1.1 up to Day 99, 46 healthy subjects in Study CT-P16 1.2 up to Day 99 and 689 NSCLC patients in Study CTP16 3.1 up to cut-off date, using validated assays for ADAs and NAbs, in line with current relevant regulatory guidelines. In Study CT-P16 1.1, ADA and NAb incidences at each timepoint from Day 1 to Day 99 and the proportion of subjects who had postdose ADA positive results was generally similar between the three treatment groups: 2 (4.3%) patients for the CT-P16 and the EU-Avastin treatment group, and 3 (6.3%) patients for the US-Avastin treatment group. Although the number of ADA positive patients was small, the ADA titer results up to Day 99 showed comparable distribution among the CT-P16, EU-AVASTIN and US-AVASTIN treatment groups. Among the ADA positive patients, no patient showed positive results for NAb. In Study CT-P16 1.2, there was no confirmed ADA positive samples, and thus NAb assessment was not conducted. In Study CT-P16 3.1, the proportions of patients who had post-treatment ADA or NAb positive results were similar between the CT-P16 and the EU-AVASTIN treatment groups: 74 (21.4%) patients for the CT-P16 treatment group and 80 (23.3%) patients for the EU-AVASTIN treatment group. There is limited experience in patients with ADA to bevacizumab, but the data to date have not shown an apparent effect of ADA on PK, efficacy or safety.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Several PK/PD analyses were performed including several PD endpoints collected in Studies Metafore, BABH and CoBeVaro.

Study HHT-PS1 / Metafore

A pharmacometrics model-based PKPD analysis was conducted based on Metafore to describe the relationship between bevacizumab plasma concentrations and cardiac index and epistaxis.

In total, 25 patients were treated and analysed.

Cardiac index

The observed cardiac index data is shown in Figure 3.

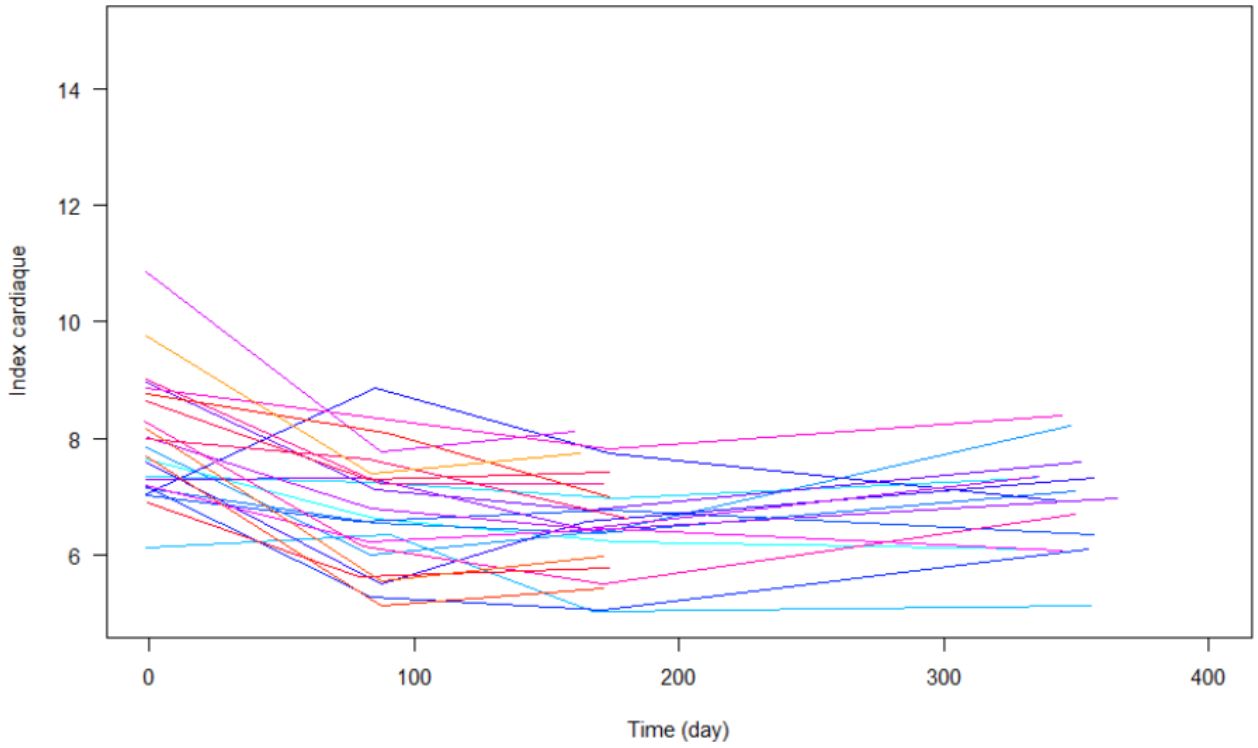


Figure 3: Variation of cardiac index for the 25 patients.

An effect delay model was used to describe the PKPD relationship with 4 transit compartments. The drug effect was described using an inhibitory Emax model with a corresponding EC50 estimate of 3.72 mg/L. Descriptions of individual changes in CI (Figure 4) were obtained using the PK-PD models, and the pharmacokinetic model and the CI sub-model adequately described observed data.

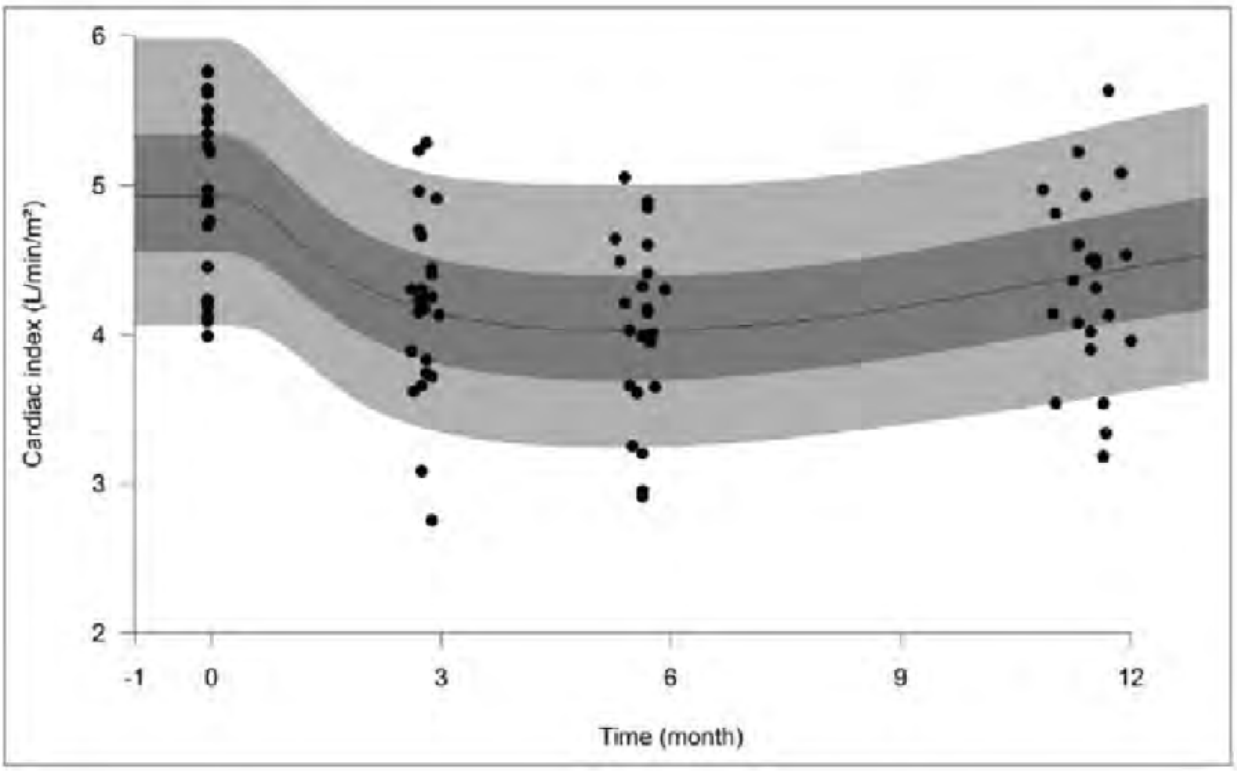


Figure 4: Observed and model-predicted cardiac index (CI) over time in patients. Closed circles are observed CI in patients treated with 6 injections de 5 mg/kg bevacizumab every other week. Continuous line and shaded areas represent median and 5th, 25 th, 75 th and 95th percentiles of model-predicted CI.

Epistaxis

Daily epistaxis duration was categorized by 10 minute classes (d ETX): "0" was for no epistaxis, "1" was for less than or equal to 10 min per day, "2" was for 11 to 20 min per day, etc., and "7" was for an epistaxis duration of more than 1 hour per day. The observed epistaxis durations are summarized in Table 15.

Table 14: Numbers and proportions of occurrence of each category for different time periods.

Catégorie	avant BVZ		0 à 3 mois		3 à 6 mois		6 à 9 mois		9 à 18 mois		tous les tps	
0	520	52.7%	1325	59.2%	1479	70.1%	1565	76.3%	1327	72.2%	6216	67.4%
1	252	25.5%	590	26.3%	497	23.6%	386	18.8%	426	23.2%	2151	23.3%
2	92	9.3%	156	7.0%	104	4.9%	75	3.7%	50	2.7%	477	5.2%
3	47	4.8%	79	3.5%	18	0.9%	17	0.8%	16	0.9%	177	1.9%
4	26	2.6%	22	1.0%	7	0.3%	7	0.3%	6	0.3%	68	0.7%
5	18	1.8%	19	0.8%	3	0.1%	0	0.0%	2	0.1%	42	0.5%
6	13	1.3%	26	1.2%	0	0.0%	2	0.1%	5	0.3%	46	0.5%
7	19	1.9%	23	1.0%	1	0.0%	0	0.0%	5	0.3%	48	0.5%
total	987		2240		2109		2052		1837		9225	

The epistaxis model aimed to describe the probability (risk) of occurrence of the different daily-epistaxis duration classes. The best description of l variation over time (l(t)) was obtained using a sigmoid inhibitory function and 4 transit effect compartments (Table). The corresponding EC50

parameter was estimated to 5.48 mg/L. The modelling of daily epistaxis durations categorized according to the concentration of BVZ in the effect compartment yields satisfactory results (Figure 5).

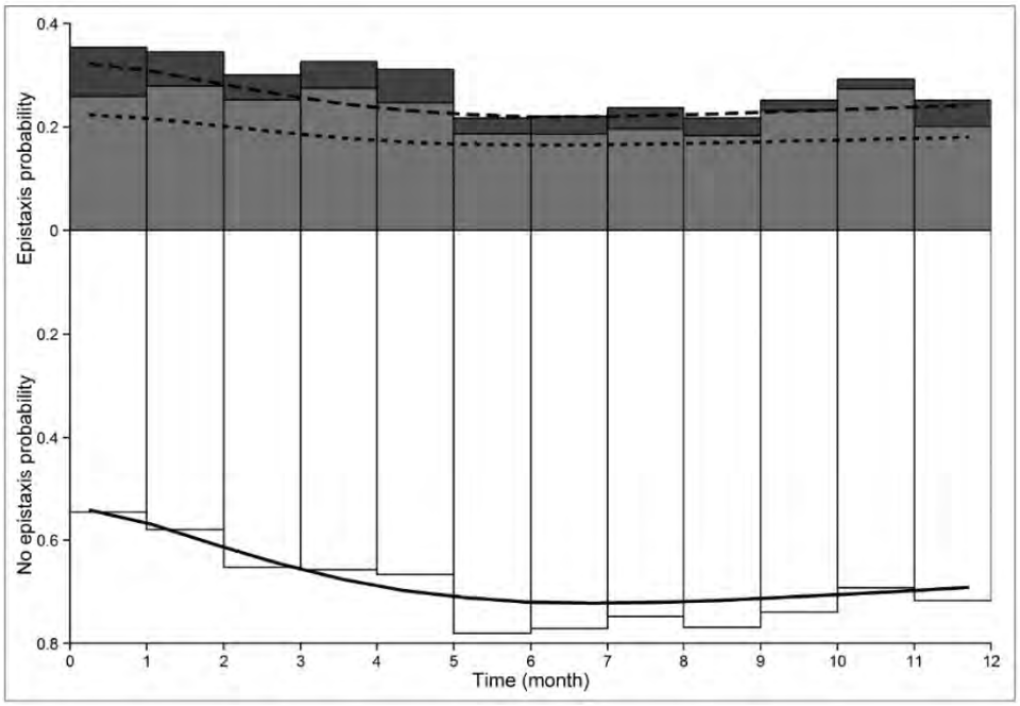


Figure 5: Observed frequencies and model-predicted probabilities of epistaxis daily durations. White, gray and dark gray bars are 'no epistaxis', 'less than or equal to 10 min' and '11 to 20 minutes' mean daily epistaxis observed frequencies, respectively. Solid, dashed and long-dashed lines are the model predicted probabilities for 'no epistaxis', 'less than or equal to 10 min' and 'less than or equal to 20 min' daily epistaxis, respectively.

Simulations

Simulation of bevacizumab concentrations, CI and epistaxis duration in 5,000 virtual patients that were treated with maintenance dosing regimens (DR) consisting of repeated 5 mg/kg injections every 3 months (DR2), 2 months (DR3) or 1 month (DR4) led to sustained effects while an induction treatment every year (DR1) did not lead to a long-term control of symptoms (Figure 6). An infusion of 5 mg/kg bevacizumab every month (DR4) gave the best results (Figure 6). The superiority of this regimen was particularly marked for epistaxis, with 28, 34, 43 and 60% of patients with less than 20 min of daily epistaxis at 24 month for DR1, DR2, DR3 and DR4, respectively. However, in terms of cardiac index, DR2, 3 and 4 were similarly effective since they were able to maintain 41%, 45% and 50% of patients with a CI < 4 L/min/m2 at 24 months, respectively (Figure 6), compared with 21% with DR1.

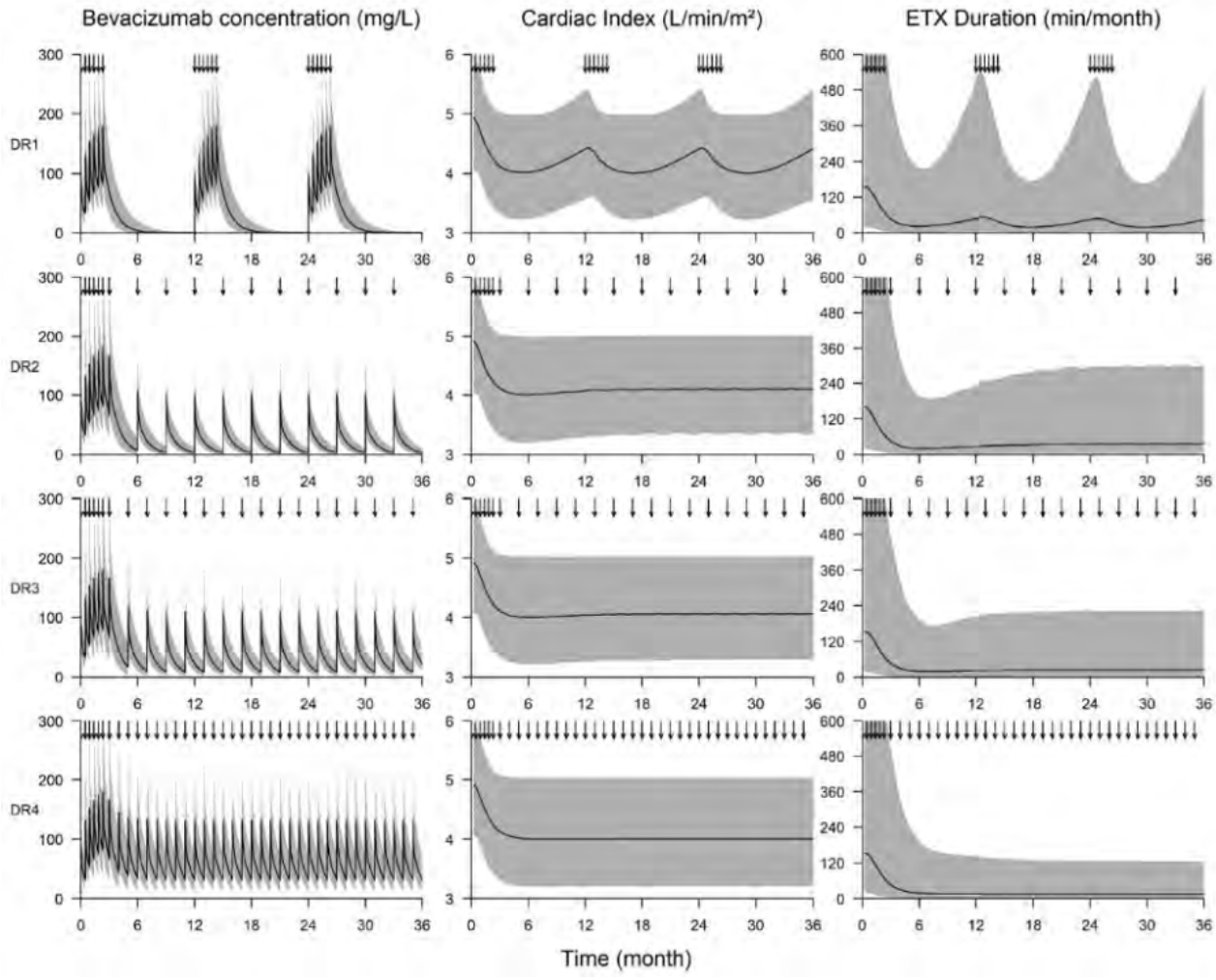


Figure 6:Simulations of bevacizumab concentrations and effects obtained with 4 different maintenance dosing regimen over 3 years. DR1 consists in 6 injections of 5 mg/kg bevacizumab, every over week, every year (3 upper panels). DR2, DR3 and DR4 consist in 6 injections of 5 mg/kg bevacizumab, every over week, followed by injections of 5 mg/kg every 3, 2 and 1 months, respectively (lower panels). Solid lines and shaded areas are median and 5th -95 th percentiles of simulated bevacizumab concentrations (left panels), simulated cardiac index (center panel) and simulated epistaxis duration (right panel).

Study HHT-PS2 / BABH

PKPD analyses were conducted for Study BABH to characterise the relationship between bevacizumab concentrations and the number of required red blood cell (RBC) transfusions.

Of the 12 patients who received bevacizumab, the median elimination half-lives and residual concentrations of bevacizumab at day 14, before the 2nd injection, were 16.4 (13.1–23.3) days and 24.8 (15.5–38.0) mg/L, respectively. The decreases in RBC units transfused and in epistaxis after treatment were not related to day 14 bevacizumab concentrations. However, the five patients with above-median exposure to bevacizumab (day 14 concentration higher than the median value) had a greater decrease in RBC units transfused than patients with below-median exposure (Figure 7, p = 0.03). Additionally, there was a significant association between bevacizumab exposure (none, below-median, or above-median) and the absence of RBC units transfused (Fisher's exact test p = 0.04). The comparison while removing the patient with missing data shows a p-value of 0.06.

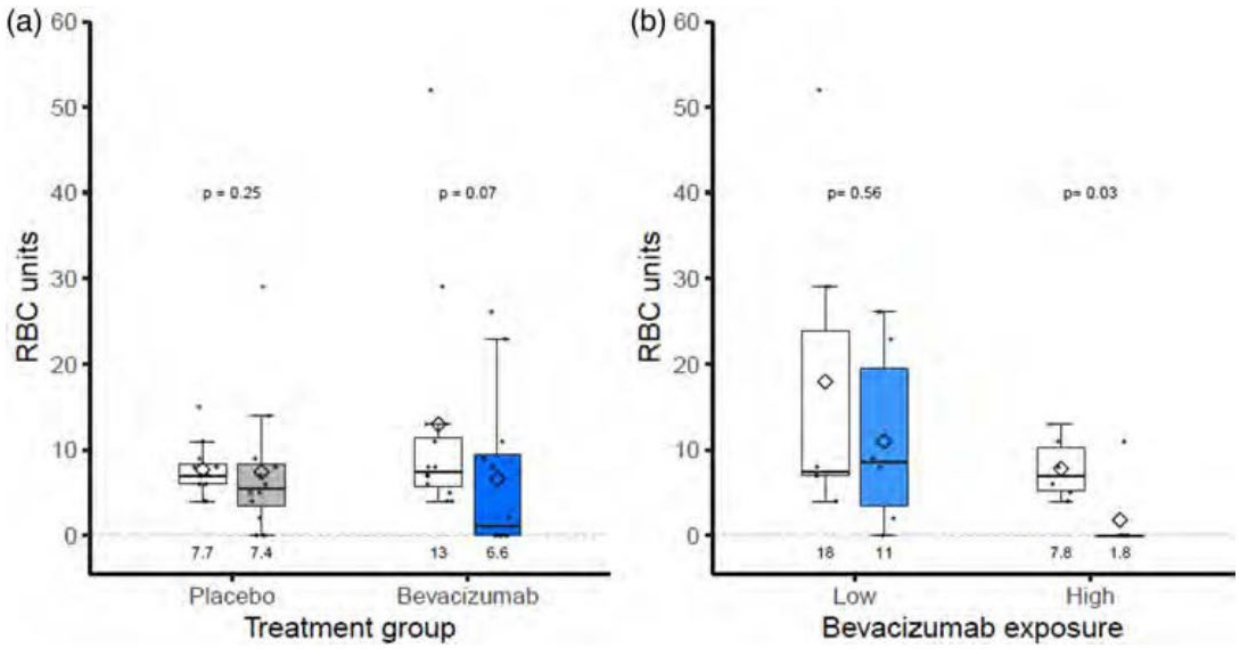


Figure 7: Number of red blood cell units transfused as the function of treatment groups (A) and bevacizumab exposure (B), 3 months before the treatment (white) and 3 months after its end (gray/blue). Low and high are subgroups of bevacizumab-treated patients with serum bevacizumab concentrations at day 14 below (or equal) or above-median value, respectively. Dots represent the individual values. The lines of boxes represent the 25th, 50th, and 75th percentiles. Diamonds represent mean values.

An additional pharmacometrics model-based PKPD analysis was conducted. A total of 362 transfusion outcomes were available from 24 patients. Without bevacizumab treatment, the rate of RBC unit transfusion was supposed constant over time. Bevacuzimab was assumed to inhibit the rate of RBC unit transfusion using an inhibitory Emax model. An effect compartment model was used to describe a delay between bevacizumab plasma concentrations and effect. The parameter estimates are shown in Table.

The PK-PD model confirmed a large delay between bevacizumab treatment start and substantial decrease of RBC unit transfusion rate which occurred approximately 100 days after beginning of bevacizumab treatment (Figure 8).

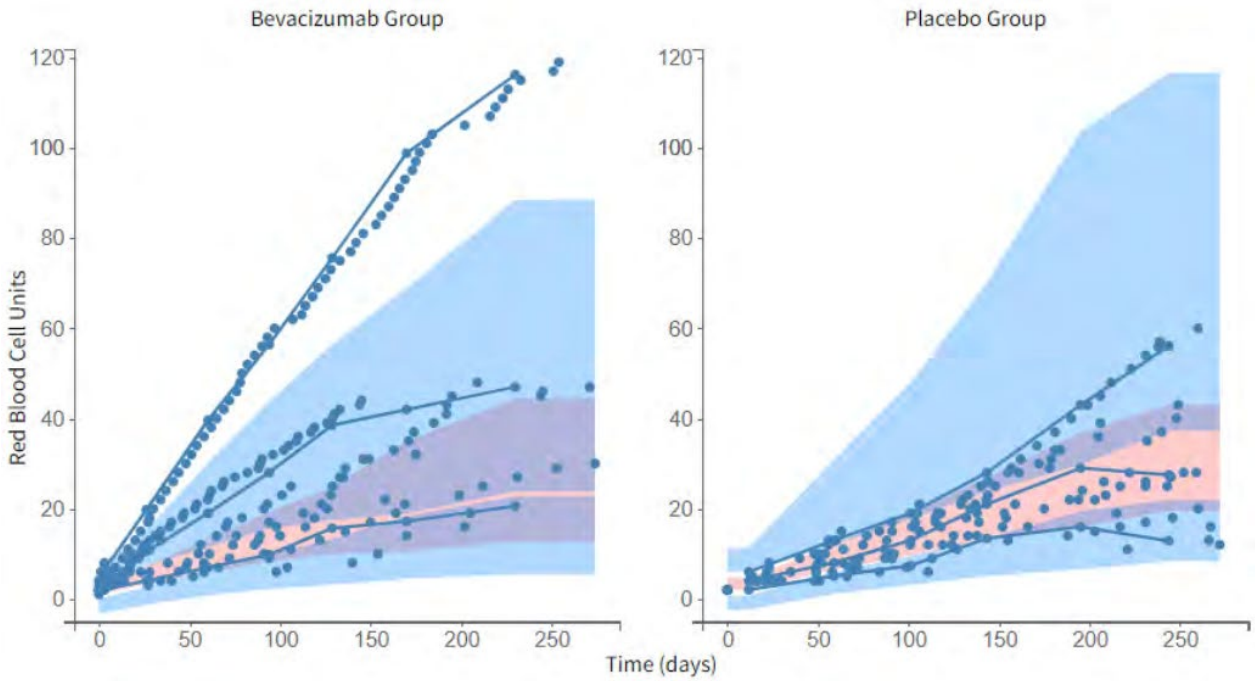


Figure 8: Visual predictive checks (VPC) of RBC unit transfusion outcomes over time in bevacizumab (left) and placebo (right) groups. The limited number of patients led to difficulties in describing the large interindividual variability in transfusion outcomes over time. Blue dots represent transfusion outcomes, blue, pink then blue areas represent 90% prediction intervals for 10th, 50th and 90th transfusion unit percentiles, lines represent median transfusion unit profiles for each interval.

Simulation aimed at evaluating the influence of 6 different maintenance dosing regimen on bevacizumab concentrations over time and the number of RBC units received were performed. These were performed following alternative maintenance dosing regimens (DR) after induction (6 infusions of 5 mg/kg of bevacizumab every 2 weeks).

The probability of target attainment (PTA) plot evidenced that all dosing regimen resulted in a reduction in transfusion of at least 30% and up to 80% after one year of treatment (Figure 9).

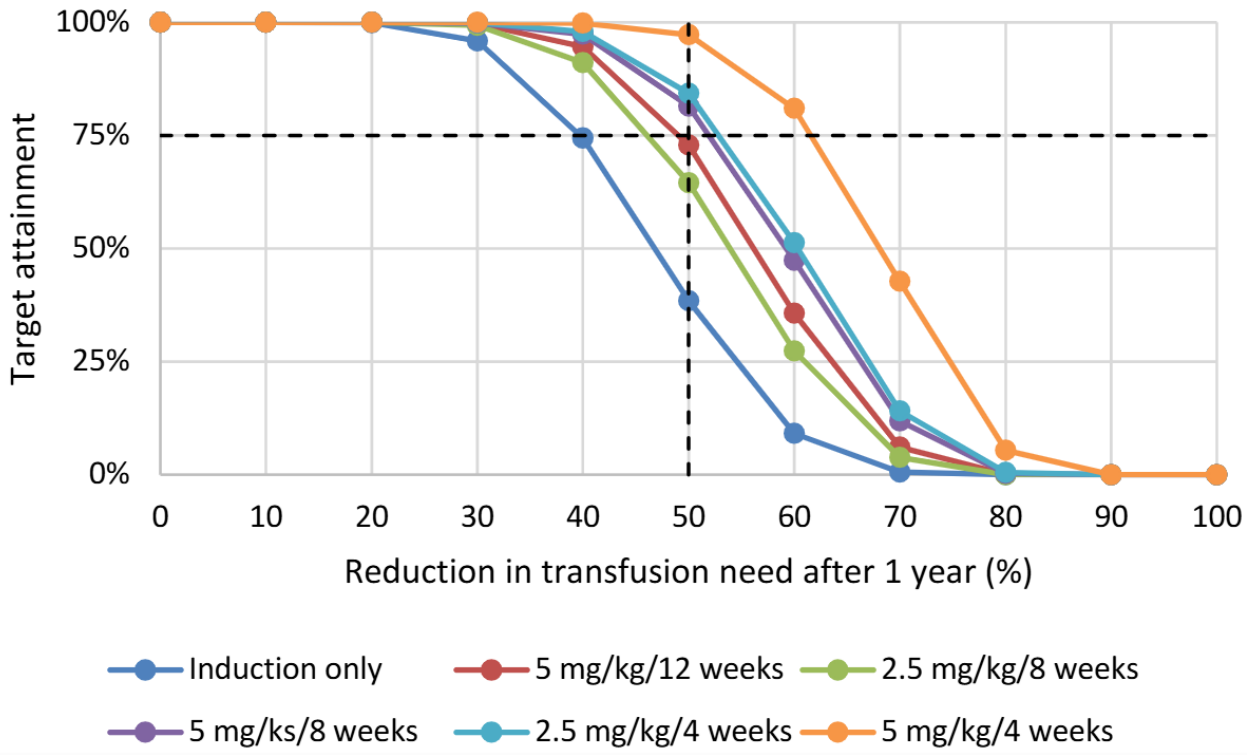


Figure 9: Probability of target attainment corresponding to the percentage of patients achieving a reduction in transfusion need after 1 year with different dosing regiments of bevacizumab maintenance. The most effective dosing regimens are located in the upper right-hand corner.

Study HHT-RS1 / Cobevaro

PKPD analyses were conducted for Study Cobevaro to characterise the relationship between bevacizumab concentrations and the number of required red blood cell (RBC) transfusions.

This registry-based study included all patients receiving bevacizumab in the context of real-world use specifically for the treatment of Rendu-Osler disease. The data included bevacizumab trough concentration measurements as some patients benefited from therapeutic drug monitoring (TDM). 89 patients of the 237 total were included for the pharmacometric evaluation of trough concentrations collected as part of routine clinical care. The PKPD analysis included 423 trough measurements.

The data was used to externally validate previously models previously fitted for Study BABH see Section above on PKPD analysis of BABH) with the overarching aim of verifying whether the previously established model structure and assumptions remained appropriate when applied to real-world populations.

Using the previous model with fixed population-level parameters, simulated concentrations and PD outcome were compared against observed data. The previous PKPD model structure was maintained (see Section above on PKPD analysis of BABH) but with re-estimation of inter-individual variability terms.

To explore the clinical implications of this modelling framework, a final simulation-based analysis was conducted to evaluate the effectiveness of the proposed maintenance dosing regimen of 5 mg/kg every 8 weeks (Q8W). A prospective simulation was performed (using the previously estimated individual PK parameters, also known as Empirical Bayes estimates [EBEs] from real-world patients), applying a standardized Q8W maintenance schedule and comparing it to a placebo scenario. The results indicated that 76% of patients would achieve a clinically meaningful reduction (≥50%) in transfusion need at one year, closely mirroring the outcomes predicted by the original clinical trial model.

5.2.5. Dose selection and therapeutic window

See Section 3.1.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Bioanalytical Methods

Quantification of bevacizumab concentration

Two analytical methods including ELISA (used in clinical study CT-P16 1.1) and MSD-ECL (used in clinical studies CT-P16 1.2 and CT-P16 3.1) were validated according to ICH M10 Bioanalytical method validation guideline. In both methods CT-P16, EU-Avastin and US-Avastin performed with analytical similarity in terms of selectivity, precision and accuracy.

MSD-ECL based method was used in the analysis of healthy and nsNSCLC patient human serum samples. The usage of same analytical method for healthy and nsNSCLC samples was acceptable since the method demonstrated selectivity for both healthy and nsNSCLC serum. The analysis of clinical samples was reliable within the given accuracy and precision ranges.

The bioanalytical methods in CT-P16 1.1, CT-P16 1.2 and CT-P16 3.1, are considered adequate and validated according to current guidelines.

HTT population

The bioanalysis used in the HHT-PS1/Metafore study was developed and validated within academia and published in 2010 (Ternant, et al.2010). The PK assay setup seem appropriate for the purpose, reflecting the pharmacologically active fraction of bevacizumab.

Performance metrics for the assay was presented in table format by the applicant, but no detailed bioanalysis report for the validation has been found to confirm the values. Although the presented data overall appears acceptable, the validation is not fully compliant with the current ICH M10 guideline. Missing information includes for example, incurred sample reanalysis, lipemic and haemolysed samples, hook effect and parallelism. Other flaws in the bioanalytical method are that blanks from the relevant patient population (HHT) was not used, it is unclear if standards and QCs were prepared independently, there were only three QC levels included in the validation, the number of replicates for each sample was two, and not three. A matrix effect was potentially observed for the highest QC in human serum, as it was measured as -30% of the nominal value. Furthermore, it is not clear if the validated QC range is bracketing the concentration in the study samples. Stability was tested for the samples at only one concentration (25 mg/L), but all tested samples were within ±20% of the nominal value. Freeze-thawing was not tested.

Overall, the bioanalytical method for measuring bevacizumab in serum of HHT is not completely validated according to the M10 guideline, however, the performed validation appears overall adequate, and issues are not further pursued. No within-study bioanalysis reports for the studies in HHT patients could be found in the dossier, therefore the performance in these studies could not be assessed. The Applicant is asked to provide within-study bioanalysis reports, if available, for the proprietary studies in HHT, PS1/Metafore study, HHT-PS2/BABH and HHT-RS1/CoBevaRo (**OC**).

PD-biomarkers

ELISA-methods were used in HHT-PS1/Metafore to quantify BMP9 and VEGF, however, no further details on the methodology or validation were provided in the dossier. Since these biomarkers are not

considered essential for the overall efficacy or PK/PD assessment in HHT, this issue is not further pursued.

Immunogenicity

In general, the bioanalytical methods used for ADA and Nab assessment in the clinical studies; CT-P16 1.1, 1.2 and 3.1 have been appropriately described and validated according to relevant guidelines. No ADA or nAb assays has been performed on samples from the patient group HHT.

Biosimilarity

According to the MAH, Orblid corresponds strictly to an approved biosimilar to Avastin in terms of pharmacokinetic and pharmacodynamic characteristics, but with the intended indication; adult patients with confirmed Hereditary Hemorrhagic Telangiectasia (HHT).

The Marketing Authorisation of the approved biosimilar in oncology was granted with the same indications as the originator. According to the Guideline on similar biological medicinal products "If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification", furthermore "there is no regulatory requirement to repeat the demonstration of biosimilarity against the reference product, e.g. in the context of a change in the manufacturing process, once the Marketing Authorisation has been granted".

Given that the approved biosimilar is an identical product to Orblid, and no major quality cycle changes expected to change the overall PK of Orblid since the approval of the approved biosimilar has been made, conclusions on biosimilarity can be extrapolated from the submitted studies of the approved biosimilar to Orblid.

The three CT-P16 1.1, 1.2 and 3.1 studies have been previously assessed in the original registration procedure. The assessment concluded that PK similarity could be established between the approved biosimilar and the reference product Avastin.

CT-P16 1.1 (pivotal PK-similarity study)

All 90% CIs for test-to-reference/comparator of the primary PK parameters (i.e. $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max}) were within the pre-specified acceptance range of 80.00 to 125.00 (including 100.00) demonstrating that the PK of the CT-P16 is comparable with the EU-Avastin and US-Avastin. The secondary PK parameters (i.e. T_{max}, Vz, λz, $t_{½}$, CL, $\%AUC_{ext}$) were also comparable between studied treatments. A total of 9 subjects were excluded from pharmacokinetic (PK) analyses: 4 from the $AUC_{0\text{-inf}}$ analysis due to an insufficient interval (less than 1.5 of the half-life) for determining λz, and 5 from the $AUC_{0\text{-last}}$ analysis because they withdrew before the final sampling time on day 99. The exclusions were in line with the statistical analysis plan (SAP). Sensitivity analyses were performed including the subjects who were previously excluded, which showed that 90% CIs of geometric LS mean ratios were entirely contained within the predefined equivalence margin of 80.00 to 125.00, thus PK biosimilarity remained unchanged. A sensitivity analysis of primary PK parameters (i.e. Cmax, AUC0-last, and AUC0-inf), excluding subjects with pre-treatment measurable concentrations of bevacizumab was also performed, which also did not change the PK biosimilarity conclusion.

The protein contents were within specification limits, and highly similar between test and reference products (test CT-P16: 25.3 mg/mL, reference EU-Avastin: 25.3 mg/mL, reference US-Avastin: 25.4 mg/mL)

CT-P16 1.2 (supportive PK study)

All 90% CIs for the test-to-reference ratios of the AUCs were within the pre-specified acceptance range of 80.00 to 125.00 (including 100.00) demonstrating the PK similarity between CT-P16 and EU-Avastin. The mean secondary PK parameters ($t_{1/2}$, λz, CL, Vz, and $\%AUC_{ext}$) were comparable between the two treatment groups. The inter-subject variability was low in all PK parameters also in this study. A sensitivity analysis excluding one subject with a significantly lower Cmax and later Tmax showed a 90% CI that included 100.00. The subject likely received a subcutaneous infusion instead of IV infusion, based on their serum bevacizumab concentration profile.

The protein content of EU-Avastin was within specification limits, and highly similar between test and reference products (test CT-P16: 25.0 mg/mL, reference EU-Avastin: 24.7 mg/mL).

CT-P16 3.1 (clinical study in NS-NSCLC patients)

In the phase III clinical study, the observed C_{trough} concentrations were comparable between CT-P16 group and EU-Avastin group from baseline through cycle 6.

Overall, Orblid can be considered biosimilar, from a PK perspective, to EU-Avastin.

Immunogenicity

Immunogenicity was evaluated during the CT-P16 clinical development programme and has been previously assessed in the context of CT-P16 biosimilar marketing authorisation application for oncology indications. In the oncology setting (CT-P16 3.1), which involved a relatively short treatment duration, no clinically meaningful differences in ADA or nAb incidence were observed between CT-P16 and EU-Avastin. However, the number of ADA-positive patients was small, precluding any meaningful assessment of potential impact of immunogenicity on bevacizumab PK. No immunogenicity data in the target population (HTT) has however been submitted. This is considered a relevant limitation, as treatment in oncology is typically of shorter duration and frequently involves concomitant cytotoxic therapies that may suppress immune responses.

Given that the development of an antibody response can be different for different therapeutic indications. The applicant should discuss, with references to peer-reviewed literature, the potential risks of immunogenicity in the HTT population. Compared to the oncologic indications, long-term use is expected to be more frequent when used for the HHT indication, and the applicant is requested to discuss the possible impact of immunogenicity. (**Safety OC**)

ADME

No new data on absorption or metabolism have been provided in the target population HHT. Volume of distribution, distribution and elimination half-lives in HHT patients were provided by pop-PK modelling and the two latter are reported in the SmPC.

Overall, the half-life of bevacizumab in HHT patients ranged from 17.6 to 24.0 days and is similar to oncology patients. Clearance was in a similar range in HHT patients compared with oncology patients. There is a discrepancy in the SmPC regarding distribution half-life stated as 1.6 days in HHT referencing Azzopardi et al 2015, but the table states 1.4 days referencing Dupuis-Girod et al 2012. Lu et al 2008 states that $t_{1/2\beta}$ (i.e. elimination half-life) is 19.9 (17.9, 22.5) days and not 21.5 days.

No Cmax or AUC in HHT patients was reported in the SmPC. See overall SmPC comment on section 5.2 (**LoQ**)

Special populations

No dedicated studies in special populations have been conducted, and none are needed. The Applicant should provide data for the summary table on number of elderly subjects in the different age categories studied in clinical trials of HHT (**OC**).

Pharmacokinetics in the target population (HHT)

The Applicant has provided reports of three studies of Avastin in HHT patients: HHT-PS1/Metafore, HHT-PS2/BABH, and HHT-RS1/Cobevaro (the latter of Avastin and other biosimilars). These studies evaluated the efficacy and safety of bevacizumab in HHT patients and provided supportive PK data.

For HHT-PS1/Metafore, the PK results presented are very limited. A figure representing observed and modelled PK data for 12 patients (not the whole data set of n=25) have been provided, but no PK parameters or nominal values are presented.

For HHT-PS2/BABH, pre-dose concentrations were measured and reported for 14 days and 3 months after the first administration. A total of 12 patients received bevacizumab, and four patients had missed administrations or discontinued treatment. The concentration at 14 days ranged from 15.5 mg/L to 38 mg/L, and at 3 months from 7.5 mg/L to 117.7 mg/ml.HHT-RS1/Cobevaro was a registry-based real-world study, where serum through concentrations were collected in 123 patients, with a total of 520 samples collected between 2010 and 2023. The average trough concentration was 18.0 mg/L, with a median of 13.4 mg/L. The maximum concentration measured was 89.3 mg/L and 1st and 3rq quantiles 3.4 mg/L and 28.6 mg/L, respectively. The average trough concentrations appear to be in a similar range as in the HHT-PS2/BABH study, while no Ctrough values have been reported for HHT-PS1/Metafore, comparison cannot be made.

In Cobevaro, the inclusion of patients treated with different bevacizumab products introduces heterogeneity into the PK dataset, as individual exposure data cannot be attributed to a single product. This heterogeneity limits the interpretability of the PK data and reduces their value for product-specific PK characterisation and model data validation. The proposed description of PK in the target population is not appropriate to include in SmPC 5.2. The Applicant should replace the information based on the PopPK modelling with a brief description of the mean and variability of AUC and Cmax in the respective target population (see **SmPC comment/LoQ**).

The pharmacokinetics in the target population were described using PopPK modelling, as described below. However, the PK models and real-world data provided do not fully address uncertainties long-term pharmacokinetics and dose optimisation. The selected dose and dosing interval for long-term treatment in HHT has not been supported. Furthermore, there are uncertainties related to long-term pharmacokinetics and immunogenicity which has not been addressed (**MO**).

PopPK modelling

The PK model is considered useful for describing PK in the target population. Furthermore, the PopPK model serves as input for subsequent PKPD analyses.

Overall, the reporting of the PopPK models was very brief at the time of submission which is a considerable limitation. Based on the Summary of Clinical Pharmacology Studies, no formal PopPK reports with complete details appears to have been submitted. For Study HHT-PS1 / Metafore, a publication including a very brief description of the PopPK model was submitted. For Study HHT-PS2 / BABH, a very brief modelling report was submitted. Since the reporting was very brief, it was not possible to perform an adequate assessment the PopPK modelling.

For Study HHT-PS1 / Metafore, a total of 317 PK observations were included from 25 patients. This is considered a rather limited amount of data to develop a PopPK model. The parameter estimates and their RSEs appear overall reasonable which could suggest that the dataset is reasonable. The PK sampling included both pre-dose and post-dose samples following the first and subsequent administrations. The covariate distributions appear overall reasonable.

For Study HHT-PS2 / BABH, a total of 107 bevacizumab concentrations were available from 12

patients randomized to active treatment. This is considered a limited amount of data to develop a PopPK model. The parameter estimates and their RSEs appear overall reasonable but the RSE for V2 was >30% which suggests that the dataset is rather limited. The covariate distributions appear overall reasonable.

In study HHT-RS1/Cobevaro, pre-dose (trough) bevacizumab concentrations were collected in more than 100 patients, with valid PK results available for 89 patients. In total, 520 PK samples were obtained. The mean through concentration was 18.0 mg/L, with considerable variability observed. However, PK sampling in HHT-RS1/Cobevaro was predominantly cross-sectional and was not conducted according to a predefined sampling schedule. The majority of samples were collected during the early phase of treatment or at isolated time points, with only very limited longitudinal sampling during long-term treatment. Consequently, the dataset is largely cross-sectional and does not allow a robust assessment of time-dependent PK behaviour, inter-individual variability or long-term exposure metrics, such as steady-state AUC or trough concentrations (part of the Clinical MO).

The description of the covariate modelling was suboptimal. The Applicant should further describe the covariate modelling approach for the PopPK model development. The Applicant should provide more details regarding the results of the covariate model development. The Applicant should also report the eta-shrinkages for the final model (**OC**).

Since the documentation was too brief, it was not possible to adequately assess the PopPK modelling. The provided goodness-of-fit plots included observations vs typical predictions, observations vs individual predictions and NPDE-based diagnostics. This is not sufficient to assess whether the final models give acceptable description of the observed PK data. The Applicant should provide visual predictive check (VPC) for the final PopPK models for Studies Metafore and BABH. In addition, the Applicant should provide standard goodness-of-fit plots for conditional weighted residuals (CWRES) including CWRES vs population predictions and CWRES vs time since the most recent dose (**OC**).

The model codes and outputs should be provided to allow further assessing the appropriateness of the final PopPK models (**OC**).

Of note, the PopPK analysis was based on the product Avastin.

Mechanism of action

The general pharmacological action of bevacizumab is well-described, and the substance has been used clinically for oncological indications since 2004 when AVASTIN was approved.

The overall rational for use of bevacizumab in treatment of HHT is clear given the described overexpression of VEGF. The mechanism of action when used for bleedings is plausible however for patients with cardiac manifestations, the mechanism of action is less clear, and no clinical data has been presented showing regress of the AVMs in the short timeframe studied. The applicant is requested to further clarify (**OC**).

PKPD analyses

The PKPD analyses are considered to have rather low impact for the overall benefit-risk assessment. The PKPD analyses are considered potentially useful for descriptive purposes, describing exposure-response in the target population.

The Applicant performed PKPD analyses from Studies BABH, Metafore and Cobevare.

The PKPD analyses were based on the product Avastin.

<u>Metafore</u>

The Applicant performed PKPD modelling of several PD endpoints from Metafore, including cardiac index and epistaxis. According to the Applicant, exposure-response relationships were identified for cardiac index and epistaxis. However, the provided analyses have considerable limitations and thus, the results from these analyses should be interpreted with caution.

The sample size in Study Metafore was rather limited for exploring exposure-response relationships given that the models were rather complex (including models for effect delay with several transit compartments). Furthermore, only a single dose level was studied in Metafore which means that the exposure range will be too narrow to robustly characterise exposure-response relationships. The study did not include any placebo group so it is impossible to distinguish any confounding by a potential placebo effect.

The provided documentation was very brief where several of the model diagnostic plots that are normally required to evaluate this type of PKPD modelling were not included in the provided documentation. For instance, conventional VPCs and CWRES-based diagnostic plots were not provided.

For cardiac index and epistaxis, the Applicant identified exposure-response relationships. For cardiac index, the parameters uncertainty was large (>50%) which suggests that the exposure-response relationship is highly uncertain. For both cardiac index and epistaxis, the corresponding EC50 parameters were rather low in relation to the expected concentration range during the proposed dosing interval. However, the estimated EC50/CC50 parameters should be interpreted with caution due to study design limitations, especially the fact that only a single dose level was studied in Metafore.

The Applicant also performed PKPD analyses for VEGF (data not shown). However, the Applicant did not present any relevant exposure-response results for VEGF.

Taken together, no relevant exposure-response analyses of Study Metafore have been provided. There are several considerable limitations with the provided exposure-response analyses which cannot be used to support the benefit-risk assessment of Orblid. Given the very limited impact on the benefit-risk assessment of the provided analyses, the issues highlighted above are not pursued further.

<u>BABH</u>

For BABH, PKPD analyses included exposure-response analyses presented as box plots of RBC transfusions vs high/low exposure as well as several other analyses including dedicated pharmacometrics analyses. Although these analyses could be viewed as indicative of exposure-response trends between bevacizumab and various PD endpoints, the results are highly uncertain due to several limitations in the performed analyses. The sample size in Study BABH was rather small for exploring exposure-response relationships. Furthermore, only a single dose level was studied in BABH which means that the exposure range will be too narrow to robustly characterise exposure-response relationships.

The box plots of RBC transfusions for high vs low exposure indicated an exposure-response relationship according to the Applicant (with a p-value of 0.03). However, this is considered highly uncertain due to the general shortcomings of the study highlighted above. Furthermore, the analysis is a subgroup analysis with a very limited number of patients per group (n=5). This may rather be a chance finding since there were no relevant correlation between day 14 concentrations and RBC transfusions.

The modelling of longitudinal PD data from BABH did not identify any relevant exposure-response relationship. The developed PKPD model did not give acceptable description of the observed number

of RBC transfusions which is a main limitation of the provided analysis. Since the model is not considered acceptable for describing the observed data, the provided simulations are not considered reasonable.

Taken together, no relevant exposure-response analyses of Study BABH have been provided. There are several considerable limitations with the provided exposure-response analyses which cannot be used to support the benefit-risk assessment of Orblid. Given the very limited impact on the benefit-risk assessment of the provided analyses, the issues highlighted above are not pursued further.

Cobevaro

There are main concerns with the dataset used for the analyses. Real world data have the considerable limitation that the study was not performed under controlled settings which may be required for regulatory decision-making. Furthermore, only patients that were subject to TDM were included in the PKPD analysis, which is another limitation. It is unclear if patients were selected for TDM due to toxicity and/or lack of efficacy which could introduce significant bias/confounding. It seems that patients were assigned a single dose level/regimen which is a limitation since this results in a rather narrow exposure range which may be insufficient for characterising an exposure-response relationship.

The Applicant appears to have re-estimated variability parameters, but did not re-estimate any fixed effect parameters. This is not a reasonable strategy and may have introduced significant bias in the estimated EBEs. Furthermore, the provided goodness-of-fit plots were very limited and did not allow for an adequate assessment of the models performance. The PKPD model were assumed to be the same as in BABH (but with re-estimated IIV parameters). The PKPD model in BABH did not give acceptable description of the BABH data. Thus, the BABH model is not considered as a reasonable to apply for the CoBeVaro analysis, either.

Since the PKPD model is not considered acceptable for describing the observed data, the provided simulations are not considered reasonable.

Taken together, no relevant exposure-response analyses of Study Cobevaro have been provided. There are several considerable limitations with the provided exposure-response analyses which cannot be used to support the benefit-risk assessment of Orblid. The dossier lacks robust empirical evidence to support the proposed posology for chronic long-term use. The PK models and real-world data provided are exploratory and do not fully address uncertainties related to exposure–response relationships. Given the very limited impact on the benefit-risk assessment of the provided analyses, the issues highlighted above are not pursued further.

Product information

The proposed SmPC section 5.2 includes a paragraph with PK information derived from the PopPK modelling:

As observed with other antibodies, the pharmacokinetics of bevacizumab are well described by a two-compartment model. Overall, in all clinical trials, bevacizumab disposition was characterized by a low clearance, a limited volume of the central compartment (Vc), and a long elimination half-life. This enables target therapeutic bevacizumab plasma levels to be maintained with a range of administration schedules (such as once every 2 or 3 weeks) (Azzopardi et al., 2015).

The proposed text is not appropriate to include in SmPC 5.2. The Applicant should replace the information based on the PopPK modelling with a brief description of the mean and variability of AUC and Cmax in the respective target population (HHT patients with severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnea despite well-conducted

cardiological medical treatment and HHT patients with a severe hemorrhagic form [epistaxis and/or digestive bleeding] of the disease with dependence on transfusions and/or intravenous iron) (**SmPC comment**).

5.2.6.2. Conclusions

CT-P16 (Orblid) can be considered biosimilar to EU-Avastin based on the presented PK data. Although the biological rationale for the use of bevacizumab in HHT is recognised, the submitted clinical pharmacology dossier does not provide sufficient evidence to support the proposed dosage for long-term chronic use. The application lacks immunogenicity data in the target population, and adequate dose-finding or exposure–response evidence. The PK/PD models and real-world data are subject to methodological limitations and largely rely on reference product data. Consequently, there are significant uncertainties regarding long-term pharmacokinetics, immunogenicity risk, and dose optimisation of the biosimilar product submitted for authorisation. (**MO**)

The general pharmacological action of bevacizumab is well-described. No clinical pharmacological studies have been performed concerning the HHT indication, but the overall rational for use of bevacizumab in this population is clear. The applicant is however requested to discuss the mechanism of action in relation to the hepatic/cardiac indication (**OC**).

5.3. Clinical efficacy

5.3.1. Dose response studies

No dose finding studies have been conducted for the applied indication. The proposed dose regimen for ORBLID relies on two treatment phases. First, an induction regimen of 5 mg/kg dosing every 2 weeks for a total of 6 infusions. This induction phase should be followed by a maintenance regimen of 5 mg/kg dosing every 8 weeks.

Despite the request from the CHMP in 2015 to have *"a considerably enlarged clinical program to encompass further dose selection based on clinical response criteria"* because *"Without evaluation of other doses or dosing regimens it is not possible to judge whether the proposed dose and schedule are optimal in the setting of HHT"*, no lower induction doses have been tested. This is because bevacizumab is intended to be used in a specific heterogenous population of HHT, which is already a rare disease without subgroup considerations, making it difficult to design appropriate dose finding studies. Nonetheless, in 2023 the CHMP stated that *"Ultimately, in the absence of dedicated dose finding studies in the target indication, a clear benefit for patients should be evident from the data available from both clinical studies as well as bibliographic data in support of the desired dosing schedule in HHT patients".* According to the applicant, with a rationale building upon the lowest dose regimen of the oncologic treatment scheme (AVASTIN SmPC) this 5mg/kg induction phase is a worldwide commonly accepted dose regimen as it is the common denominator of all, but one studies provided in the application. Yet, slight variations in the number of inductions doses have been found across those, with a consensus on a minimum of 4 doses and a maximum of 6 doses.

The progressive nature of the disease has been linked to the need for subsequent treatment following this induction phase in severe HHT patients. In the literature, this subsequent dosing relies on two patterns depending on physician practices: either intermittent maintenance (also identified as re-

induction) corresponding to another induction scheme as needed by the clinical state of patients; or continuous maintenance relying on systematic and planned administrations with a given time interval between doses (i.e., monthly, every 2 months, every 3 months). In HHT-RS1 (CSR HHT-RS1 / Cobevaro), it has been noted that in a real-world setting, this dosing time interval of continuous maintenance is adapted to patients' clinical state. During 2023 Protocol Assistance, the CHMP noted that *"In a retrospective bibliographic study [HHT-RS5 (Al-Samkari et al. 2021)], continuous maintenance treatment trended better compared to intermittent maintenance treatment, however no specific treatment scheme seems to be deducible from the data provided"*.

5.3.2. Main studies: Efficacy in HHT patients presenting with severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnea despite well-conducted cardiological medical treatment

5.3.2.1. HHT-PS1 / Metafore Study

5.3.2.1.1. METAFORE: Hereditary hemorrhagic telangiectasia: Study of the efficacy and tolerance of bevacizumab used to treat severe hepatic forms

5.3.2.1.2. Study design

Study HHT-PS1 / Metafore (efficacy and safety study of AVASTIN® in HHT patients with hepatic AVM and cardiac repercussions): a single center, phase 2, prospective, uncontrolled, open label study with Gehan design, which was designed to demonstrate the efficacy and safety of AVASTIN® in HHT patients with symptomatic hepatic AVMs following an induction period of 6 bevacizumab infusions at 5mg/kg and followed by a 12 months follow-up. In this study, 25 patients received at least one dose and were included in the safety population.

The study was carried out using Gehan's 2-stage design.

- The aim of the first stage was to verify that the product tested was not inefficient in the pathology studied, by means of an intermediate analysis of 7 patients that was carried out after inclusion and follow- up for 3 months, to verify the occurrence of at least one success that made it possible to continue the study.
- The second stage made it possible to estimate the efficacy of the product tested by means of a final statistical analysis.

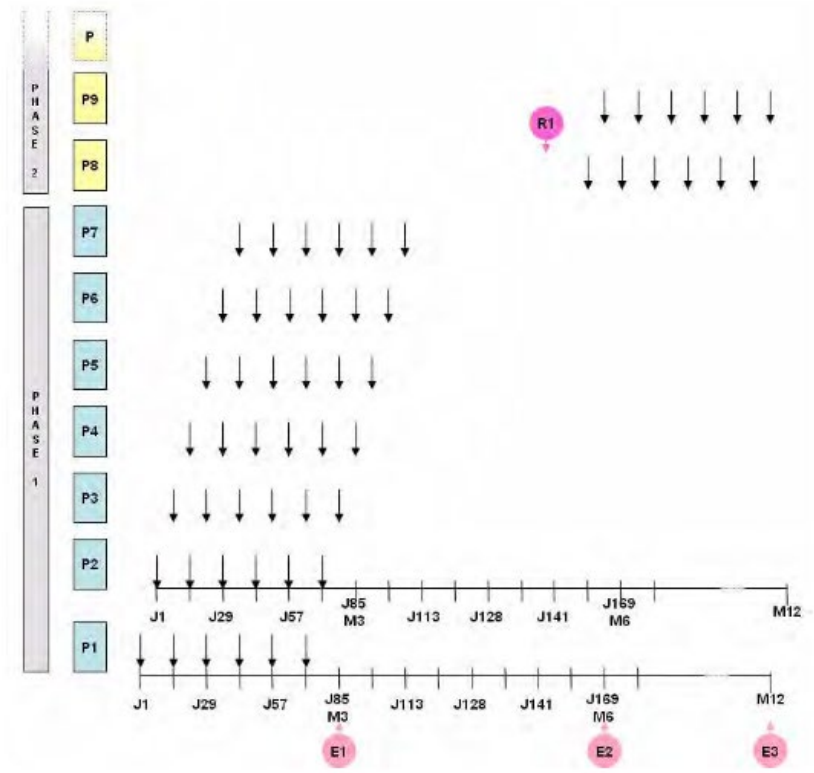


Figure 10: Study schema. P = patient number, E = Evaluation, R = Meeting of the Scientific Committee

Treatment

The bevacizumab or Avastin was administered to each patient in the study lying down at a dose of 5 mg/kg once every 14 days intravenously, with a total of 6 injections as in the 2 studies published on the use of bevacizumab in this indication. In accordance with the Summary of product characteristics (SPC), the volume of bevacizumab needed for the preparation was taken and diluted in the administration volume required with an injectable sodium chloride solution 9 mg/ml (0.9 %).

All concomitant treatments necessary for management of the patients were authorized during the study and were documented in the data collection register specific to the study.

Randomisation and blinding

The study was not randomised nor blinded.

Patient population

Inclusion criteria

General criteria:

- Age ⩾ 18 years and <70 years

Criteria specific to the condition:

- Patients monitored for clinically confirmed HHT (presence of at least 3 of the Curaçao criteria) and/or molecular biology.

- Patients with severe liver involvement linked to HHT (diameter of the hepatic artery > 8 mm if unique or an anatomical variant with dilated hepatic arteries).
- Patients with a high cardiac output on ultrasound with an index > 3.9 l/min/m² in men, 3.6 l/min/m² in women, in relation to their hepatic involvement.

Criteria concerning the absence of associated pathologies:

- Haematological function: Polynuclear neutrophils $\geqslant 1.0x10^9$/L and platelets $\geqslant 100x10^9$/L.
- Coagulation profile: INR (International Normalized Ratio) $\leqslant 1.5$ (except for patients on anticoagulants) and aPTT ≤ 1.5 x upper limit for laboratory standards.
- Kidney function: creatininemia $\leqslant 1.25$ x upper limit for laboratory standards. Patients with urine test proteinuria $\geq 2+$ must have 24h proteinuria that must be ≤ 1 g/24 hours

Exclusion criteria

General criteria:

- Women who are pregnant or likely to become so during the study, and who do not take adapted contraception.

Criteria related to the medical history:

- Patients whose diagnosis of HHT has not been confirmed.
- Presence at the time of inclusion of atrial fibrillation on the electrocardiogram, because of the risk of thrombosis and embolism.
- Presence of at least one cerebral arteriovenous malformation on brain imaging carried out in the year preceding inclusion.
- Existence of colon or sigmoid colon diverticulitis that manifested clinically in the 6 months preceding inclusion, that is, any patient with violent abdominal pain in the left iliac fossa, associated with a high temperature (>38°C).
- Past history of thrombosis in the 6 months preceding inclusion.
- Unresolved infectious episode treated with antibiotics.
- Patients presenting with arterial hypertension that is uncontrolled at the time of inclusion (systolic BP > 150 mmHg and/or diastolic BP > 100 mmHg), with or without treatment. Patients with arterial hypertension can be included when the blood pressure values have been normalized by means of an adapted medical treatment

Criteria related to the surgical history:

- Major surgery (including open biopsies), or severe trauma in the 28 days prior to the start of the treatment.

Criteria related to the treatments in progress:

- Regular or recent use of non-steroidal anti-inflammatories or antiplatelet agents in the 10 days prior to the first administration of bevacizumab.
- Use of oral or parenteral anticoagulants or thrombolytic agents in the 28 days prior to inclusion. (Anticoagulants administered for prophylaxis purposes are authorized).

5.3.2.1.3. Objectives and estimands

Primary objective

The main objective was to test the efficacy of bevacizumab on decreasing cardiac output in patients with severe hepatic involvement in hereditary haemorrhagic telangiectasia and high output cardiac failure.

No statistical hypothesis was defined.

Estimands for the primary objective

The estimand framework was not applied.

Statistical methods for estimation and sensitivity analysis on primary estimand<s>

Analysis populations

Efficacy population: The efficacy population composed of all the patients who have received the product at least once and for whom the primary endpoint was available, that is, for whom measurement of the cardiac index was available on inclusion and at 3 months. Nevertheless, patients who withdrew from the study after having received at least one injection and no measurement of cardiac index at 3 months was considered assessable and classified as failures.

Main analysis methods

The success rate at 3 months was calculated and matched to the exact confidence interval at 95% (Fleiss) initially on evaluation of the first 7 patients treated (1st stage of the Gehan design), then in a second stage on the entire study population.

Missing data

Any missing data were not replaced. One patient who withdrew from the study after the 2nd injection for personal reasons was considered a failure in the analysis.

Sensitivity/supplementary analyses

No sensitivity or supplementary analyses were performed.

Planned subgroup analyses

No subgroup analyses were performed. All patients who satisfied the inclusion criteria and who had received at least one injection were studied.

Sample size determination

The hypothesis on the a priori efficacy of the treatment was 30%. By accepting a power of 90%, it was necessary to include 7 patients in this preliminary phase. The scientific committee met after evaluation of the 7th patient. If, during the preliminary phase, no success had been observed, the study would have been stopped. If at least one success (complete response or partial response) had been observed among the 7 patients in the preliminary phase, the study would have been continued.

The number of successes that was observed during the preliminary phase made it possible to determine the number of patients needed for the 2nd so-called follow-up phase. This number

depended a priori on the percentage of efficacy (30%), the beta risk value retained (10%), the precision percentage (standard error) retained (10%) and the number of successes observed during the preliminary phase. It was necessary to include 18 patients in this second phase (if the beta was at 10%), our efficacy hypothesis of 30% conserved, or a total of 25 patients for the two phases of the study.

Error probabilities, adjustment for multiplicity

No adjustments for multiplicity were performed since no statistical hypothesis was defined for the primary endpoint.

Interim analyses

The primary endpoint was first evaluated on the first 7 patients treated (1st stage of the Gehan design), then in a second stage on the entire study population. The scientific committee was scheduled to meet for evaluation after the 7th patient. If, during the preliminary phase, no success had been observed, the study would have been stopped. If at least one success (complete response or partial response) had been observed among the 7 patients in the preliminary phase, the study would have been continued. The number of successes that was observed during the preliminary phase made it possible to determine the number of patients needed for the 2nd so-called follow-up phase.
Secondary objectives

- To evaluate clinical, ultrasound and biological cardiac evolution.
- To evaluate the efficacy of bevacizumab on hepatic anomalies in hereditary hemorrhagic telangiectasia (number, size, hepatomegaly, hepatic flow rate) and the quickness of the hepatic vascular response.
- To evaluate the efficacy of bevacizumab on epistaxis in hereditary hemorrhagic telangiectasia.
- To evaluate the efficacy of bevacizumab on the skin lesions present before treatment.
- To evaluate efficacy on possible associated pulmonary lesions.
- To evaluate efficacy on possible associated digestive lesions
- To evaluate quality of life (using SF26)

Estimands for the secondary objectives

The estimand framework was not applied.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

Analysis populations

Efficacy population: The efficacy population composed of all the patients who have received the product at least once and for whom the primary endpoint was available, that is, for whom measurement of the cardiac index was available on inclusion and at 3 months. Nevertheless, patients who withdrew from the study after having received at least one injection and no measurement of cardiac index at 3 months was considered assessable and classified as failures.

Main analysis methods

Parameters were presented descriptively by mean (standard deviation); median (minimum-maximum) and confidence interval, for the quantitative variables and in number (percentage) for the qualitative variables. Comparative tests (paired Wilcoxon test or mixed models) were carried out to study

evolution of these parameters over time.

Missing data

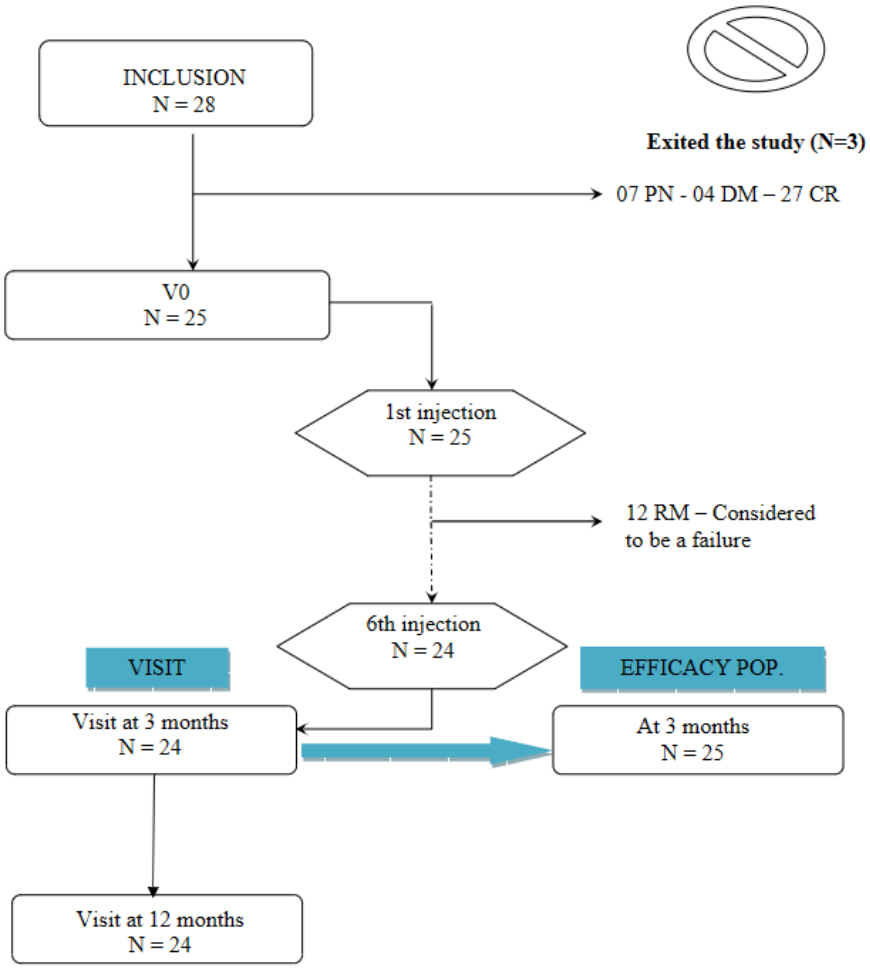
Any missing data were not replaced.

5.3.2.1.4. Results

Participant flow and numbers analysed

A total of 28 patients were included in the study. 3 patients left the study early in the process before receiving their injections (see table below) and were replaced. 1 patient left the study after having received at least one injection (personal convenience). This patient was retained in the analysis (considered to be a failure).

Figure 11. Participant flow



Deviations from study plan

Table 15. Amendments (Metafore study)

Version	Date	Amendment	CPP (Ethics) Committee	AFSSAPS authorization	Modifications
No. 1	August 25, 2008	-	January 05, 2009	January 14, 2009	
No. 2	February 04, 2009	1	February 09, 2009	February 24, 2009	Remark: amendment made before the first inclusions. 1 - Examinations to screen for cerebral AVM: dating from less than 5 years (*instead of less than 1 year*). 2 - PK samples: 5 ml in a dry tube (*instead of 3 ml in EDTA*), storage at -80°C (*instead of -70°C*). 3 - PK sample times: 2 h after the end of administration (*instead of 10 min and 3 h at D1 and 10 min for the other visits*).
No. 3	March 12, 2009	2	March 23, 2009	April 10, 2009	1 - Suppression of the statement "excluding treatment with betablockers" for the inclusion criterion concerning the increase in cardiac output. 2 - Details regarding the inclusion criterion for the diameter of the hepatic artery: diameter of the hepatic artery > 8 mm in case of a single hepatic artery or anatomical variant with dilated hepatic arteries. 3 - Cardiac monitoring: ECG is not performed at each follow-up visit, only at the first visit before treatment. 4 - ENT monitoring: suppression of the oral exam.
No. 4	October 22, 2009	3	November 23, 2009	January 29, 2010	1 - Revision of the ENT monitoring: ENT examinations using an endonasal endoscope are maintained on visits V1 (before treatment), V7 (3 months), V9 (6 months) and V11 (12 months). 2 - Addition of ferritin level at each blood work-up. 3 - Contrast-enhanced liver ultrasound, suppression of variables for the 3rd injection, suppression of S in an ascending curve, suppression of T1/3 and T2/3 in a descending curve. 4 - Suppression of the phrase "a minimum delay of at least 1 day will be left between each new patient" (§4.1.3.)

Changes from protocol-specified analyses:

- The "statistical analysis" section of the protocol presented essentially the variables available for each of the objectives. The investigator was thus contacted to define which parameters were the most important from a clinical point of view. These parameters are presented in the main analysis with a presentation of the characteristics and statistics tests, the other parameters are the subject of lists.
- Comparisons with mixed models (inclusion, 3 months, 6 months; and inclusion, 3 months, 6 months, 12 months) of the different parameters were added or became replacements for tests 2 in pairs. In case of significant values, multiple comparison tests were added.

- Addition of a blind reading of cardiac index at inclusion, 3 months and 6 months.
- Efficacy analysis performed at 6 months in May 2011 (article written).
- The decision to pass on to stage 2 of Gehan's design was taken after inclusion and the follow-up of first 5 patients included with at least one injection. Calculation of the number of additional patients was made after evaluating the first 7 patients, and concluded that 18 additional patients should be included

Baseline data

Table 16. Patient characteristics at inclusion

	No. (%)	Mean (SD)	Median (Range)
Age, y	25 (100)	57.44 (8.6)	59 (35-68)
Sex			
Female	24 (96)		
Male	1 (4)		
Presence of PAVMs	8 (32)		
Gene mutation			
ACVRL1	22 (88)		
ENG	2 (8)		
SMAD4	1 (4)		
Cardiac index, L/min/m^2	24	5.01 (0.67)	5.05 (4.1-6.2)
Dyspnea[a]			
Class II	17 (68)		
Class III	8 (32)		
Left-ventricular filling pressures			
Low	10 (40)		
Limit	8 (32)		
High	7 (28)		
sPAP, mm Hg	25 (100)	37.36 (11.5)	33 (23-79)
Duration of epistaxis, min/mo	25 (100)	221 (239.7)	179 (0-947)
Hemoglobin, g/L	25 (100)	118.7 (22.5)	120 (51-168)
Liver enzymes, U/L			
AST	25 (100)	33 (12.1)	31 (16-57)
ALT		30 (16.1)	25 (7-71)
Alkaline phosphatase		127 (60.2)	104 (47-259)
GGT		160 (151.4)	138 (16-702)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; PAVMs, pulmonary arteriovenous malformations; sPAP, systolic pulmonary artery pressure.
SI conversion factors: To convert AST, ALT, alkaline phosphatase, and GGT to μkat/L, multiply by 0.0167.
[a] According to the New York Heart Association.

Outcomes and estimation

Data from the first stage in Gehan's design are provided in Table while the main analysis for the entire population is provided in Table .

Table 17. Analysis of the main judgment criterion for the first 7 patients

Variable	Modalities	Number (%)
Success at 3 months	no	2 (28.6)
	yes	5 (71.4)
Complete or partial decrease	Absence of response	2 (28.6)
	Complete response	1 (14.3)
	Partial response	4 (57.1)

Table 18. Analysis of the main judgment criterion (efficacy population)

Variable	Modalities	Number (%)
Success at 3 months	no	5 (20.0)
	yes	20 (80.0)
Complete or partial decrease	Absence of response	5 (20.0)
	Complete response	3 (12.0)
	Partial response	17 (68.0)

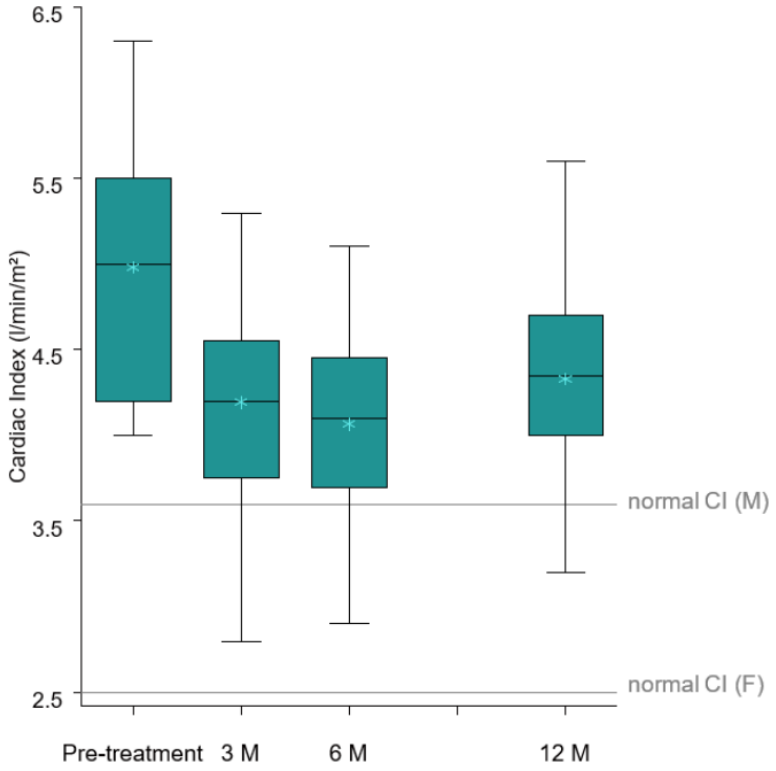
Table 19. Cardiac index values and cardiac index read blind, evolution and response

Variable	Modalities	D-1	M3	M6	M12
Cardiac index	n	25	24	24	24
	median (min-max)	5 (4-6.3)	4.2 (2.8-5.3)	4.1 (2.9-5.1)	4.35 (3.2-5.6)
	mean(std)	4.98 (0.66)	4.20 (0.61)	4.07 (0.58)	4.33 (0.61)
	Interval at 95%	4.71-5.25	3.94-4.45	3.82-4.31	4.07-4.58
Cardiac index (n=24)	n	24	24	24	24
	median (min-max)	4.95 (4-6.3)	4.2 (2.8-5.3)	4.1 (2.9-5.1)	4.35 (3.2-5.6)
	mean(std)	4.95 (0.65)	4.20 (0.61)	4.07 (0.58)	4.33 (0.61)
	Interval at 95%	4.67-5.22	3.94-4.45	3.82-4.31	4.07-4.58
Success*	no		5 (20.0)	2 (8.0)	2 (8.0)
	yes		20 (80.0)	23 (92.0)	23 (92.0)
Success type*	Absence of response		5 (20.0)	2 (8.0)	2 (8.0)
	Complete response		3 (12.0)	5 (20.0)	4 (16.0)
	Partial response		17 (68.0)	18 (72.0)	19 (76.0)
Cardiac index read blind**	n	24	23	22	
	median (min-max)	5.05 (4.1-6.2)	4.2 (2.9-5.2)	4.1 (3-5.1)	
	mean(std)	5.01 (0.67)	4.20 (0.59)	4.06 (0.60)	
	Interval at 95%	4.72-5.29	3.94-4.45	3.80-4.33	
Cardiac index read blind (% evolution)**	n		23	22	
	median (min-max)		-18 (-30-27)	-19 (-36-17)	
	mean(std)		-14.83 (13.41)	-17.55 (11.29)	
	Interval at 95%		-20.62--9.03	-22.55--12.54	
Success (read blind)**	Missing		1	2	
	no		4 (16.7)	3 (13)	
	yes		20 (83.3)	20 (87)	
Success type (read blind)**	Missing		1	2	
	Absence of response		4 (16.7)	3 (13)	
	Complete response		3 (12.5)	5 (21.7)	
	Partial response		17 (70.8)	15 (65.2)	

**patient 12RM received two injections and wanted to leave the study; in this analysis, she is considered a failure (Absence of response)*
***The data on CD were unavailable for patient 01BM (in 3 times), for patient 12RM (at M3 and M6), and for patient 24TM (at M6). The blind reading of the data at 12 months was not carried out.*

The evolution of CI over time, with representation of the normal CI values for males (M) and females (F) is provided in Figure 12.

Figure 12. Representation of cardiac index values during the study (n=25 before treatment and n=24 after)



Functional cardiac impairment and dyspnoea were captured with the NYHA international classification (Table 21). Six months after the start of treatment, 6 out of 8 patients in class III according to the NYHA grade improved to class II, and 10 of the 16 patients who were in class II improved to class I (functional improvement in 67% of the patients).

Table 20. Evaluating dyspnea and functional impairment (NYHA international classification).

Variable	Modalities	V0	M3	M6	M12
n	n	25	25	24	24
Dyspnea (NYHA)	Class I	1 (4.0)	5 (20.0)	11 (45.8)	8 (33.3)
	Class II	16 (64.0)	16 (64.0)	11 (45.8)	13 (54.2)
	Class III	8 (32.0)	4 (16.0)	2 (8.3)	3 (12.5)

Ultrasound evaluation (cardiac doppler ultrasound)

Cardiac doppler ultrasound did not reveal significant modification in the following parameters evaluated before treatment and at M3, M6 and M12 – filling pressures, left ventricle surface, pulmonary artery systolic pressure (PASP) – except for a significant decrease in filling pressures at M3 compared to pretreatment.

Table 21: Cardiac doppler evaluation

Variable	Modalities	D-1	M3	M6	M12	P-value 6m	P-value 12m
	n	25	24	24	24		
Filling pressures	Low	10 (40.0)	16 (66.7)	12 (50)	10 (41.7)	0.0480	0.0755
	High	7 (28.0)	1 (4.2)	2 (8.3)	5 (20.8)		
	Limits	8 (32.0)	7 (29.2)	10 (41.7)	9 (37.5)		
LV surface	n	25	24	24	24	0.3727	0.4573
	median (min-max)	22 (14-39)	20 (13-29)	20 (13-30)	21 (14-34)		
	mean(std)	22.16 (5.30)	20.63 (4.44)	20.42 (4.29)	22.13 (5.61)		
	Interval at 95%	19.97-24.35	18.75-22.5	18.6-22.23	19.76-24.49		
PASP (in mmHg)	n	25	24	24	24	0.0612	0.0937
	median (min-max)	33 (23-79)	31.5 (23-46)	30.5 (25-42)	32.5 (27-46)		
	mean(std)	37.36 (11.5)	32.96 (5.97)	32.08 (5.32)	34.46 (6.19)		
	Interval at 95%	32.61-42.11	30.44-35.48	29.84-34.33	31.84-37.07		
PASP (in mmHg) - categorized	Missing	0	1	0	0	0.0724	0.1465
	<40 mmHg	17 (68.0)	21 (87.5)	22 (91.7)	20 (83.3)		
	>= 40 mmHg	8 (32.0)	3 (12.5)	2 (8.3)	4 (16.7)		

The results of BNP investigations is not reported in the study report.

Evaluation of nosebleeds

Number and duration of nosebleeds, and number of patients with a >30% improvement are recorded for each month until M6, and at M11 (Table 22).

Table 22. Data on nosebleeds.

Variable	Modalities	D1 to M1	M3 to M4	M5 to M6	M10 to M11	P-value 12m
Nosebleeds	n	24	24	24	21**	/
	No	3 (12.5)	3 (12.5)	5 (20.8)	4 (19.0)	
	Yes	21 (87.5)	21 (87.5)	19 (79.2)	17 (81.0)	
If nosebleed = yes						
Number of monthly episodes	n	21	21	19	17	/
	median (min-max)	21 (1.03 - 79)	16 (2 - 97.43)	7.23 (1 - 73.92)	12 (1 - 100)	
	mean(std)	29.14 (22.72)	20.00 (21.30)	14.06 (19.42)	18.86 (25.38)	
	CI at 95 %	[18.80; 39.48]	[10.30; 29.69]	[4.70; 23.42]	[5.81; 31.91]	
Total monthly duration (min)	n	21	21	19	17	/
	median (min-max)	214 (3 - 947.22)	67 (2.07 - 420.57)	36 (1 - 330.67)	33 (4.13 - 307.79)	
	mean(std)	252.18 (239.78)	114.92 (131.84)	57.14 (76.48)	80.38 (90.58)	
	CI at 95 %	[143.04; 361.33]	[54.90; 174.93]	[20.27; 94]	[33.81; 126.95]	
In all patients						
Number of monthly episodes	n	24	24	24	21	0.1596
	median (min-max)	18.785 (0 - 79)	11.7 (0 - 97.43)	5.6 (0 - 73.92)	8 (0 - 100)	
	mean(std)	25.50 (23.36)	17.50 (20.98)	11.13 (18.14)	15.27 (23.93)	
	CI at 95 %	[15.63; 35.36]	[8.64; 26.36]	[3.47; 18.79]	[4.37; 26.16]	
Total monthly duration (min)	n	24	24	24	21	0.0010
	median (min-max)	178.8 (0 - 947.22)	62 (0 - 420.57)	20.335 (0 - 330.67)	24.8 (0 - 307.79)	
	mean(std)	220.66 (239.27)	100.55 (128.93)	45.23 (71.69)	65.07 (87.23)	
	CI at 95 %	[119.62; 321.7]	[46.11; 155]	[14.96; 75.5]	[25.36; 104.78]	
Improvement of 30%	No	-	8 (33.3)	6 (25.0)	9 (42.9)	/
	Yes	-	16 (66.7)	18 (75.0)	12 (57.1)	

** The nosebleed grids at M10 for patients 13 LD, 23 BJ and 28 MM were not recovered*
CI: confidence interval
/: not calculated

Haemoglobin and transfusions

No significant difference in haemoglobin levels was observed at 6 months nor 12 months compared to pretreatment. This study did not specifically includes an anaemic population. Indeed, mean(std) and median (min-max) pretreatment haemoglobin levels were respectively 118.72 (22.45) and 120 (51-168) g/L, while normal haemoglobin range are 138 - 172 g/L in males and 121 - 151 g/L in females, and all but one study participants are females. A total of 5 patients required one or more transfusions (1 to 25) in the course of the study.

Table 23. Haemoglobin

Variable	Modalities	V0	V1 - D1	M3	M6	M12	P-value 6m	P-value 12m
Hemoglobin (g/l)	n	25	25	24	24	24	0.3828	0.4940
	median (min-max)	120 (51-168)	117 (68 - 170)	119.5 (67-169)	128.5 (53-169)	121.5 (53-164)		
	mean(std)	118.72 (22.45)	117.64 (22.7)	122.33 (20.59)	126.54 (23.39)	118.33 (23.32)		
	Interval at 95%	109.45-127.99	108.27 - 127.01	113.64-131.03	116.67-136.42	108.49-128.18		

* The model with repeated measurements considers the values V1-D1, M3 and M6
** The model with repeated measurements considers the values V1-D1, M3, M6 and M12

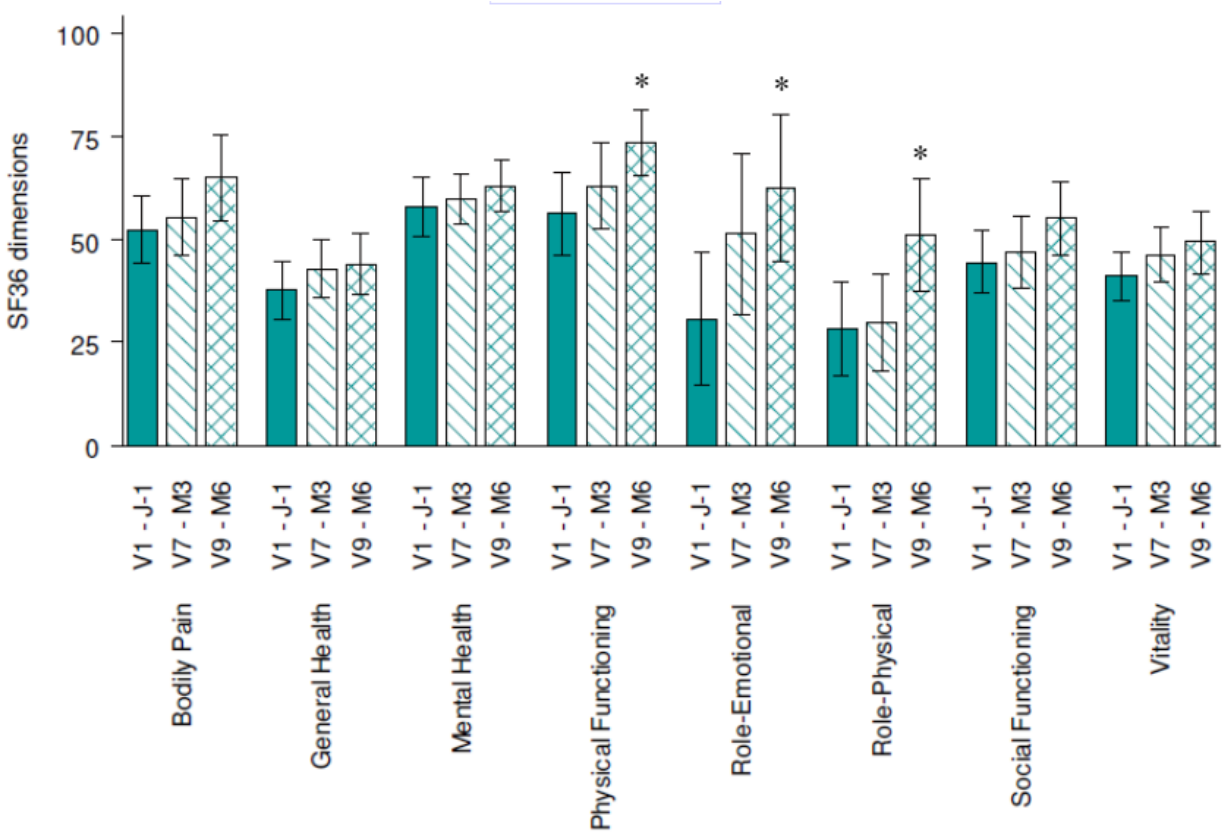
Evaluating telangiectasias, skin, pulmonary and digestive lesions

No significative difference in the presence of telangiectasias, skin, pulmonary and digestive lesions was observed along the course of the study.

Quality of Life and Satisfaction Analyses

Quality of life was assessed by mean of the SF-36 questionnaire. Responses are classified in 8 different categories belonging to either physical or mental component. Among them, the following ones were significantly improved at M6 : Physical Functioning, Role – Physical, Role-Emotional (Table 24).

Table 24: Evolution of Quality of Life. * indicates a significant difference compared to J-1 (i.e. day 1)



5.3.2.2. HHT-RS1 / CoBevaRo study

5.3.2.2.1. Real-life data study of the French cohort of patients with Rendu Osler disease treatment with bevacizumab

5.3.2.2.2. Study design

The HHT-RS1 /CoBevaRo is a retrospective study of data from the CIROCO registry of French HHT patients treated with Avastin or biosimilars between 2009 and 2023. According to the applicant, the CIROCO database, which includes 5,973 unique individuals diagnosed with HHT, is representing an estimated 52.5% of the theoretical HHT population in France. This study is based on the secondary use of real-world data originally collected in routine clinical practice, not specifically for research purposes.

The data was extracted from the CIROCO data warehouse hosted at the Hospices Civils de Lyon on October 23, 2023, a French university hospital and national reference centre for HHT. The dataset includes patients diagnosed with HHT who were followed at the Hospices Civils de Lyon. The data covers a retrospective period of patient follow-up from 1957-11-11 to 2023-12-31, corresponding to

routine care visits and clinical follow-up. No active recruitment or additional follow-up was performed specifically for this study.

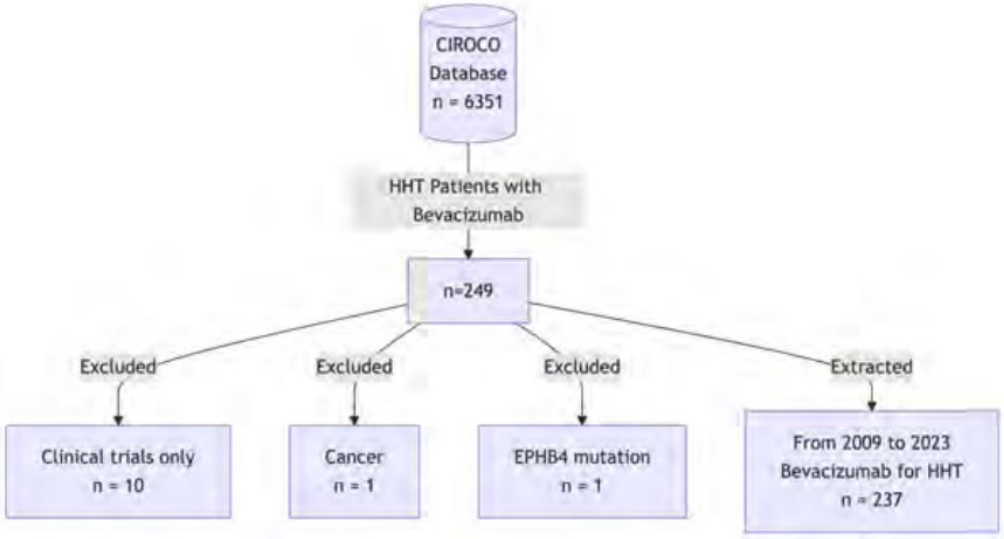


Figure 13: Flowchart of data extraction from the CIROCO database

Treatment

In the retrospective study HHT-RS1/Cobevaro, the number of administrations varies greatly among subjects, as length of follow-up is also highly variable. A total of 4974 bevacizumab administrations has been provided for this analysis, 2725 (55%) were Avastin and 2249 (45%) one of its biosimilars. Among the biosimilars:

- 54 administrations were ABEVMY® in 5 patients,
- 11 administrations were ALYMSYS® in 3 patients,
- 143 administrations were AYBINTIO® in 16 patients,
- 268 administrations were bevacizumab with unspecified speciality in 22 patients,
- 1441 administrations were MVASI® in 126 patients,
- 11 administrations were VEGZELMA® in 1 patient,
- 321 administrations were ZIRABEV® in 46 patients.

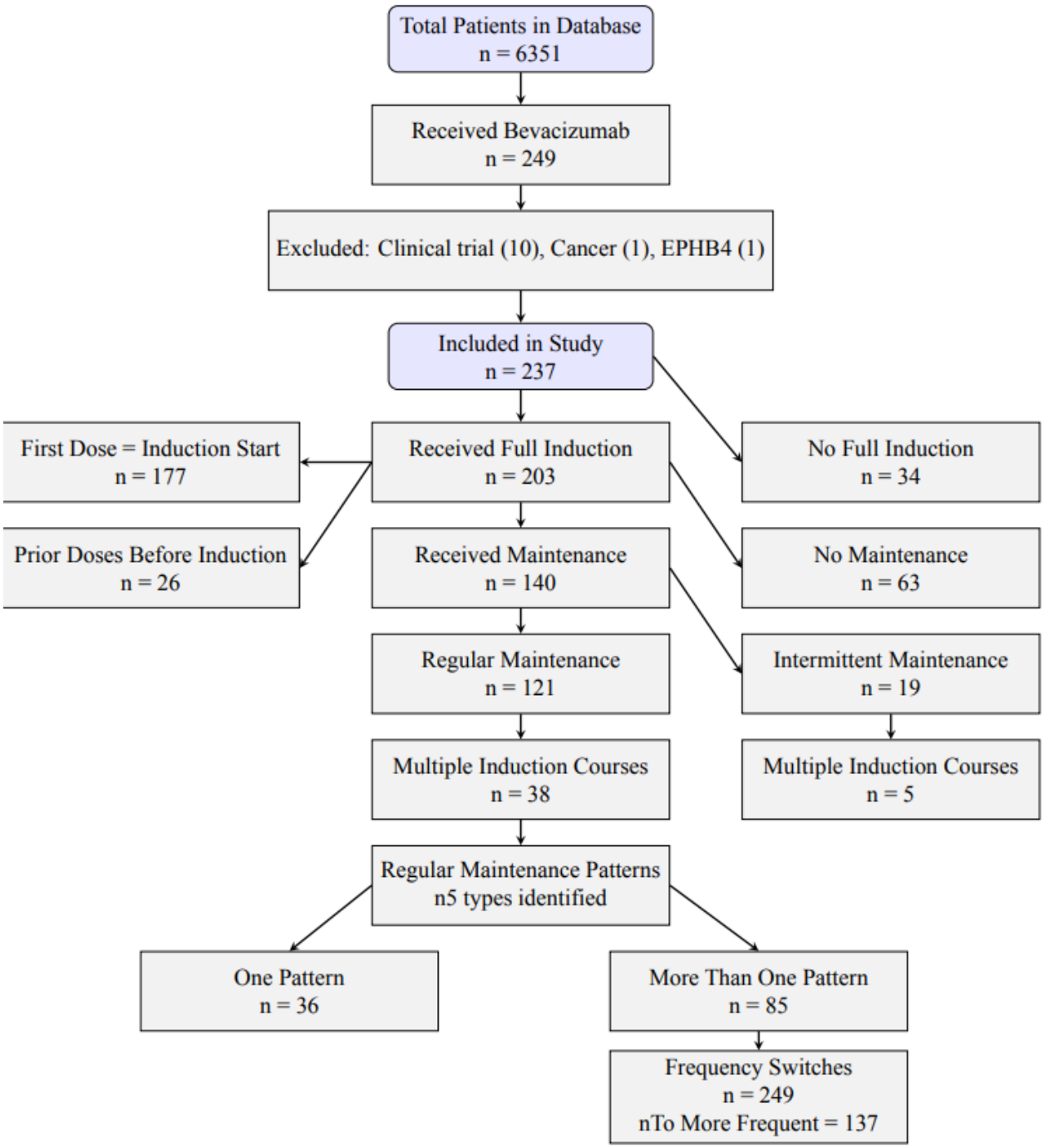
Aside from induction and maintenance phases, the database reports different bevacizumab doses administered in the treatment of HHT patients ranging from 1 mg/kg to 10 mg/kg. Out of the total 4974 bevacizumab infusions, 4565 (92%) were the standard dose of 5 mg/kg in 232 patients (98%). Out of the 409 (8%) remaining bevacizumab infusions of the dataset, 240 (5%) were a higher dosing in 23 patients (10%), either 7.5 mg/kg or 10 mg/kg, and 162 (3%) were a lower dosing comprised between 4.9 and 1 mg/kg in 14 patients (6%). 1 patient was treated with the biosimilar under evaluation (ORBLID)

Among the 237 patients of the dataset:

- 197 (83%) received only 5 mg/kg doses of bevacizumab counting for 3722 infusions (75%),
- 35 (15%) received 5 mg/kg plus another dosage counting for 1208 infusions (24%),

- 2 (1%) never received the standard 5 mg/kg counting for 37 infusions (1%),
- 3 (1%) did not had any of their administered dosage filled in the database counting for 7 infusions

Figure 14: Description of patient database



Randomisation and blinding

Not applicable.

Patient population

Among the 6,351 patients recorded in the CIROCO database, 249 patients were identified as having received bevacizumab treatment up to December 31st, 2023. After excluding 10 patients treated exclusively in clinical trials, 1 patient with a cancer diagnosis, and 1 patient with an EPHB4 mutation, a final cohort of 237 patients treated with at least 1 dose of bevacizumab for HHT between 2009 and 2023 was retained for analysis.

All patients included in the final dataset had been followed in routine care settings. The duration and quality of medical records were assessed to ensure completeness for key study variables, including baseline characteristics, treatment exposure, and outcome measures. Only patients with adequate documentation allowing for meaningful analysis were included.

Duration of follow-up after treatment initiation and considered exposed to bevacizumab (induction or maintenance treatment) in the included patients were a mean 3.2 years and a median of 2.4 years (range 0-14 years).

Inclusion criteria were:

- Adult patients (≥18 years old);
- Diagnosed with HHT, based on clinical and/or genetic criteria;
- Treated with bevacizumab for HHT-related indications;
- Managed and treated in France.

Exclusion criteria were:

- Patients who objected to the secondary use of their medical data;
- Patients treated with bevacizumab exclusively within the context of a clinical trial;
- Patients with alternative diagnoses or clinical contexts inconsistent with the study objective (e.g., patients with cancer receiving bevacizumab for oncologic purposes, or patients with an EPHB4 mutation not typically associated with classical HHT phenotypes).

5.3.2.2.3. Objectives and estimands

Primary objective

The primary objective was to describe the real-world use of bevacizumab in French HHT patients. The primary endpoints were descriptions of bevacizumab's prescriptions (dosing, treatment duration and patterns, number of infusions).

No statistical hypothesis was defined.

Estimands for the primary objective

The estimand framework was not applied in this study.

Statistical methods for estimation and sensitivity analysis on primary estimand

The primary objective for this study was to describe the real-world use of bevacizumab in French HHT patients. The primary endpoints were descriptions of bevacizumab's prescriptions (dosing, treatment duration and patterns, number of infusions). No statistical methods were described. Efficacy analyses were performed for secondary objectives and endpoints described below.

Secondary objectives

The following secondary objectives were defined:

- to evaluate the safety of bevacizumab's use in HHT patients
- to evaluate the clinical efficacy of bevacizumab in HHT patients
- to compare the efficacy and safety profile of AVASTIN® towards its biosimilars
- to describe and compare the safety and efficacy of bevacizumab in subgroups of HHT patients

Secondary endpoints:

- the nature and frequency of adverse events (AEs) collected during treatment with bevacizumab
- the evolution of clinical parameters: the number of transfusions, the need for iron supplementation, the concentration of haemoglobin and cardiac index values.
- the type of drug product used (i.e., AVASTIN® or one of its biosimilars)
- the clinical profile of patients treated with bevacizumab: age at first infusion with bevacizumab, the gene mutation involved in the disease and the type of arteriovenous malformations (AVMs)

No statistical hypotheses were formulated for secondary objectives.

Estimands for the secondary objectives

The estimand framework was not applied.

Statistical methods for estimation and sensitivity analysis on the secondary estimand

Analysis sets

Only patients who have received at least one full induction course (n = 203) were included in this efficacy analysis.

Main analysis methods

The primary analyses of the efficacy endpoint included within-subject comparisons of key clinical parameters before and after the initiation of bevacizumab (Avastin or its biosimilars). These parameters included red blood cell transfusion requirements, iron supplementation quantity, hemoglobin levels, cardiac index, and epistaxis frequency. Group comparisons were also conducted between patients receiving AVASTIN® versus biosimilars, with transfusion requirements as the primary endpoint.

Continuous variables were compared using either Student's t-test or one-way ANOVA, as appropriate. Prior to any parametric testing, normality of distribution was assessed using the Shapiro-Wilk or Kolmogorov-Smirnov tests. For non-normally distributed continuous variables, non-parametric tests were employed, including the Wilcoxon signed-rank test (for paired samples) and the Friedman test (for repeated measures across more than two paired groups). Categorical variables were analysed using the Chi-square test.

To further assess treatment effects while accounting for confounding factors and repeated measures within patients, mixed effects models (linear or generalized) were applied. The choice of model depended on the distributional characteristics of the outcome variable, for example, zero-inflated

negative binomial models were used for transfusion count data and iron amounts infused. Random effects were included to account for patient-level variability. Model diagnostics were conducted to assess key assumptions, including the normality of residuals (Q-Q plots, Kolgomorov Smirnov test) and potential over dispersion and outliers.

For models involving variable selection, a combination of clinical relevance and statistical criteria (*e.g.*, $p < 0.20$ in univariate analyses) was used to introduce variables into multivariate models. Backward elimination and Akaike Information Criterion (AIC/BIC) were considered to optimize model fit and parsimony.

Missing data

All calculations excluded missing values, no imputation was performed for missing values, with the exception of the body weight variable, which was required for dose normalization.

Sensitivity/supplementary analyses

Several sensitivity analyses were conducted to assess the robustness and consistency of the treatment effect across time periods and analytic approaches.

First, to evaluate the stability of the treatment effect over time, comparisons were extended beyond the initial 6-month pre/post design to include a third time window: the 6 to 12 months post-treatment period. This approach was used to determine whether any observed benefit persisted or waned over time.

Second, to verify that the analytical conclusions were not dependent on the statistical method used, longitudinal mixed-effects models were fitted for key continuous outcomes (RBC transfusion needs, iron supplementation, hemoglobin concentration).

These models took into account within-subject variability and allowed for a more flexible modelling of individual patient trajectories. The results obtained were consistent with those from the primary within-subject comparisons.

Subgroup analyses

Subgroup analyses were stratified by clinical presentation (i.e., treatment indication). Interaction terms were tested within multivariable models to explore effect modification by key patient characteristics.

Table 25: Definitions of clinical presentation.

	Group 1	Group 2	Group 3	Group 4
Description	Serious bleeds with severe anaemia requiring RBC units transfusions and/or iron supplementation	Liver AVMs resulting in High Cardiac Output (HCO)	Both Serious bleeds with severe anaemia and HCO	Other
Definition criteria (*Within the 6 months before first bevacizumab infusion*)	At least one **RBC unit transfused** OR one **iron infusion** OR **anemia** characterized by at least one low hemoglobin(Hb) level (Hb < 100 g/L regardless of patient sex)	**Average cardiac index** > 3.6 in women and 3.9 in men on the last measurement	Combination of both criteria	Exclusion criteria, none of the 4 criteria (anemia, IV iron, transfusions, cardiac index)

Sample size determination

No formal sample size calculation has been performed.

Error probabilities, adjustment for multiplicity and interim analyses

No error probability is defined. No type I error control is defined for the overall study. For the mixed model analyses, p-values were adjusted using the Holm method, to account for Type I error inflation.

5.3.2.2.4. Results

Participant flow and numbers analysed

All 237 patients were retained for the descriptive analyses and the safety analysis.

For efficacy analyses, only patients who received a complete induction course were considered eligible. The number of patients included varied depending on the availability of relevant baseline and post-treatment data for each endpoint, as follows:

- red blood cell transfusion need: 135 patients,
- IV iron supplementation: 154 patients,
- hemoglobin concentrations: 143 patients,
- cardiac index measurements: 63 patients,
- epistaxis frequency: 95 patients.

This stratification reflects both endpoint-specific data availability and the application of pre-specified filtering criteria to identify patients with sufficient pre-treatment severity and evaluable follow-up windows. These filters included the presence of abnormal values for each endpoint (e.g., epistaxis frequency ≥3, cardiac index >3.6–3.9 L/min/m^2) and adequate time coverage (data in the 6 months prior to and up to 12 months following induction).

As this is a retrospective, real-world study, follow-up durations and data completeness varied across individuals and endpoints. No formal censoring or loss to follow-up occurred, as data was extracted from the longitudinal registry as available in clinical practice. Follow-up was anchored relative to each

patient's first bevacizumab dose (T0), allowing for harmonized within-subject comparisons over defined pre- and post-treatment intervals (typically −6 months to +12 months).

Based on the clinical manifestations of the disease regarding bleeding and HCO, 4 groups of patients have been identified by the physicians of HCL.

Triggers for bevacizumab prescription were provided by the HCL in the population:

- Severe epistaxis (n = 65, 27%) 32
- Severe digestive bleeds (n = 25, 11%)
- HCO associated with hepatic AVM (n = 27, 11%)
- Severe epistaxis + severe digestive bleeds (n = 42, 18%)
- Severe epistaxis + HCO associated with hepatic AVM (n = 43, 18%)
- Severe digestive bleeds + HCO associated with hepatic AVM (n = 7, 3%)
- Severe epistaxis + severe digestive bleeds + HCO associated with hepatic AVM (n = 18, 8%)
- Other reason (n = 10, 4%)

Overall, severe epistaxis was found as a prescription trigger in 168 patients (71%), digestive bleed in 92 patients (39%), and HCO associated with hepatic AVM in 95 patients (40%)

High Output Cardiac Failure

Among the 203 patients receiving at least one full induction course, only those with at least one abnormal cardiac index value (> 3.6 in women, > 3.9 in men) within the 6 months period prior to first bevacizumab infusion have been included for the analysis of this endpoint (n = 63). Among these 63 patients, 37 patients did not have any cardiac index evaluation after starting the treatment. Hence, these subjects were removed from this analysis. This sums up to 26 patients analysed for primary efficacy before and after treatment (regarded as 6 months after treatment. In the manuscript, evaluation is also made 12months after treatment, where 13 patients had an valid echocardiogram.

Deviations from study plan

Changes from protocol-specified analyses

No analyses were pre-specified in the protocol.

Baseline data

Table 26: Baseline data 6 months before treatment in the total population

	Clinical Groups				
	Group 1	**Group 2**	**Group 3**	**Group 4**	**Total**
n	135 (57%)	22 (9%)	64 (27%)	16 (7%)	237
Death, n (%)	26 (19%)	2 (9%)	28 (44%)	4 (25%)	60 (25%)
Females, n (%)	70 (52%)	20 (91%)	44 (69%)	6 (38%)	140 (59%)
Age (years) at 1st infusion, mean ± sd	64.8 ± 10.9	60.1 ± 14.4	64 ± 10.6	56.7 ± 13.9	63.6 ± 11.6
Transplant, n (%)	3 (2%)	0 (0%)	2 (3%)	0 (0%)	5 (2%)
Epistaxis, n (%)	134 (99%)	21 (95%)	64 (100%)	16 (100%)	235 (99%)
Pulmonary AVM, n (%)	53 (39%)	8 (36%)	16 (25%)	3 (19%)	80 (34%)
Hepatic AVM, n (%)	55 (41%)	18 (82%)	52 (81%)	7 (44%)	132 (56%)
Neurologic AVM, n (%)	1 (1%)	0 (0%)	3 (5%)	1 (6%)	5 (2%)
Digestive AVM, n (%)	70 (52%)	4 (18%)	28 (44%)	2 (12%)	104 (44%)
Genetic Variants					
ACVRL1, n (%)	76 (56%)	17 (77%)	47 (73%)	12 (75%)	152 (64%)
ENG, n (%)	43 (32%)	2 (9%)	10 (16%)	2 (12%)	57 (24%)
Unknown mutation, n (%)	16 (12%)	3 (14%)	7 (11%)	2 (12%)	28 (12%)
Need for RBC transfusions					
Overall prior treatment need for transfusions, n (%)	127 (94%)	11 (50%)	57 (89%)	8 (50%)	203 (86%)
6 months prior treatment need for transfusions, n (%)	115 (85%)	5 (23%)	50 (78%)	2 (12%)	172 (73%)
Need for IV Iron supplementation					
Overall prior treatment need for IV iron, n (%)	100 (74%)	7 (32%)	43 (67%)	4 (25%)	154 (65%)
6 months prior treatment need for IV iron, n (%)	89 (66%)	0 (0%)	32 (50%)	0 (0%)	121 (51%)
Anemia					
Overall prior treatment anemia, n (%)	129 (96%)	15 (68%)	61 (95%)	9 (56%)	214 (90%)
6 months prior treatment anemia, n (%)	116 (86%)	4 (18%)	56 (88%)	2 (12%)	178 (75%)
Abnormal cardiac index					
Overall prior treatment abnormal cardiac index, n (%)	16 (12%)	22 (100%)	64 (100%)	2 (12%)	104 (44%)
6 months prior treatment abnormal cardiac index, n (%)	12 (9%)	20 (91%)	58 (91%)	2 (12%)	92 (39%)
Treatment groups					
Induction only, n (%)	27 (20%)	10 (45%)	24 (38%)	2 (12%)	63 (27%)
Regular maintenance, n (%)	78 (58%)	10 (45%)	29 (45%)	4 (25%)	121 (51%)
Intermittent maintenance, n (%)	9 (7%)	1 (5%)	5 (8%)	4 (25%)	19 (8%)
Other schedule	21 (16%)	1 (5%)	6 (9%)	6 (38%)	34 (14%)
Cumulative sum of RBC units transfused per patient					
Overall prior treatment RBC units, mean ± sd, median (IQR)	40 ± 56, 22 (45)	6 ± 15, 0 (3)	38 ± 60, 18 (38)	5 ± 10, 1 (5)	35 ± 55, 14 (42)
6 months prior treatment RBC units, mean ± sd, median (IQR)	12 ± 17, 8 (17)	0 ± 0, 0 (0)	14 ± 20, 7 (19)	0 ± 0, 0 (0)	12 ± 18, 5 (16)
Average Hb concentration (g/L) per patient					
Overall prior treatment Hb (g/L), mean ± sd, median (IQR)	92.3 ± 16.2, 89.8 (18.5)	122.5 ± 21, 121.6 (27.2)	97.6 ± 13.8, 97 (17.2)	107.2 ± 29.7, 108.5 (44.3)	97.4 ± 19.1, 95 (22.8)
6 months prior treatment Hb (g/L), mean ± sd, median (IQR)	85.5 ± 13.8, 85 (18)	131.7 ± 18.5, 128.5 (22.8)	92.7 ± 14.1, 93 (17.6)	129.8 ± 15.6, 123 (26)	92.1 ± 19.5, 89 (22.6)
Cumulative sum of Iron quantity (mg) per patient					
Overall prior treatment Iron (mg), mean ± sd, median (IQR)	8066 ± 11229, 4500 (8950)	1209 ± 2955, 0 (550)	7697 ± 12079, 3500 (7650)	983 ± 1927, 200 (1050)	6947 ± 10919, 2900 (8400)
6 months prior treatment Iron (mg), mean ± sd, median (IQR)	2468 ± 3489, 1400 (3350)	0 ± 0, 0 (0)	2993 ± 4077, 1600 (3700)	0 ± 0, 0 (0)	2426 ± 3603, 1200 (3600)
Average cardiac index (L/min/m2) per patient					
Overall prior treatment cardiac index, mean ± sd, median (IQR)	3 ± 0.6, 3 (0.7)	4.6 ± 0.7, 4.4 (0.8)	4.6 ± 1, 4.4 (1.1)	2.4 ± 0.6, 2.2 (0.5)	4 ± 1.1, 4 (1.5)
6 months prior treatment cardiac index, mean ± sd, median (IQR)	3.2 ± 0.6, 3.4 (0.6)	4.9 ± 0.7, 4.9 (0.6)	4.9 ± 0.8, 4.8 (1.1)	NaN ± NA, NA (NA)	4.5 ± 1.1, 4.4 (1.2)
Average Epistaxis Frequency per patient					
Overall prior treatment epistaxis frequency, mean ± sd, median (IQR)	4.6 ± 1, 5 (1.1)	4.4 ± 1.2, 5 (1)	4.5 ± 1, 4.7 (1)	4.6 ± 0.6, 4.9 (0.8)	4.6 ± 1, 5 (1.1)
6 months prior treatment epistaxis frequency, mean ± sd, median (IQR)	4.7 ± 1.3, 5 (1.2)	3.7 ± 1.5, 4 (1.5)	4.4 ± 1.3, 4.9 (1.3)	4.6 ± 0.5, 5 (1)	4.6 ± 1.3, 5 (1.3)

Table 27: Baseline data on patients included in the cardiac index subgroup

	Adverse Events		
	Excluded	**Included**	**Total**
n	174 (73%)	63 (27%)	237
Death, n (%)	38 (22%)	22 (35%)	60 (25%)
Females, n (%)	93 (53%)	47 (75%)	140 (59%)
Age (years) at 1st infusion, mean ± sd	64.1 ± 11.2	62.2 ± 12.4	63.6 ± 11.6
Transplant, n (%)	5 (3%)	0 (0%)	5 (2%)
Epistaxis, n (%)	173 (99%)	62 (98%)	235 (99%)
Pulmonary AVM, n (%)	62 (36%)	18 (29%)	80 (34%)
Hepatic AVM, n (%)	82 (47%)	50 (79%)	132 (56%)
Neurologic AVM, n (%)	4 (2%)	1 (2%)	5 (2%)
Digestive AVM, n (%)	82 (47%)	22 (35%)	104 (44%)
Genetic Variants			
ACVRL1, n (%)	107 (61%)	45 (71%)	152 (64%)
ENG, n (%)	48 (28%)	9 (14%)	57 (24%)
Unknown mutation, n (%)	19 (11%)	9 (14%)	28 (12%)
Need for RBC transfusions			
Overall prior treatment need for transfusions, n (%)	152 (87%)	51 (81%)	203 (86%)
6 months prior treatment need for transfusions, n (%)	130 (75%)	42 (67%)	172 (73%)
Need for IV Iron supplementation			
Overall prior treatment need for IV iron, n (%)	120 (69%)	34 (54%)	154 (65%)
6 months prior treatment need for IV iron, n (%)	99 (57%)	22 (35%)	121 (51%)
Anemia			
Overall prior treatment anemia, n (%)	159 (91%)	55 (87%)	214 (90%)
6 months prior treatment anemia, n (%)	134 (77%)	44 (70%)	178 (75%)
Abnormal cardiac index			
Overall prior treatment abnormal cardiac index, n (%)	41 (24%)	63 (100%)	104 (44%)
6 months prior treatment abnormal cardiac index, n (%)	34 (20%)	58 (92%)	92 (39%)
Clinical groups			
Group 1, n (%)	134 (77%)	1 (2%)	135 (57%)
Group 2, n (%)	3 (2%)	19 (30%)	22 (9%)
Group 3, n (%)	21 (12%)	43 (68%)	64 (27%)
Group 4	16 (9%)	0 (0%)	16 (7%)
Treatment groups			
Induction only, n (%)	34 (20%)	29 (46%)	63 (27%)
Regular maintenance, n (%)	92 (53%)	29 (46%)	121 (51%)
Intermittent maintenance, n (%)	14 (8%)	5 (8%)	19 (8%)
Other schedule	34 (20%)	0 (0%)	34 (14%)
Cumulative sum of RBC units transfused per patient			
Overall prior treatment RBC units, mean ± sd, median (IQR)	37 ± 53, 18 (45)	29 ± 59, 6 (30)	35 ± 55, 14 (42)
6 months prior treatment RBC units, mean ± sd, median (IQR)	12 ± 17, 6 (16)	12 ± 20, 3 (15)	12 ± 18, 5 (16)
Average Hb concentration (g/L) per patient			
Overall prior treatment Hb (g/L), mean ± sd, median (IQR)	94.7 ± 18.2, 92.4 (20.6)	104.4 ± 19.6, 102.5 (23.5)	97.4 ± 19.1, 95 (22.8)
6 months prior treatment Hb (g/L), mean ± sd, median (IQR)	87.9 ± 16.1, 86.2 (20.5)	102.7 ± 23, 98.4 (26.4)	92.1 ± 19.5, 89 (22.6)
Cumulative sum of Iron quantity (mg) per patient			
Overall prior treatment Iron (mg), mean ± sd, median (IQR)	7350 ± 10602, 3600 (9000)	5867 ± 11747, 1200 (6100)	6947 ± 10919, 2900 (8400)
6 months prior treatment Iron (mg), mean ± sd, median (IQR)	2389 ± 3395, 1400 (3400)	2530 ± 4162, 800 (3300)	2426 ± 3603, 1200 (3600)
Average cardiac index (L/min/m2) per patient			
Overall prior treatment cardiac index, mean ± sd, median (IQR)	3.4 ± 0.9, 3.2 (0.9)	4.7 ± 0.9, 4.5 (1)	4 ± 1.1, 4 (1.5)
6 months prior treatment cardiac index, mean ± sd, median (IQR)	3.5 ± 0.9, 3.4 (0.6)	4.9 ± 0.8, 4.9 (1)	4.5 ± 1.1, 4.4 (1.2)
Average Epistaxis Frequency per patient			
Overall prior treatment epistaxis frequency, mean ± sd, median (IQR)	4.5 ± 1, 5 (1.1)	4.6 ± 0.9, 4.8 (1)	4.6 ± 1, 5 (1.1)
6 months prior treatment epistaxis frequency, mean ± sd, median (IQR)	4.6 ± 1.3, 5 (1.4)	4.5 ± 1.4, 5 (1.3)	4.6 ± 1.3, 5 (1.3)

Outcomes and estimation

High output cardiac heart failure

Effect at 6 months after treatment

26 patients in total had cardiac index measurements 6 months before and after bevacizumab infusion.

CI before treatment ranged from 3.8 L/min/m2 to 6.9 L/min/m2 with a median of 5 L/min/m2 (95% CI [4.6, 5.2]). 6 months after the first bevacizumab's dose, cardiac indexes significantly dropped to a median of 3.8 L/min/m2 (95% CI [3.6, 4.4], p < 0.0001), with a robust estimate of the median paired reduction of 1.04 L/min/m2 (95% CI [0.73, 1.35]).

Among these 26 patients:

- 10 had a normalized average cardiac index (< 3.9 L/min/m2 in men and < 3.6 L/min/m2 in women),
- 13 had a decreased average cardiac index above normal values, and
- 3 did not respond to treatment showing a worsening of the disease or no difference from baseline

Effect at 12 months after treatment

To evaluate the stability of this effect up to one year after the first dose, 13 patients were identified with cardiac index measured until then. Among these, the median cardiac index also significantly decreased from 5 L/min/m^2 to 3.86 L/min/m^2 after 6 months.

The median paired reduction over this period was 1.09 L/min/m^2 (95% CI [0.70, 1.43]; p = 0.0007, Holm-adjusted). This effect appeared to vanish over the M6–M12 period, with a re-increase to a median of 4.30 L/min/m^2. Although this value does not significantly differ from the M0–M6 post-treatment period (median difference: –0.33, 95% CI [–0.79, 0.12]; p = 0.15, Holm-adjusted), it remains significantly lower than before treatment (median difference: 0.66, 95% CI [0.42, 1.03]; p = 0.0007, Holm-adjusted).

The applicant claims that the results of this real-world analysis provide compelling evidence that bevacizumab is effective in managing both major clinical manifestations of HHT—bleeding and high-output cardiac failure—in a broad, non-trial population. The observed reductions in transfusion needs, IV iron use, and epistaxis, as well as increased haemoglobin levels and lowered cardiac index, support its therapeutic role across diverse HHT phenotypes.

5.3.2.3. HHT-PS4 (Chavan et al. 2017)

5.3.2.3.1. Emerging role of bevacizumab in management of patients with symptomatic hepatic involvement in Hereditary Hemorrhagic Telangiectasia

The study was provided as a letter to the editor published in American Journal of Hematology (Am J Hematol 2017 Nov;92(11):E641-E644).

5.3.2.3.2. Study design

Single-centre, non-blinded and non-controlled prospective study of 21 patients between October 2010-April 2016. Limited information available on the study design.

Treatment

Bevacizumab (5 mg/kg/dose, 6 doses administered every two weeks). The entire therapy was repeated at follow-up if symptoms causing significant clinical impairment recurred.

Randomisation and blinding

Not applicable.

Patient population

Inclusion criteria

All HHT patients with symptomatic hepatic involvement requiring invasive therapy.

Exclusion criteria

Asymptomatic patients with hepatic involvement, patients without hepatic involvement and those who had undergone previous liver transplantation were excluded from the cohort.

5.3.2.3.3. Objectives and estimands

Primary objective

The primary objective of the study was to evaluate changes in the grade of abdominal pain, cardiac output and the New York Heart Association (NYHA) stage before and three months after bevacizumab treatment.

The primary endpoint was to determine the changes in the grade of abdominal pain (capsular pain, ischemic cholangiopathy, abdominal angina), cardiac output and the New York Heart Association (NYHA) stage in HHT patients with hepatic involvement before and three months after systemic bevacizumab therapy.

The authors hypothesize that systemic bevacizumab therapy alleviates liver related pain and cardiac overload thus obviating the need for hepatic arterial embolization (HAE) or liver transplantation (LT)

Statistical methods for estimation and sensitivity analysis on primary estimands

No protocol has been provided by the applicant and hence no planned analyses are presented. The results for the different efficacy endpoints are presented descriptively, in means and confidence intervals, and with associated p-values. It is not stated which statistical tests are used.

No information regarding sample size determination, planned subgroup analyses, missing data, error probabilities and multiplicity adjustments are outlined in the publication.

Secondary objectives

The secondary endpoints included the epistaxis response to therapy, the change in haemoglobin after therapy, the necessity for repeat therapies, and the safety and tolerability of bevacizumab.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

No protocol has been provided by the applicant and hence no planned analyses are presented. The results for the different efficacy endpoints are presented descriptively, in means and confidence intervals, and with associated p-values. It is not stated which tests are used.

No information regarding sample size determination, planned subgroup analyses, missing data, error probabilities and multiplicity adjustments are outlined in the publication.

5.3.2.3.4. Results

Participant flow and numbers analysed

21 prospective patients with symptoms of liver involvement of HHT are included between October 2010 and April 2016. Treatment assigned were bevacizumab (5 mg/kg/dose, 6 doses administered every two weeks). The entire therapy was repeated at follow-up if symptoms causing significant clinical impairment recurred. Insufficient clinical improvement post-therapy during the study period necessitated HAE in three patients. Two stabilized thereafter and required no further therapy. The third patient required additional liver transplantation.

Baseline data

Table 28: Measured parameters in 21 patients before (b) and 3 months after (a) therapy with bevacizumab

Pat. No.	Gender Age	Epistaxis (NCI-grade)		Capsular pain/Abd. angina (NRS-grade)		Hb (g/dl)		Cardiac output (l/min)		NYHA-Stage	
1	(F) 63 years	2	1	5	2	15·0	15·2	7·7	5·1	3	2
2	(F) 57 years	3	1	4	2	12·8	13·1	8·0	5·1	2	1
3	(F) 42 years	2	1	2	2	11·7	12·5	4·9	5·2	2	1
4	(F) 59 years	3	1	4	1	7·1	12·1	8·3	5·9	4	2
5	(M) 60 years	2	0	2	1	13·8	14·4	12·6	8·2	3	1
6	(F) 56 years	3	0	4	0	9·6	12·3	5·1	5·4	2	1
7	(F) 66 years	2	1	0	0	12·6	11·9	7·0	7·6	3	2
8	(F) 60 years	3	1	5	2	9·3	10·0	7·5	4·6	4	3
9	(M) 58 years	3	1	4	0	11·2	13·9	19	8·9	3	2
10	(F) 67 years	3	1	0	0	11·3	10·7	7·0	6·8	3	2
11	(M) 47 years	0	0	0	0	15·6	15·2	9·7	5·8	3	2
12	(F) 54 years	3	1	0	0	7·5	9·8	5·5	5·7	2	1
13	(F) 52 years	2	1	4	3	7·2	9·1	7·1	6·0	4	3
14	(F) 71 years	3	1	0	0	9·9	13·0	6·2	4·3	2	1
15	(F) 59 years	2	1	2	0	13·3	14·4	6·3	4·5	2	1
16	(F) 62 years	3	1	5	1	7·3	10·6	11·6	4·8	3	1
17	(M) 59 years	2	1	6	2	12·9	13·7	13·5	10·0	2	1
18	(M) 48 years	3	1	0	0	11·3	12·2	9·2	8·2	2	1
19	(F) 46 years	1	1	7	1	9·0	11·8	13·3	9·8	3	1
20	(M) 63 years	3	1	4	0	7·8	12·4	5·9	5·9	3	1
21	(F) 71 years	2	1	4	2	10·9	12·0	8·3	8·3	4	4

Abd. Angina = Abdominal angina; (F) = Female; Hb (g/dl) = Hemoglobin (gram / deciliter); l/min = liter/minute; (M) = Male; NCI = National Cancer Institutes common toxicity criteria scale (Version 3); No. = Number; NRS = Numerical Rating Scale; NYHA = New York Heart Association; Pat. = Patient.

The median patient age was 58 years (range 42–71 years) and median follow-up was 33 months (range 3–70 months). 15/21 patients were female.

Outcomes and estimation

Abdominal pain

Abdominal pain was a presenting symptom in 15 patients. The NRS grades pretherapy and post-therapy were 2–7 and 0–3 respectively. Mean pain grade improved from 3.0± 2.2 (95% CI 1.99–3.91) pretherapy to 0.9±1.0 post-therapy (95% CI 0.48–1.33) (P < .001).

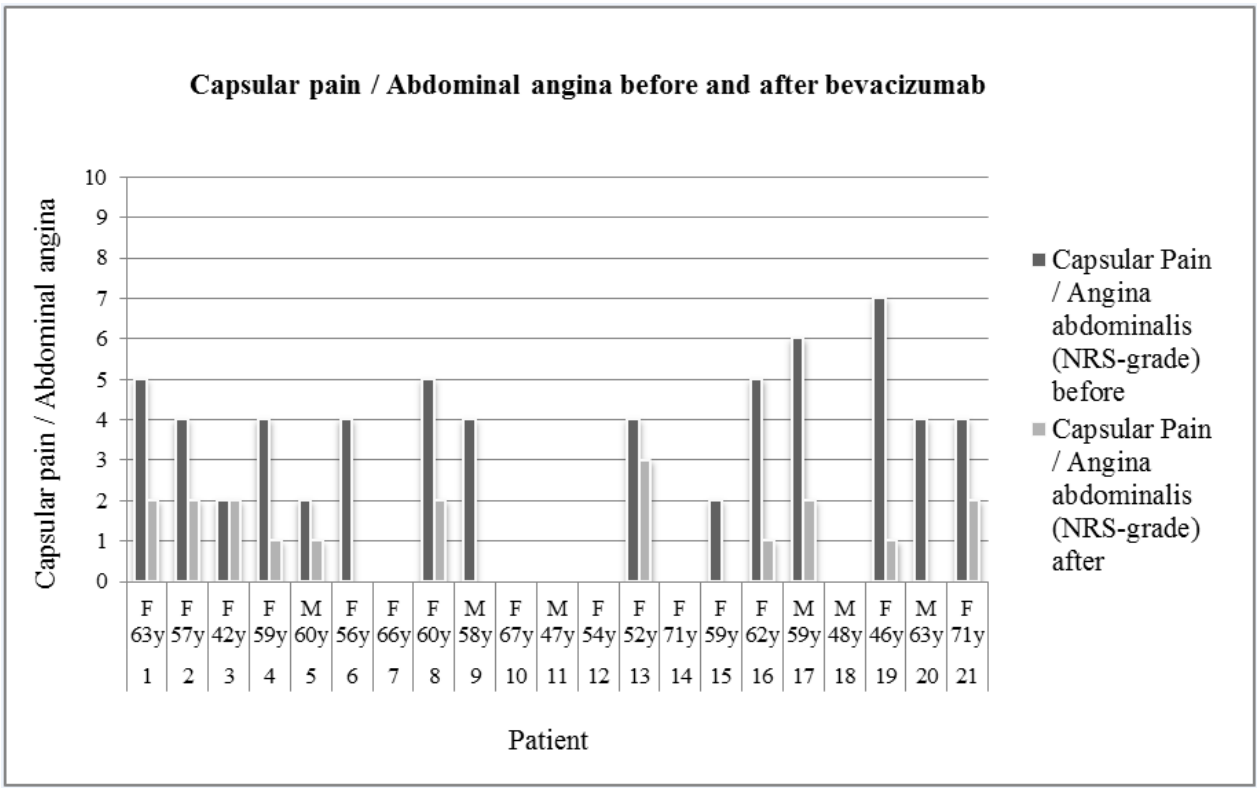


Figure 15: Individual presentation on abdominal pain before and after treatment.

Cardiac output

Cardiac output pretherapy ranged between 4.9 L/min and 19 L/min (mean 8.7 L/min ±3.5) (95% CI 7.25–10.24). Following therapy, the mean value fell according to the authors significantly to 6.5 L/Min ±1.8 (95% CI 5.73–7.24) (range 4.3 L/min-10.0 L/min) (P < .0008)

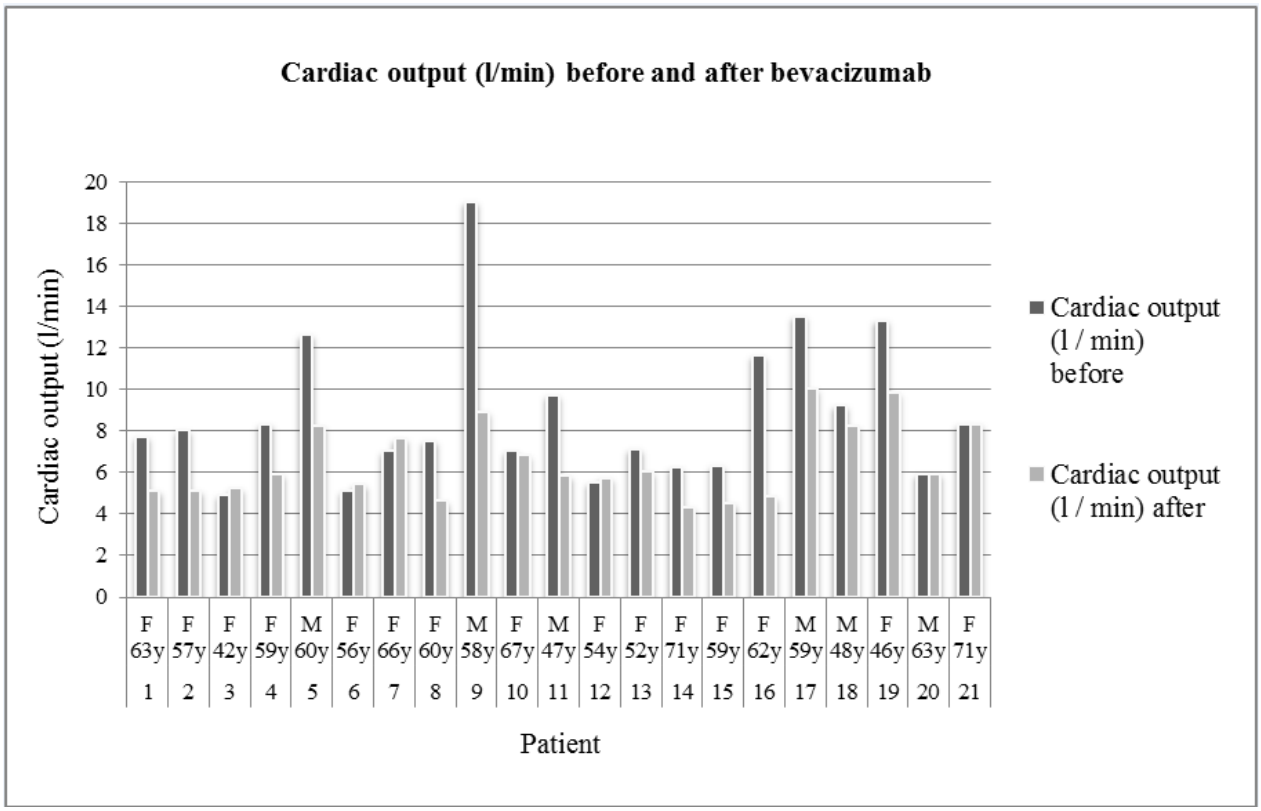


Figure 16: Individual presentation on cardiac output before and after treatment.

The fall in cardiac output was according to the authors associated with an improvement in the signs and symptoms of cardiac decompensation as signified by the mean NYHA stage improving from 2.8 ±0.7 (95% CI 2.49–3.13) pretherapy to 1.6 ±0.9 (95% CI 1.25–1.99) (P < .0001)

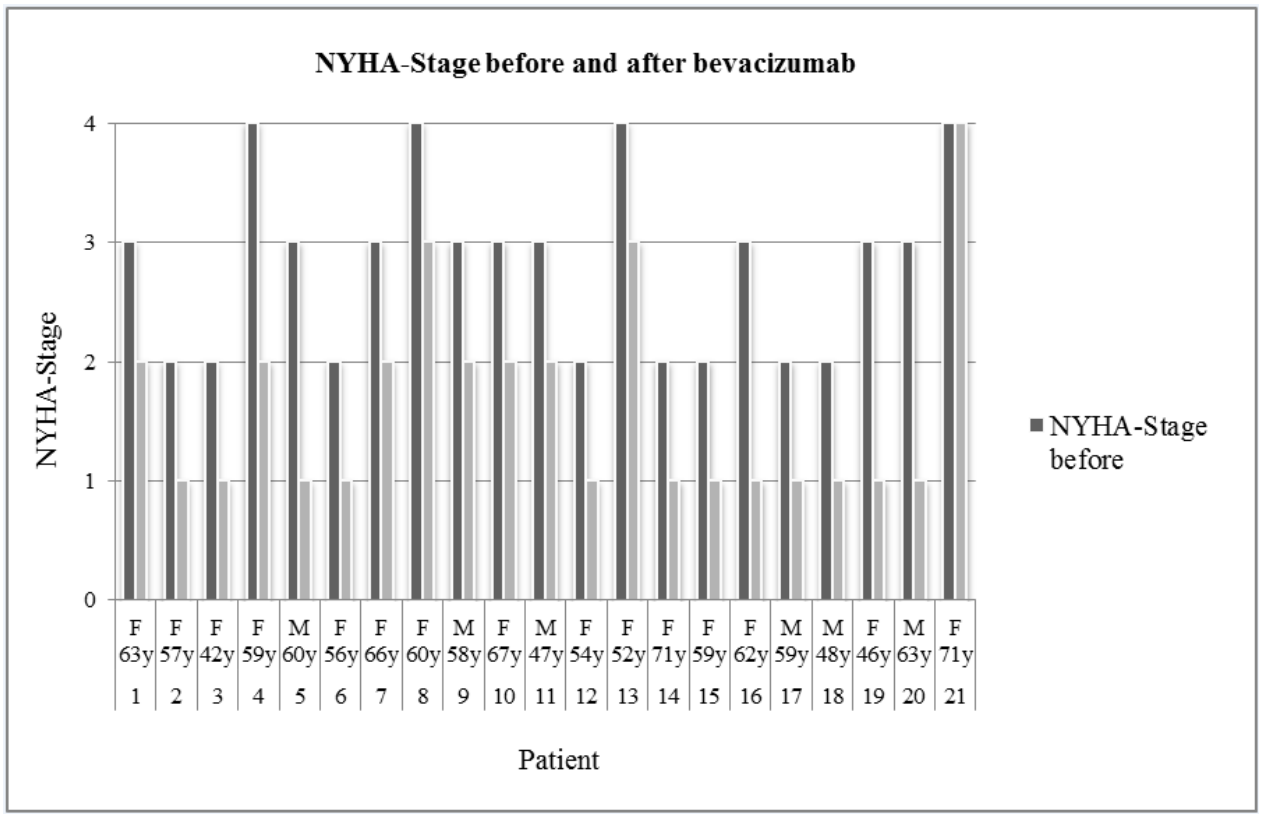


Figure 17: Individual presentation on NYHA stage before and after treatment.

Insufficient clinical improvement post-therapy necessitated HAE in three patients. Two stabilized thereafter and required no further therapy. The third patient required additional liver transplantation.

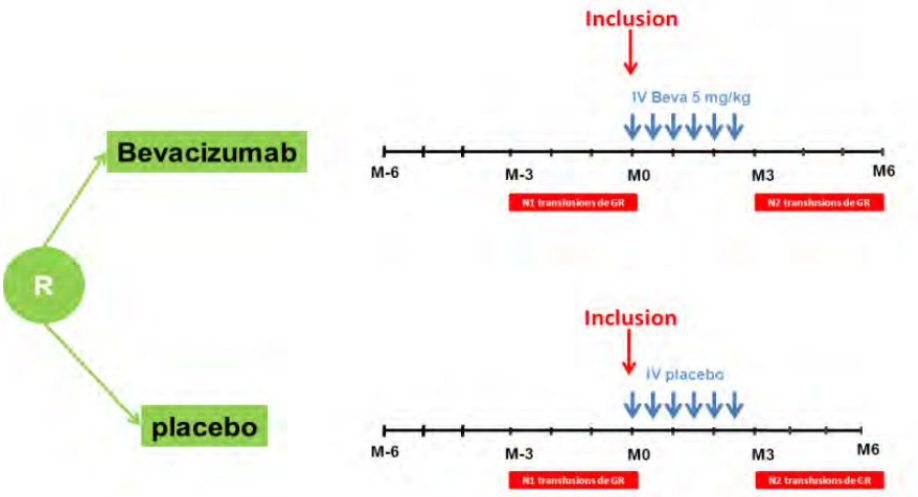
5.3.3. Main studies: Efficacy in HHT presenting severe hemorrhagic form (epistaxis and/or digestive bleeding) of the disease with dependence on transfusions and/or intravenous iron

5.3.3.1. HHT-PS2 / BABH Study

5.3.3.1.1. BABH Study: Efficacy and safety of bevacizumab on severe bleeding associated with Hemorrhagic Hereditary Telangiectasia (HHT). A national, randomized multicenter phase III study

5.3.3.1.2. Study design

Figure 18: Study schema



Treatment

AVASTIN (bevacizumab) was used for this study. Each vial contains 100 mg or 400 mg of bevacizumab in respectively 4 ml or 16 ml of solution for dilution.

The placebo presents in the form of a MACOPHARMA Easyflex + bag of injectable solution of NaCl 0.9% (100 ml).

Each patient included in the study received in total 6 perfusions, each administered 14 days apart, at the dose of 5 mg/kg of bevacizumab or placebo.

No other experimental treatment for treating the haemorrhages could be used during the study. Should nasal or gastrointestinal surgery be required during the study, the study treatment must be stopped and patient follow-up continued.

All the other concomitant treatments needed to manage the patients were authorized during the study and were documented and collected in the CRF.

Randomisation and blinding

Participant were randomised in a 1:1 ratio to either active treatment (bevacizumab) or placebo through the intermediary of an IWRS, based on a single randomization list for all centres.

The study was double blind, that is, neither the investigator nor the patient was aware of the nature of the treatment administered. The healthcare personnel were not aware of the treatment administered either, only the pharmacy functioned in open-label mode. The solutions for perfusion, bevacizumab and placebo, were prepared the day of administration by the pharmacy in the hospital centre in which the patient was managed for the study. To guarantee the blinding of the bevacizumab or placebo preparation, the final volume of the bevacizumab preparation had to be the equivalent of the placebo preparation. The volume equivalent to the volume of bevacizumab solution to be injected in the bag was thus removed. The bag was labelled in accordance with the regulations in force: "bevacizumab (5 mg/kg) or placebo".

Unblinding was possible during the study on request to the Anti-Poison Centre in Lyon (24H/24H) by any doctor managing a patient, or by the sponsor. Any request for unblinding was exceptional and had to be justified. It could only be envisaged if knowledge of the nature of the treatment effectively received modified the patient's management. The number of the Anti-Poison Centre in Lyon was included on the card given to each patient indicating they were participating in a clinical trial. The person requesting the unblinding was obliged to communicate the name of the study, the patient's identification number and treatment code, the name of the investigating doctor, as well as the nature of the event imposing the unblinding and the date of the last treatment.

After unblinding, the treatment being studied will be stopped.

Patient population

The study was conducted in four centres in France (Lyon, Montpellier, Ambroise Paré and Angers).

Inclusion criteria

The study enrolled adult patients, monitored for clinically and/or biologically confirmed HHT, having required blood transfusions related to nosebleeds or digestive bleeding (at least 4 units of RBC in the 3 months preceding inclusion)

Exclusion criteria

- Women who are pregnant or currently breastfeeding. Women of child-bearing age but not using reliable contraception during the treatment and the 6 months following the end of the treatment.
- Patients whose diagnosis of HHT has not been confirmed clinically and/or with molecular biology.
- Current infection and/or a temperature > 38°C
- Patients who have received injections of Avastin in the 6 months prior to inclusion
- Patients who have had an interventional endoscopy for digestive bleeding or ENT surgery must wait 3 months after the procedure if the bleeding persists.
- Patients who have had surgery in the month preceding inclusion, or who have scheduled surgery within 6 months.
- Patients with peripheral arteriopathy complicated by ulceration
- Patients with unhealed wounds.
- Past history of thrombosis in the 6 months preceding inclusion.
- Anticoagulant treatment
- Uncontrolled hypertension

5.3.3.1.3. Objectives and estimands

Primary objective

To evaluate the efficacy of 6 intravenous injections of bevacizumab, 6 months after the start of the treatment, on the number of units of red blood cells transfused in patients with hereditary hemorrhagic telangiectasia with severe hemorrhages resulting in anemia.

The percentage of patients who responded to the treatment in each group was compared. An effect of bevacizumab was defined by a decrease of 50% in transfusions between the 3-month period immediately prior to the treatment and the period 3 to 6 months after the end of the treatment.

The study was design to show superiority of bevacizumab towards placebo in reducing the number of units of red blood cells transfused 6 months after the start of treatment.

Estimands for the primary objective

The estimand framework was not applied.

Statistical methods for estimation and sensitivity analysis on primary estimands

Analysis sets

The ITT (intention to treat) population: includes all the patients included and randomized who started the treatment. The patients were analysed in their randomization group.

The PP (per protocol) population: includes all the patients who received at least 5 perfusions of the treatment being studied and who attended the end of protocol visit. In addition, to be analysed in this population, the patients had to have respected the perfusion protocol (14 days between two perfusions over a duration of 70 day +/- 14 days). Patients who underwent nasal or gastrointestinal surgery were excluded from this population.

Primary analysis (main evaluation criterion): number of transfusions

The analyses were performed on the ITT population. Analysis was also performed on the PP population. The number of transfusions (in units of red blood cells = RBC) was calculated for the 3-month period (#12 weeks) prior to the treatment and for the period from the 3rd month to the 6th month after the start of the treatment. Efficacy was considered acquired for a patient if the number of units of RBC decreased by at least 50% between these 2 periods (a decrease of 50% was considered a success).

The percentage of patients with success was calculated in each group and was compared using the Chi² test (or the Fisher exact test).

A descriptive analysis of the number of units of RBC was performed for the 3 periods and presented with "boxplots".

Planned subgroup analyses

No subgroup analyses were planned nor performed.

Sample size determination

It was hypothesized that 80% of the patients in the treatment group decreased the number of red blood cell transfusions by at least 50% versus 20% in the placebo group. An exact Fisher test with a bilateral significance level of 0.050 would have a power of 81% to detect the difference between a proportion in group 1 (p1) of 0.200 and a proportion in group 2 (p2) of 0.800 when the sample size in each group is 12.

Error probabilities, adjustment for multiplicity and interim analyses

The significance threshold was set to 5%. No adjustment for multiplicity was defined.

Secondary objectives

1. Hemoglobin levels measured before (M0), at 3 months and at 6 months after the start of the treatment.
2. Clinical efficacy criteria:
    - Evolution in the monthly duration of nosebleeds and the frequency of the episodes at 3 and 6 months after starting the treatment. Evaluation grids for the bleeding will be completed by patients 3 months before the start of the treatment and throughout the duration of the study (6 months)
    - Evolution in the scores obtained on the quality of life questionnaire, SF-36, and the severity of the nosebleeds (ESS) completed on inclusion (M0), at the end of the treatment (M3) and at the end of the study (M6).
3. Tolerance of the repeated perfusions of bevacizumab with observation of adverse events at each visit.
4. The presence of digestive bleeding 6 months after the start of the treatment in patients who had such bleeding before inclusion, a criterion evaluated with digestive endoscopy (video capsule).
5. A pharmacokinetics study based on assays of residual bevacizumab before each new perfusion and two hours after the first perfusion.

Estimands for the secondary objectives

The estimand framework was not applied.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

Analysis populations

The ITT (intention to treat) population: includes all the patients included and randomized who started the treatment. The patients were analysed in their randomization group.

The PP (per protocol) population: includes all the patients who received at least 5 perfusions of the treatment being studied and who attended the end of protocol visit. In addition, to be analysed in this population, the patients had to have respected the perfusion protocol (14 days between two perfusions over a duration of 70 day +/- 14 days). Patients who underwent nasal or gastrointestinal surgery were excluded from this population.

Secondary analyses

Relative evolution of hemoglobin level was to be computed by subtracting the baseline value from the M3 value and the M6 value. Delta was to be compared between groups using student t-test (or Mann-Whitney in case of non-normality). All hemoglobin levels recorded during the study was planned to be graphically presented, and a mixed model was also to be adjusted. The mixed model adjusted for time, treatment and their interaction, which was not pre-specified in the protocol.

Relative evolution of epistaxis, measured in terms of the frequency, duration and ESS, was to be computed by subtracting the baseline value from the M3 value and M6 value (each value represents an average on a 3-month period). Delta was to be compared between groups using student t-test (or Mann-Whitney in case of non-normality). A mixed model will also be adjusted. The mixed model adjusted for time, treatment and their interaction, which was not pre-specified in the protocol.

Relative evolution of SF36 (overall and by items) and ESS was planned to be computed by subtracting the baseline value from the M3 value and from the M6 value. Delta was to be compared between groups using students t-test (or Mann-Whitney in case of non-normality). A mixed model was also to be adjusted. The 2 overall scores were calculated at the start of the study, at 3 months and at 6 months, as well as the differences 3 months-before and 6 months before. Mixed models integrating the time, treatment and their interaction were carried out with a graphic presentation for the overall scores.

Additional analyses not pre-specified

No analysis method was pre-specified for evaluating of ferratin values. The mean ferritin values were calculated and analysed in the same manner as hemoglobin (see above). Iron perfusions were also given in a descriptive manner.

The analysis method for the mean HHS score was not specified in the protocol. The mean HHS score was calculated for the 3 periods (before/during/after), as well as the differences (absolute and relative) during-before and after-before. They were compared between the groups with the Student t test (or the Mann-Whitney in case of non-normality).

Missing data

The nosebleed grids were completed by the patients. If the value for one day was missing, it was replaced by the mean of the 4 values before and the 4 values after. This strategy was applied up to 10 consecutive days over a period of 3 months (84 days). If the missing values were consecutive, more than 10 days and less than 30 days, a daily average was calculated using the data available and

multiplied by the number of days in the period. If the missing data covered more than 30 days, the patient was excluded from the analysis for this nosebleed criterion.

5.3.3.1.4. Results

Participant flow and numbers analysed

In total, between September 27, 2017 and March 28, 2020, 24 patients were randomized in the BABH study

Figure 19: Participant flow

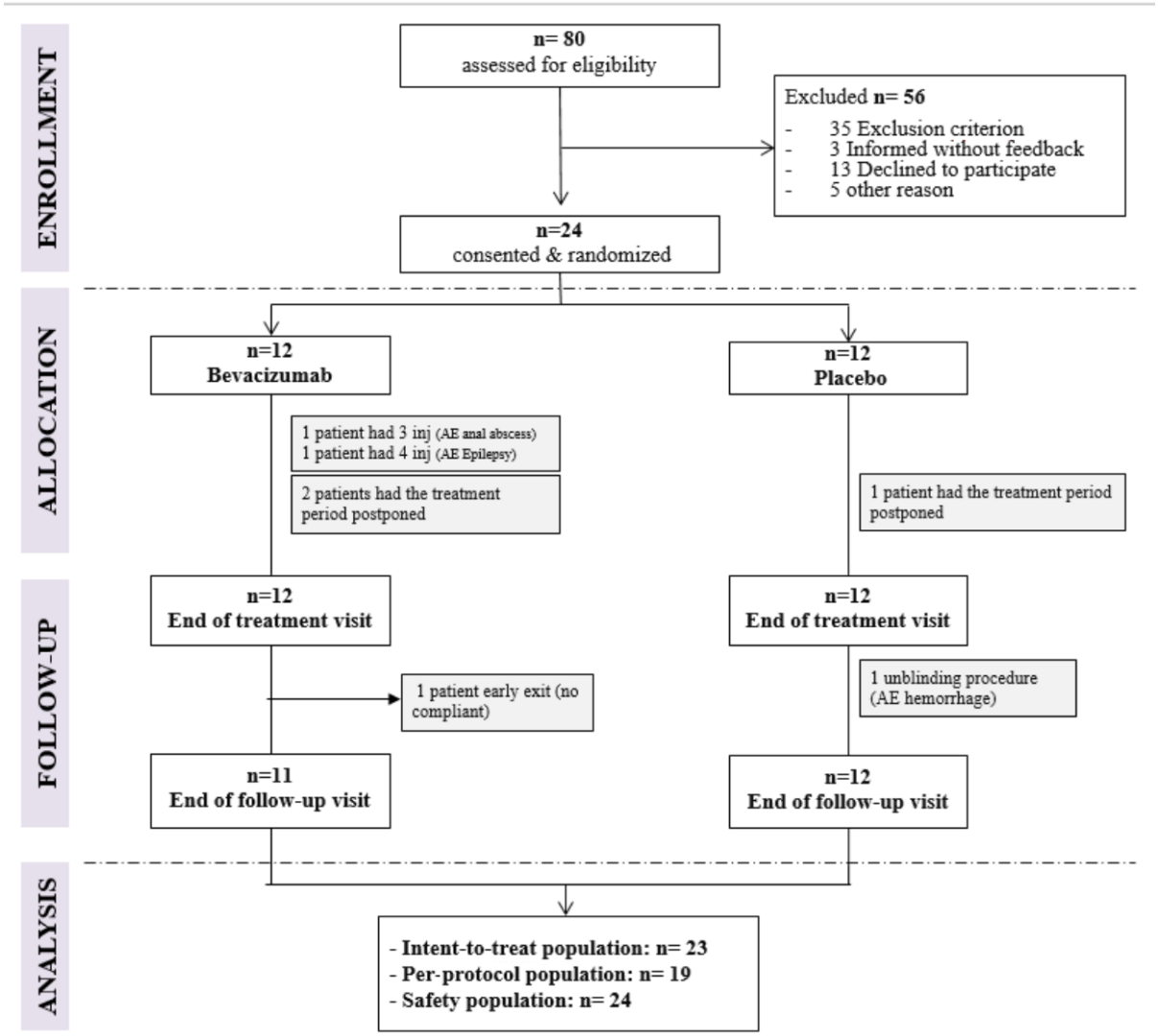


Table 29. Compliance of administration of bevacizumab/placebo

Variable	Modalities	Global	Placebo group n(%)	Beva group n(%)	P-value
Number of perfusions	n perfusions	139	72	67	0.1662•
	n patients	24	12	12	
	median (min-max)	6 (3—6)	6 (6—6)	6 (3—6)	
	mean(std)	5.79 (0.72)	6 (0)	5.58 (1)	
Detail for the patients who did not receive all 6	3	1 (50)		1 (50)	.
	4	1 (50)		1 (50)	
No. of perfusions postponed	Missing	237 (.)	119 (.)	118 (.)	.
	Yes	3 (100)	1 (100)	2 (100)	

Deviations from study plan

Table 30. Protocol amendments

Version	Date	Amendment	CPP	ANSM	Modifications
1	Mar 16, 17	-		Apr 19, 17 Questions	Initial version submitted
2 **+ NIC V4**	Apr 20, 17	-	May 19, 17 Sud Est-I **Favorable opinion**	May 12, 17 **Authorization**	FIC: Add date of birth; support person; reflection period for informed consent; insist on the probability of receiving the placebo Protocol: add non-inclusion criterion (§4.2.5, §6.3); add monitoring of liver function and CBC (§6.3 to 6.6); justification of divergences in the use set out in the protocol/MA; justify the inclusion criterion of 3 units of RBC over 3 months / to 4 units of RBC over 3 months in the RTU (§4.2.4)
3 **+ NIC V5**	Jan 08, 2018	1	Feb 23, 2018 Sud Est-I **Favorable opinion**	Jan 24, 18 **Authorization**	More precise definition of the rules for counting the number of transfusions per period §4.3.1, §4.3.2. Specification of the definition of the ITT group (exclusion of the patient after randomization if not perfused) §4.5, §6.3, § 9.2.1.1 Add possibility of a urinary pregnancy test §6.4 Specification of the follow-up visits after postponing a perfusion §6.5 Add possibility of evaluating proteinuria through the protein / creatinine ratio (§ 6.7, § 7.4.3) Modification of the unblinding procedure at the end of a patient's participation in the study §11.2
4 + NIC V6	Jul 10, 19	2	Aug 30, 2019 Sud Est-I **Favorable opinion**	NA	Prolongation of the inclusion duration §4.3.1 Inclusion duration: 30 months, study duration 36 months. NIC: update GDPR

Deviations from the protocol

In total, 41 deviations were identified, 3 of which concerned the pharmacy, 4 critical deviations, 15 major deviations and 19 minor deviations. In total, 5 patients presented at least one deviation and were not considered in the PP population (Table 31).

Table 31. Protocol deviations

Subject Identifier for the Study	Group	Respect for the minimum number of perfusions	Respect for the perfusion protocol (every 14 days)	Respect for the treatment duration (70 days +/- 14 days)	Carrying out the final visit respected.
122	Beva	Yes	No	No	Yes
208	Placebo	Yes	No	No	Yes
213	Beva	Yes	No	No	Yes
318	Beva	No	Yes	No	No
405	Beva	No	Yes	No	Yes

Changes from protocol-specified analyses

The database was frozen on January 4, 2021 and a first report was edited on January 5, 2021. The analysis report was updated following the amendment to the statistical analysis plan (SAP) on March 1, 2021. Only the latest amended SAP has been provided by the applicant. The first version of the SAP was dated November 25, 2020, before database lock.

Baseline data

Table 32: Patient characteristics before treatment

Variable	Modality	All	Placebo group *n* (%)	Bevacizumab group *n* (%)	*p*
Number	*n*	24	12	12	
Age (years)	Median (min–max)	60 (42–80)	68 (42–75)	59.5 (50–80)	0.50
	Mean (SD)	61.21 (10.81)	62.5 (12.89)	59.92 (8.64)	
Females	*n* (%)	10 (41.7)	6 (50)	4 (33.3)	0.68
Mutated gene	*n* (%)				0.64
ALK1		17 (70.8)	8 (66.7)	9 (75)	
ENG		5 (20.8)	2 (16.7)	3 (25)	
Ongoing		2 (8.3)	2 (16.7)	0	
Parameters on inclusion					
Nasal surgery	*n* (%)	19 (79.2)	11 (91.7)	8 (66.7)	0.32
Nasal septum perforation	*n* (%)	8 (34.8)	5 (45.5)	3 (25)	0.40
Digestive bleeding					
No	*n* (%)	14 (58.3)	4 (33.3)	10 (83.3)	
Yes	*n* (%)	10 (41.7)	8 (66.7)	2 (16.7)	0.04
Hemoglobin level	Mean ± SD	86.09 (14.66)	84 (13.6)	88 (15.91)	0.32
(g/L)	Median (min–max)	91 (54–104)	86 (54–104)	94.5 (56–104)	
Ferritin level (ng/mL)	Mean ± SD	66.96 (117.89)	61.82 (92.97)	71.67 (141.02)	0.50
	Median (min–max)	25 (4–515)	15 (5–302)	30.5 (4–515)	
Systolic blood pressure (mmHg)	Mean ± SD	125.25 (19.54)	123.25 (23.86)	127.25 (14.84)	0.88
	Median (min–max)	127.5 (85–158)	127.5 (85–158)	125.5 (103–149)	
Diastolic blood pressure (mmHg)	Mean ± SD	68 (12.63)	66.83 (13)	69.17 (12.71)	0.60
	Median (min–max)	64.5 (47–91)	62.5 (48–88)	69.5 (47–91)	

Note: *p* is the value for the exact Mann–Whitney test or Fisher's exact test.

Outcomes and estimation

The primary endpoint analysed in the ITT and the PP population is provided in Table . The treatment was considered a success if the number of transfusions (i.e. the number of units of RBC transfused) in the 3 months after the treatment was 50% lower than the number of transfusions 3 months before the start of the treatment.

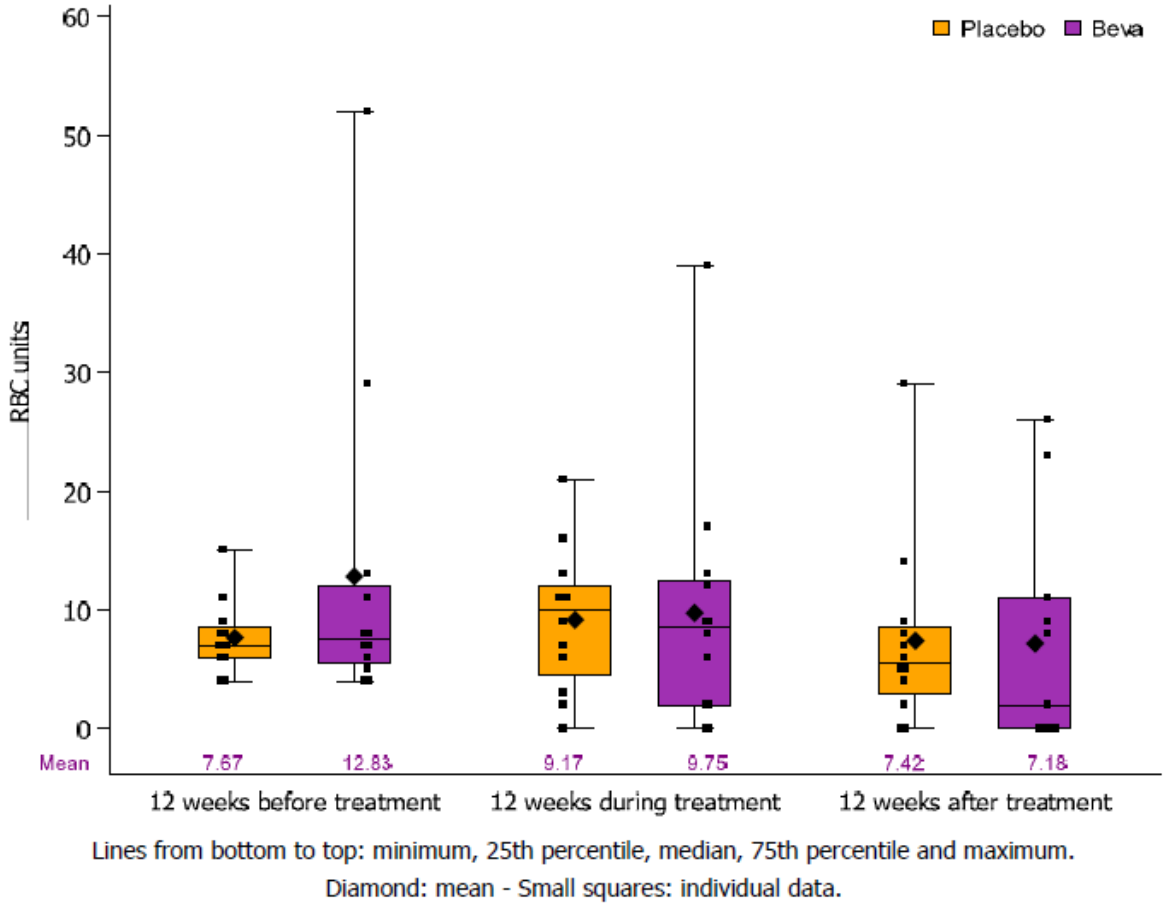
Table 33: Analysis of primary endpoint

Variable	Modalities	Global	Placebo group n(%)	Beva group n(%)	P-value
Success: Reduction of 50% in the number of units of packed RBC (ITT)	Missing	1 (.)		1 (.)	0.1461
	No	12 (52.2)	8 (66.7)	4 (36.4)	
	Yes	11 (47.8)	4 (33.3)	7 (63.6)	
Success: Reduction of 50% in the number of units of packed RBC (PP)	No	10 (52.6)	7 (63.6)	3 (37.5)	0.3698•
	Yes	9 (47.4)	4 (36.4)	5 (62.5)	

Table 34: Additional information on the elements making up the main judgment criterion.

Variable	Modalities	Global	Placebo group n(%)	Beva group n(%)	P-value
Total units RBC					
Sum of units of RBC in the BEFORE period	n	24	12	12	0.6832•
	median (min-max)	7 (4 - 52)	7 (4 - 15)	7.5 (4 - 52)	
	mean(std)	10.25 (10.3)	7.67 (3.03)	12.83 (14.07)	
Sum of units of RBC in the DURING period	n	24	12	12	0.7064•
	median (min-max)	9 (0 - 39)	10 (0 - 21)	8.5 (0 - 39)	
	mean(std)	9.46 (8.48)	9.17 (6.03)	9.75 (10.67)	
Sum of units of RBC in the AFTER period	n	23	12	11	0.6172•
	median (min-max)	5 (0 - 29)	5.5 (0 - 29)	2 (0 - 26)	
	mean(std)	7.3 (8.49)	7.42 (7.84)	7.18 (9.53)	
Diff in total units of RBC DURING-BEFORE	n	24	12	12	0.0941
	median (min-max)	-2 (-16 - 14)	1.5 (-7 - 14)	-4 (-16 - 9)	
	mean(std)	-0.79 (6.7)	1.5 (5.71)	-3.08 (7.05)	
Diff in total units of RBC AFTER-BEFORE	n	23	12	11	0.1746•
	median (min-max)	-3 (-27 - 22)	-2 (-8 - 22)	-5 (-27 - 15)	
	mean(std)	-3.13 (10.38)	-0.25 (7.75)	-6.27 (12.26)	

Figure 20: Boxplot of the number of units of RBC during the study in relation to the groups



Secondary endpoints

The secondary judgment criteria were analysed in the ITT population

Table 35: Haemoglobin data.

Variable	Modalities	Global	Placebo group n(%)	Beva group n(%)	P-value
Hemoglobin					
Hemoglobin at inclusion	n	23	11	12	0.5259
	median (min-max)	91 (54 - 104)	86 (54 - 104)	94.5 (56 - 104)	
	mean(std)	86.09 (14.66)	84 (13.6)	88 (15.91)	
Hemoglobin at 3 months	n	21	11	10	0.2031
	median (min-max)	97 (66 - 144)	96 (66 - 115)	99 (87 - 144)	
	mean(std)	98.86 (17.02)	94.27 (15.42)	103.9 (18.04)	
Hemoglobin at 6 months	n	23	12	11	0.0180
	median (min-max)	95 (60 - 116)	85 (60 - 105)	101 (78 - 116)	
	mean(std)	92.22 (15.23)	85.25 (13.57)	99.82 (13.62)	
Diff hemoglobin concentration 3 months-inclusion	n	20	10	10	0.2239
	median (min-max)	12 (-10 - 53)	11 (-8 - 19)	17 (-10 - 53)	
	mean(std)	12.95 (15.76)	8.5 (8.1)	17.4 (20.37)	
Diff hemoglobin concentration 6 months-inclusion	n	22	11	11	0.1862
	median (min-max)	7 (-17 - 43)	5 (-17 - 29)	13 (-16 - 43)	
	mean(std)	7.64 (17.17)	2.73 (12.99)	12.55 (19.93)	

Table 36. Ferritin data.

Variable	Modalities	Global	Placebo group n(%)	Beva group n(%)	P-value
Ferritin					
Ferritin at inclusion	n	23	11	12	0.4982•
	median (min-max)	25 (4 - 515)	15 (5 - 302)	30.5 (4 - 515)	
	mean(std)	66.96 (117.89)	61.82 (92.97)	71.67 (141.02)	
Ferritin at 3 months	n	20	10	10	0.8499•
	median (min-max)	31.5 (8 - 497)	32.5 (8 - 330)	31 (10 - 497)	
	mean(std)	85.8 (126.46)	89.7 (109.64)	81.9 (147.32)	
Ferritin at 6 months	n	22	11	11	0.4904•
	median (min-max)	27.5 (5.9 - 603)	32 (5.9 - 240)	23 (9 - 603)	
	mean(std)	85.95 (141.67)	66.35 (83.89)	105.55 (185.11)	
Diff ferritin concentration 3 months-inclusion	n	19	9	10	0.3222
	median (min-max)	5 (-100 - 221)	14 (-100 - 221)	2.5 (-32 - 52)	
	mean(std)	19.16 (65.76)	36.44 (90.23)	3.6 (29.03)	
Diff ferritin concentration 6 months-inclusion	n	21	10	11	0.6985•
	median (min-max)	4 (-83 - 236)	-0.05 (-83 - 185)	7 (-52 - 236)	
	mean(std)	23.42 (77.53)	17.49 (78.07)	28.82 (80.43)	

Table 37: Data on nosebleeds. For this analysis, patients 318, 405 and 412 were excluded because they had more than 30 values missing over at least one period.

Variable	Modalities	Global	Placebo group n(%)	Beva group n(%)	P-value
Total duration on each period of 12 weeks (84 days)					
Total duration of nosebleed episodes in the BEFORE period	n	21	11	10	0.1927•
	median (min-max)	679 (103 - 6294)	505.5 (103 - 4401)	928.35 (139 - 6294)	
	mean(std)	1324.14 (1561.95)	1058.4 (1333.73)	1616.46 (1806.59)	
Total duration of nosebleed episodes in the DURING period	n	21	11	10	0.2178•
	median (min-max)	724 (105 - 4172)	360 (122 - 2870)	1043.5 (105 - 4172)	
	mean(std)	1129.55 (1091.58)	895.32 (996.52)	1387.2 (1184.78)	
Total duration of nosebleed episodes in the AFTER period	n	21	11	10	0.3787•
	median (min-max)	619 (84 - 3489)	212.2 (84 - 2954)	640.5 (97 - 3489)	
	mean(std)	782.32 (923.56)	659.84 (882.01)	917.06 (996.28)	
Difference between the DURING-BEFORE periods	n	21	11	10	0.8053•
	median (min-max)	-34 (-2122 - 521)	12.1 (-1531 - 141)	-76.45 (-2122 - 521)	
	mean(std)	-194.6 (577.82)	-163.08 (468.31)	-229.26 (704.06)	
Difference between the AFTER-BEFORE periods	n	21	11	10	0.4181•
	median (min-max)	-310 (-2805 - 150)	-215 (-1447 - 75)	-526.5 (-2805 - 150)	
	mean(std)	-541.82 (708.97)	-398.56 (505.94)	-699.4 (883.1)	
Mean duration for each period of 12 weeks (84 days)					
Mean duration of nosebleed episodes in the BEFORE period	n	21	11	10	0.1927•
	median (min-max)	226.33 (34.33 - 2098)	168.5 (34.33 - 1467)	309.45 (46.33 - 2098)	
	mean(std)	441.38 (520.65)	352.8 (444.58)	538.82 (602.2)	
Mean duration of nosebleed episodes in the DURING period	n	21	11	10	0.2178•
	median (min-max)	241.33 (35 - 1390.67)	120 (40.67 - 956.67)	347.83 (35 - 1390.67)	
	mean(std)	376.52 (363.86)	298.44 (332.17)	462.4 (394.93)	
Mean duration of nosebleed episodes in the AFTER period	n	21	11	10	0.3787•
	median (min-max)	206.33 (28 - 1163)	70.73 (28 - 984.67)	213.5 (32.33 - 1163)	
	mean(std)	260.77 (307.85)	219.95 (294)	305.69 (332.09)	
Difference between the DURING-BEFORE periods	n	21	11	10	0.8053•
	median (min-max)	-11.33 (-707.33 - 173.67)	4.03 (-510.33 - 47)	-25.48 (-707.33 - 173.67)	
	mean(std)	-64.87 (192.61)	-54.36 (156.1)	-76.42 (234.69)	
Difference between the AFTER-BEFORE periods	n	21	11	10	0.4181•
	median (min-max)	-103.33 (-935 - 50)	-71.67 (-482.33 - 25)	-175.5 (-935 - 50)	
	mean(std)	-180.61 (236.32)	-132.85 (168.65)	-233.13 (294.37)	
Number of episodes for each period of 12 weeks (84 days)					
Total number of nosebleed episodes in the BEFORE period	n	21	11	10	0.5495•
	median (min-max)	90 (26 - 265)	57 (27 - 265)	115.95 (26 - 218)	
	mean(std)	107.09 (77.03)	100.15 (90.77)	114.72 (62.53)	
Total number of nosebleed episodes in the DURING period	n	21	11	10	0.5974•
	median (min-max)	78 (17 - 246)	60 (26 - 246)	99.5 (17 - 176)	
	mean(std)	99.49 (65.37)	96.65 (78.17)	102.6 (51.83)	
Total number of nosebleed episodes in the AFTER period	n	21	11	10	0.5492•
	median (min-max)	46 (12 - 240)	42 (12 - 240)	64.5 (21 - 125)	
	mean(std)	73.09 (58.67)	75.42 (75.18)	70.53 (36.8)	
Difference between the DURING-BEFORE periods	n	21	11	10	0.4746
	median (min-max)	-4 (-73 - 41)	-1 (-52 - 24)	-6.5 (-73 - 41)	
	mean(std)	-7.6 (26.75)	-3.49 (20.76)	-12.12 (32.69)	
Difference between the AFTER-BEFORE periods	n	21	11	10	0.2814
	median (min-max)	-24 (-108 - 44)	-24 (-101 - 44)	-39.15 (-108 - 13)	
	mean(std)	-34 (40.41)	-24.73 (35.21)	-44.19 (45.06)	

Figure 21: Boxplot of the duration of the nosebleeds during the study in relation to the groups

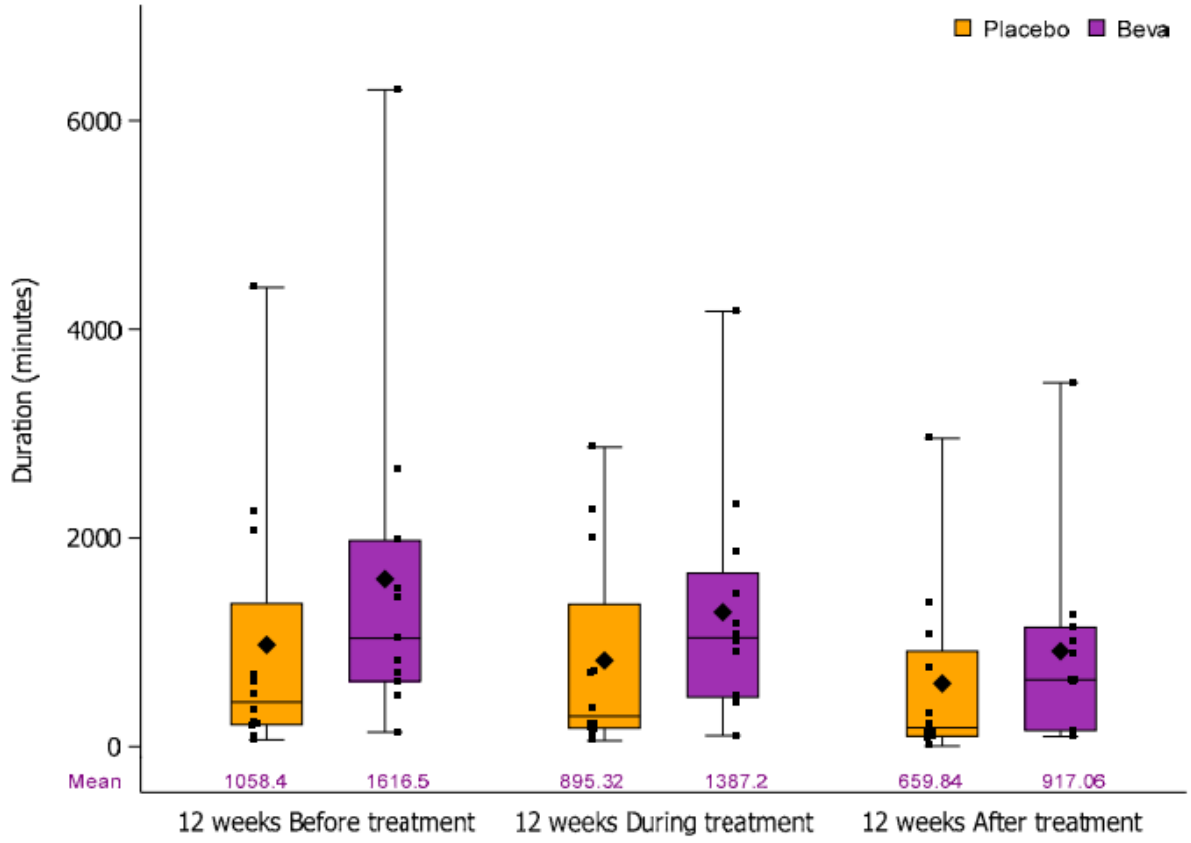
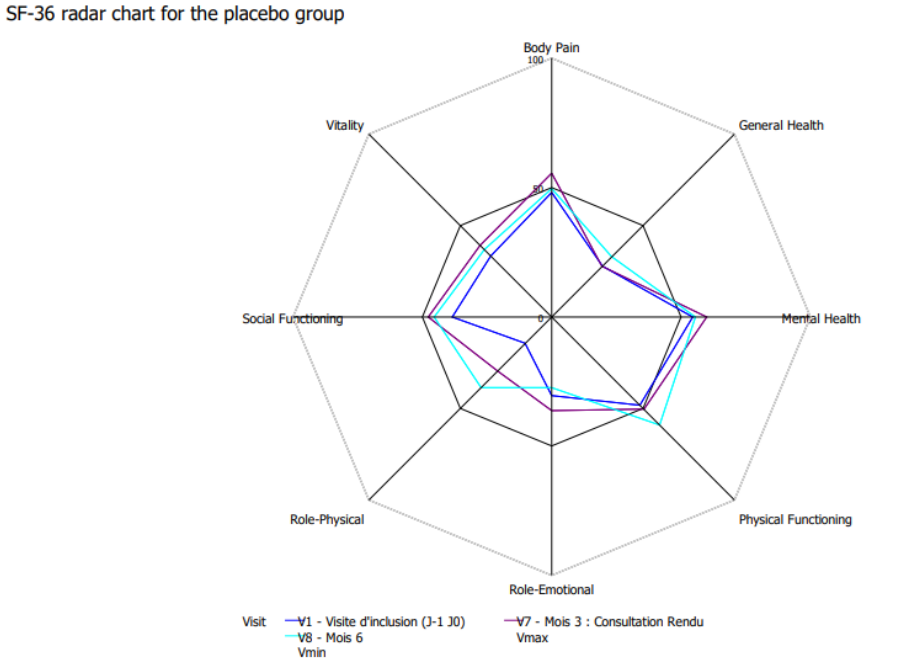


Table 38. Epistaxis severity score (ESS)

Variable	Modalities	Global	Placebo group n(%)	Beva group n(%)	P-value
NORMALIZED ESS					
Normalized ESS - inclusion	n	22	12	10	0.9736•
	median (min-max)	7.37 (0.72 - 10)	7.37 (4.24 - 10)	7.39 (0.72 - 9.09)	
	mean(std)	6.89 (2.26)	7.12 (1.83)	6.61 (2.76)	
NORMALIZED ESS - M3	n	20	10	10	0.9590
	median (min-max)	5.31 (2.43 - 8.08)	5.25 (3.04 - 8.08)	5.4 (2.43 - 7.68)	
	mean(std)	5.33 (1.66)	5.31 (1.73)	5.35 (1.69)	
NORMALIZED ESS - M6	n	20	10	10	0.2611
	median (min-max)	4.51 (1.23 - 10)	5.25 (1.23 - 10)	4.51 (2.43 - 6.09)	
	mean(std)	4.97 (2.26)	5.56 (2.92)	4.38 (1.21)	
Difference in normalized ESS between inclusion and M3	n	18	10	8	0.7963
	median (min-max)	-1.16 (-6.05 - 4.71)	-1.16 (-6.05 - 0.8)	-1.25 (-4.67 - 4.71)	
	mean(std)	-1.3 (2.4)	-1.43 (1.99)	-1.13 (2.97)	
Difference in normalized ESS between inclusion and M6	n	18	10	8	0.1198•
	median (min-max)	-1.74 (-5.94 - 0.33)	-0.62 (-5.94 - 0.33)	-2.83 (-4.35 - -0.22)	
	mean(std)	-2.04 (1.94)	-1.57 (2.27)	-2.63 (1.35)	

Figure 22: Outcome of the SF-26 quality of life questionnaire.



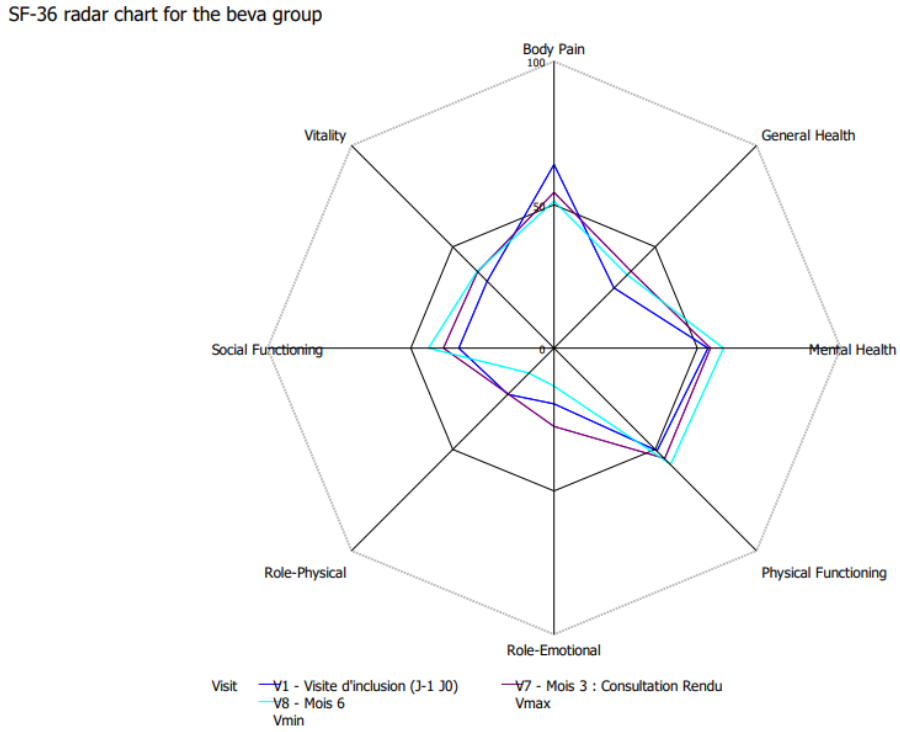


Table 39: Hematologic support score

Variable	Modalities	Global	Placebo group n(%)	Beva group n(%)	P-value
HSS score in the BEFORE period	n	24	12	12	0.8620•
	median (min-max)	8 (4 - 52)	8 (4 - 19)	8.5 (4 - 52)	
	mean(std)	12.77 (11.94)	9.8 (4.73)	15.73 (16.01)	
HSS score in the DURING period	n	23	12	11	0.5791•
	median (min-max)	11 (0 - 41.4)	11 (2 - 29)	9.6 (0 - 41.4)	
	mean(std)	12.56 (10.04)	11.8 (6.6)	13.38 (13.12)	
HSS score in the AFTER period	n	23	12	11	0.7806•
	median (min-max)	9 (0 - 39)	8.7 (0 - 29)	9 (0 - 39)	
	mean(std)	10.5 (10.4)	9.75 (7.77)	11.33 (13.04)	
Diff in the score DURING-BEFORE	n	23	12	11	0.1362
	median (min-max)	-1 (-20 - 22)	1.1 (-7.4 - 22)	-2 (-20 - 5.6)	
	mean(std)	-0.42 (8.06)	2 (7.97)	-3.05 (7.64)	
Diff in the score AFTER-BEFORE	n	23	12	11	0.2543•
	median (min-max)	-3.8 (-27 - 22)	-2.5 (-9.6 - 22)	-5 (-27 - 15)	
	mean(std)	-2.56 (10.84)	-0.05 (7.9)	-5.29 (13.2)	
Relative diff in the score DURING-BEFORE (%)	n	23	12	11	0.2420•
	median (min-max)	-18.2 (-100 - 314.3)	15.35 (-50 - 314.3)	-20 (-100 - 140)	
	mean(std)	16.09 (89.62)	39.58 (103.34)	-9.54 (67.37)	
Relative diff in the score AFTER-BEFORE (%)	n	23	12	11	0.2791•
	median (min-max)	-37.5 (-100 - 314.3)	-32.75 (-100 - 314.3)	-63.6 (-100 - 187.5)	
	mean(std)	-7.1 (101.59)	5.21 (106.6)	-20.53 (99.13)	

Ancillary analyses

The applicant highlights an explorative post hoc analysis on the treatment response in RBC units related to bevacizumab exposure below (or equal) or above the median exposure. There are however several limitations of the analysis, and the results are thus highly uncertain. This analysis is discussed in the Pharmacokinetics-Pharmacodynamics section of the report.

5.3.3.2. HHT-RS1 / CoBevaRo study

5.3.3.2.1. Real-life data study of the French cohort of patients with Rendu Osler disease treatment with bevacizumab

5.3.3.2.2. Study design

The study design has been described previously in this report when the study was presented in relation to the first indication.

5.3.3.2.3. Results

Outcomes and estimation

Data from the study concerning the indication for treatment of HHT patients presenting with severe liver damage with cardiac repercussions has been presented in in relation to the first indication.

For the indication treatment of HHT patients with severe haemorrhagic form, analyses were conducted in subpopulations of the data according to transfusion need, administration of i.v. iron and Hb during the period of 6 months before bevacizumab administration which are presented below.

Patients transfused 6 months prior to bevacizumab administration

In the transfusion-dependent population (received at least 1 RBC 6 months before bevacizumab administration), the median number of RBC units dropped from 11 in the 6 before first dose to 3 units in the 6 months after. (Figure 23)

To evaluate the stability of this effect 12 months after the first dose, 112 patients were identified with transfusion values recorded in the database up to this duration (Table 40). Data is also presented for subgroups concerning type of bleeding.

Figure 23. Within-subject comparison of the cumulative number of RBC units transfused 6 months prior first bevacizumab dose to 6 months after.

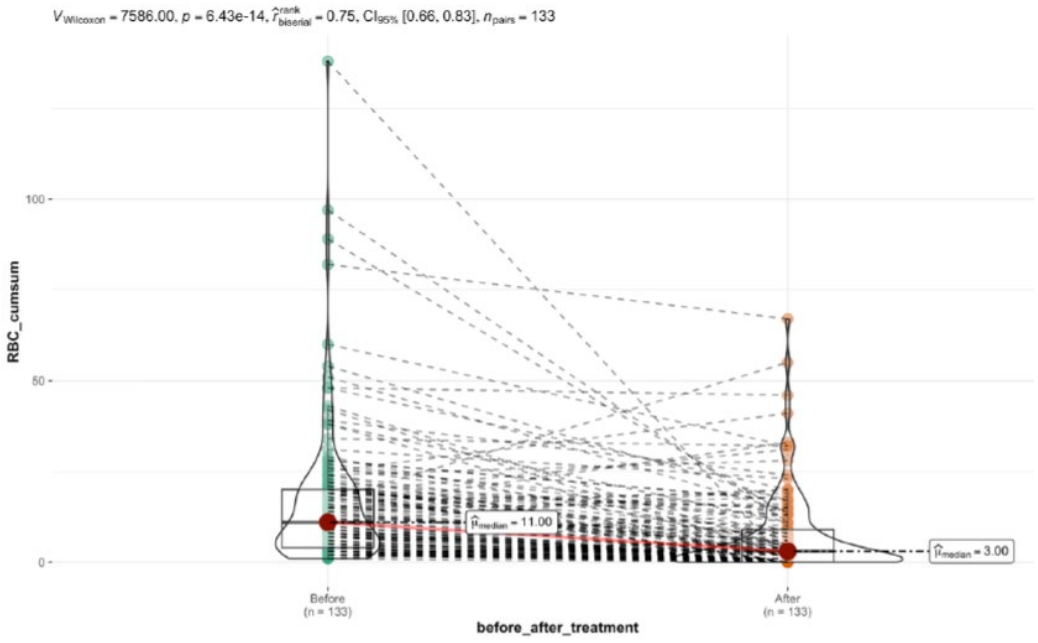


Table 40: Summary of transfusion needs 12 months after bevacizumab administration.

HHT Patients	Median RBC units transfused 6 months before first dose	Median RBC units transfused 6 months after first dose	Median RBC units transfused 6 months to 12 months after first dose	Median RBC units difference from baseline at M12 [95% CI]
All (n = 112)	12	3.5	2	-8.0 [-10.0 – -6.0]
Severe epistaxis-only subgroup (n = 57)	10	3	2	-6.0 [-8.5 – -3.5]
Digestive bleeding subgroup (n = 20)	9.5	3.5	2	-8.5 [-14.5 – -3.5]
Severe epistaxis and digestive bleed (n = 36)	18.5	3	4	-11 [-16.5 – -7.0]

Patients transfused or received IV iron 6 months prior to bevacizumab administration

Among the 203 patients having received a full induction, 152 received either RBC units or IV iron over the course of the 6 months prior to the first dose and had iron supplementation values recorded 6 months after. The analysis of this endpoint showed that the amount of iron infused dropped from 1.8 g to 0.4 g between the 6 months pre- and post-first dose, respectively. (Figure 24) To evaluate the stability of this effect one year after the first dose, 127 patients were identified with iron supplementation up to this duration. Data is also presented for subgroups concerning type of bleeding. (Table 41)

Figure 24. Within-subject comparison of the cumulative amount of iron infused 6 months prior first bevacizumab dose to 6 months after.

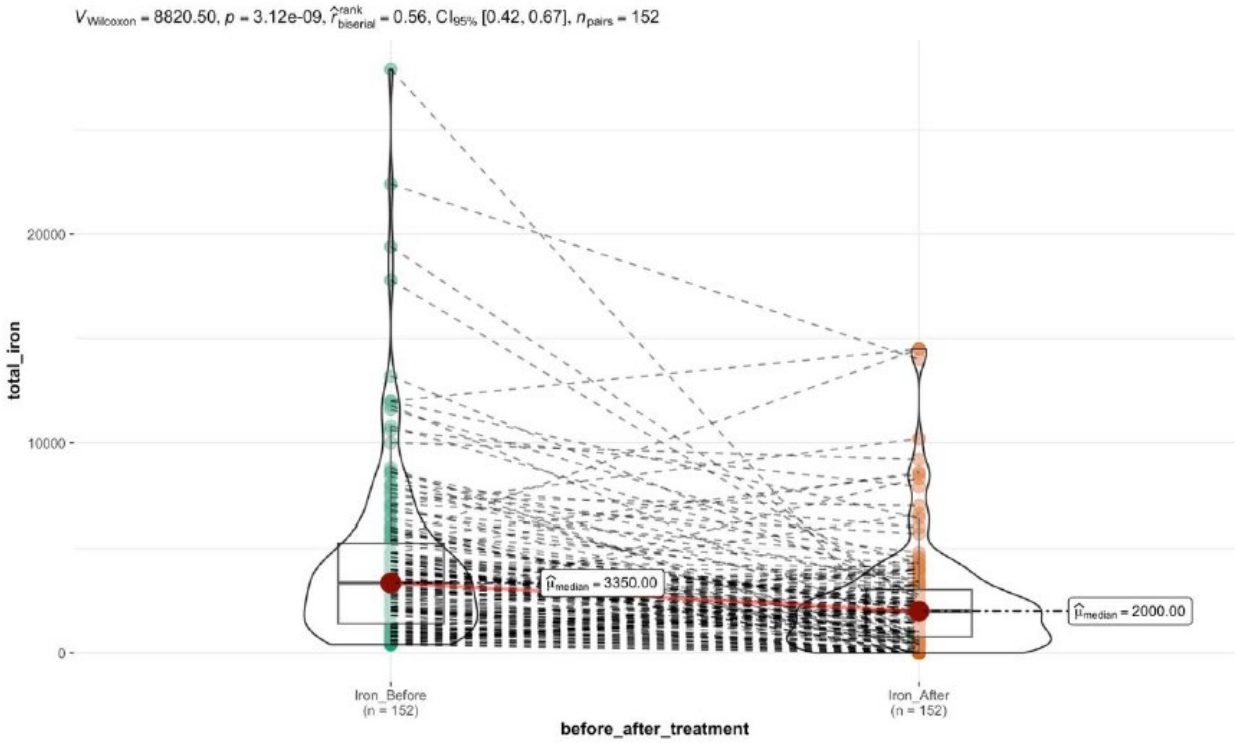


Table 41: Summary of bevacizumab effect on iron supplementation from HHT-RS1

HHT Patients	Median amount of iron (g) infused 6 months before first dose	Median amount of iron (g) infused 6 months after first dose	Median amount of iron (g) infused 6 months to 12 months after first dose	Median infused iron (g) difference from baseline at M12 [95% CI]
All (n = 127)	3.4	2.0	1.0	-1.8 [-2.2 – -1.4]
Severe epistaxis-only subgroup (n = 66)	3.0	2.1	1.0	-1.6 [-2.1 – -1.1]
Digestive bleeding subgroup (n = 19)	2.6	2.1	1.4	-1.4 [-2.7 – 0]
Severe epistaxis and digestive bleed (n = 37)	4.7	1.8	1.4	-2.7 [-3.9 – -1.7]

<u>Patients with Hb below 11 g/dL 6 months prior to bevacizumab administration</u>

The analysis of the treatment's effect on haemoglobin concentrations was carried out in patients with at least one haemoglobin measurement below 11 g/dL within the 6 months before the first bevacizumab dose (n=139). In these patients, haemoglobin levels significantly increased from an

average of 8.6 g/dL 6 months before to 10.4 g/dL 6 months after first dose. (Figure 25) To evaluate the stability of this effect up to 12 months after the first dose, 110 patients were identified with haemoglobin concentrations measured until then. Data is also presented for subgroups concerning type of bleeding. (Table 42)

Figure 25. Within-subject comparison of the average haemoglobin concentration 6 months prior first bevacizumab dose to 6 months after.

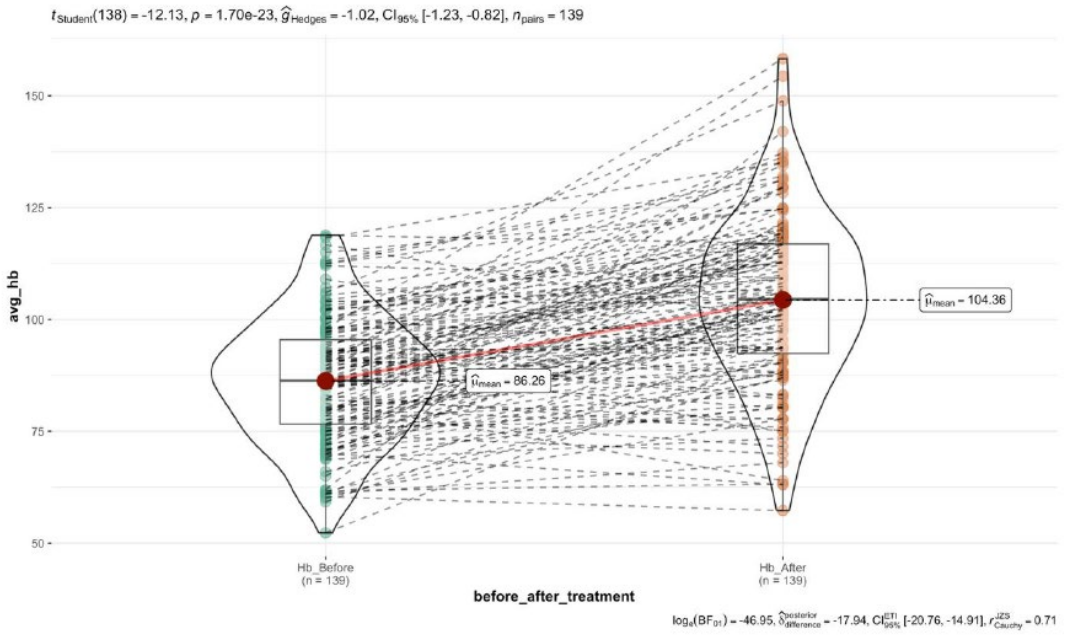


Table 42. Summary of bevacizumab effect on haemoglobin concentrations from HHT-RS1.

HHT Patients	Average hemoglobin levels (g/dL) 6 months before first dose	Average hemoglobin levels (g/dL) 6 months after first dose	Average hemoglobin levels (g/dL) 6 months to 12 months after first dose	Average hemoglobin difference (g/dL) from baseline at M12 [95% CI]
All (n = 110)	8.74	10.47	10.44	1.7 [1.3 – 2.1]
Severe epistaxis-only subgroup (n = 62)	8.92	10.40	10.60	1.7 [1.2 – 2.2]
Digestive bleeding subgroup (n = 14)	8.47	10.80	11.32	2.9 [1.1 – 4.6]
Severe epistaxis and digestive bleed (n = 32)	8.41	10.35	9.75	1.3 [0.6 – 2.1]

Effect on epistaxis

Among the 203 patients receiving at least one full induction course, only those with at least one frequency of epistaxis ≥ 3 within the 6 months period prior to first bevacizumab infusion have been included for the analysis of this endpoint (n = 95). Among these 95 patients, 21 patients did not have

any frequency of epistaxis evaluation after starting the treatment. Hence, these subjects were removed from this analysis. As shown in Figure 25, the median epistaxis frequency was 5 before the treatment. 6 months after the first bevacizumab's dose, this value dropped to 4.25.

To evaluate the stability of this effect up to 12 months after the first dose, 47 patients were identified with epistaxis frequency assessed until then.

Figure 26. Within subject comparison of the frequency of epistaxis 6 months prior first bevacizumab dose to 6 months after.

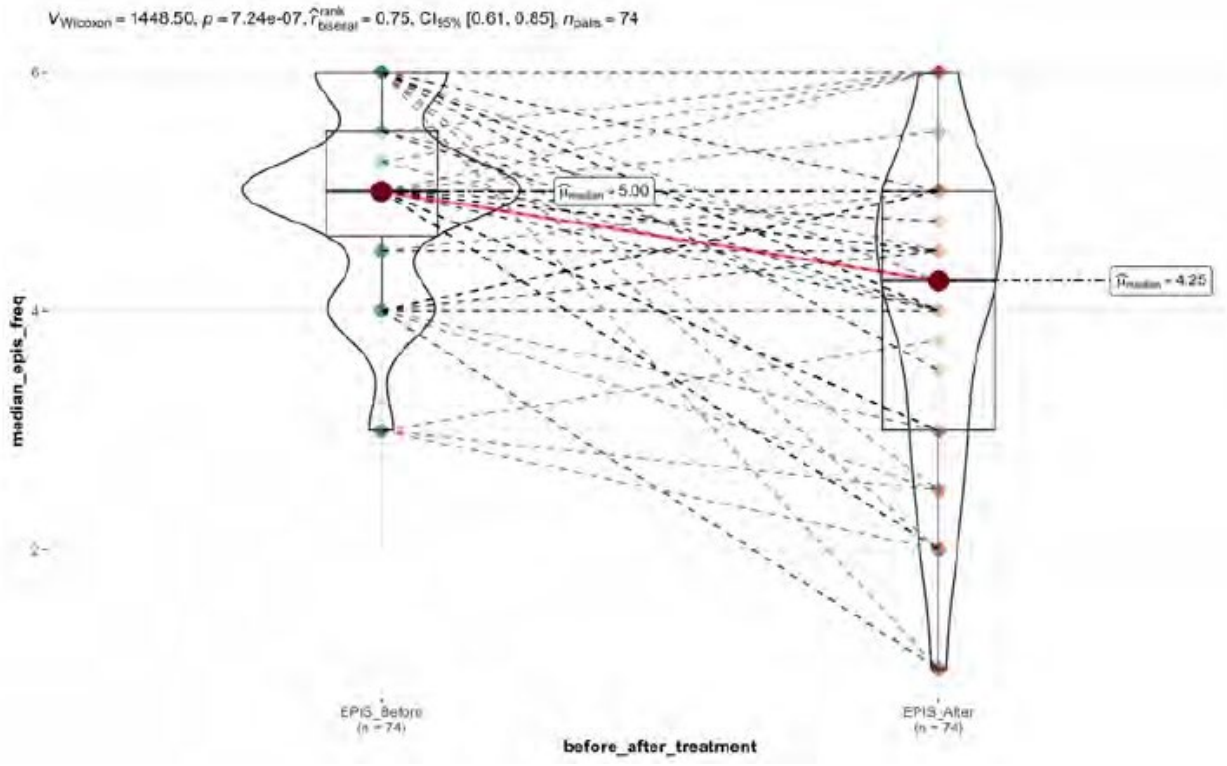
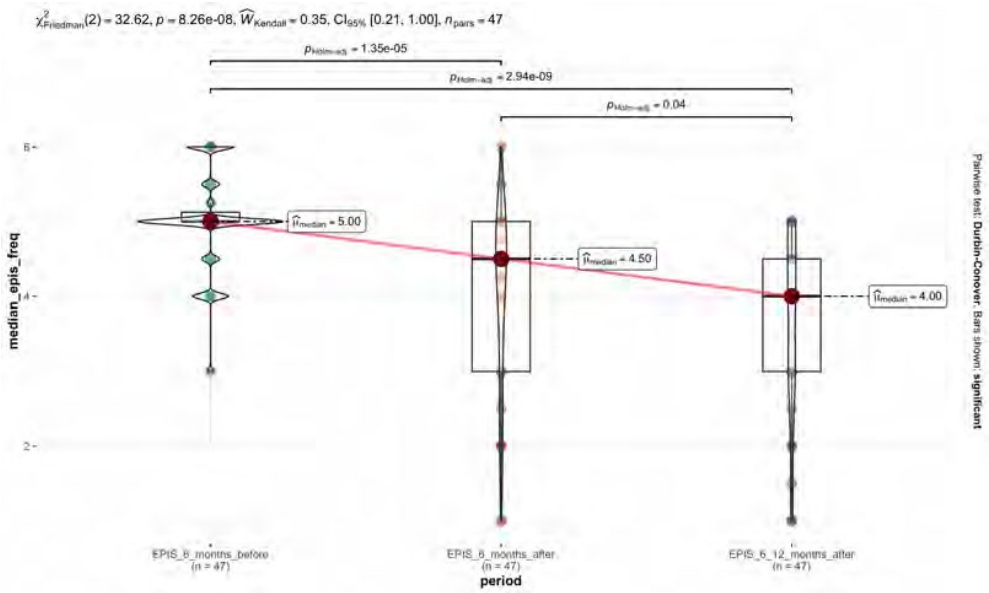


Figure 27. Within subject comparison of the frequency of epistaxis 6 months prior first bevacizumab dose to 6 months and 12 months after.



5.3.3.3. HHT-RS5 / InHIBIT-Bleed study (H. Al-Samkari et al.)

5.3.3.3.1. An international, multicenter study of intravenous bevacizumab for bleeding in hereditary hemorrhagic telangiectasia: the InHIBIT-Bleed study

The study was provided as a scientific article published in Haematologica 2021 (Volume 106(8):2161-2169)

5.3.3.3.2. Study design

This multicentre, retrospective study was approved by the Institutional Review Board of Partners Healthcare (approval 2016P002753/PHS). Nine centers in the USA and one center each in Argentina, Israel, and France participated in the study. All patients aged >18 years treated with systemic (intravenous) bevacizumab for HHT-associated bleeding (epistaxis, gastrointestinal bleeding, or both) from January 1, 2011 until May 1, 2019 were identified at each participating institution.

Treatment

Specific dosing protocols were institution dependent.

Randomisation and blinding

Not applicable.

Patient population

All patients aged >18 years treated with systemic (intravenous) bevacizumab for HHT-associated bleeding (epistaxis, gastrointestinal bleeding, or both) from January 1, 2011 until May 1, 2019 were identified at each participating institution. The study was conducted in nine centres in the USA and one centre each in Argentina, Israel, and France.

5.3.3.3.3. Objectives and estimands

Primary objective

Not applicable.

Estimands for the primary objective

Not applicable.

Statistical methods for estimation and sensitivity analysis on primary estimand<s>

Analyses

Baseline hemoglobin concentration and ESS were compared with on-treatment mean values using the paired *t*-test. Pretreatment RBC transfusion and iron infusion requirements were compared with on-treatment values using the Wilcoxon signed-rank test. To estimate the change in each outcome measure over time on treatment utilizing a method robust in the setting of missing data, a mixed effects linear model with a random intercept was also used for each outcome measure.

Missing data

Missing data were not imputed. For comparisons of means or medians, if the baseline or at least one on-treatment value for a given patient was not available, that patient was omitted from analysis of that particular outcome.

Sample size, error probabilities

No information regarding sample size determination, error probabilities and multiplicity adjustments are outlined in the publication.

Subgroup analyses

For genotype subgroup analysis, the treatment effect (difference between baseline/pretreatment values and on-treatment values) for each effectiveness measure was compared between subgroups using the two-sample t-test (Hgb and ESS) or the Mann-Whitney U test (RBC transfusions and iron infusions).

5.3.3.3.4. Results

Participant flow and numbers analysed

No information on participant flow was provided in the publication. Data was divided into different subsets for the assessment of the endpoints. The number of patients in each subset was determined by data availability for that parameter.

Baseline data

Two hundred fifty-seven HHT patients were treated with systemic bevacizumab for epistaxis, gastrointestinal bleeding, or both for the purpose of alleviating bleeding and consequent iron-deficiency anaemia at the 12 participating centres during the study period. After 19 patients had been excluded because of inadequate chart data (missing baseline data or incomplete bevacizumab dosing information), 238 patients were included in the data analysis. Table 43 lists the patients' baseline characteristics. Patients were treated for a median of 12 (range, 1-96) months, receiving a median of 11 (range, 1-74) infusions of intravenous bevacizumab. This totalled 343.9 patient years of systemic bevacizumab treatment of HHT-associated bleeding in the cohort.

Table 43. Baseline characteristics of 238 patients with hereditary hemorrhagic telangiectasia treated with bevacizumab for chronic bleeding and iron deficiency anaemia.

Characteristic	Value
Age (years), mean (range)	63 (29-91)
% Female	62
% Definite HHT by Curaçao criteria[a]	97
Genetic mutation (HHT subtype)[a]	*ENG* (HHT-1): 52 (22%) *ACVRL1* (HHT-2): 92 (39%) *SMAD4* (HHT-JPS): 4 (2%) Other pathogenic HHT mutation: 6 (3%) Mutation not identified: 4 (2%) Genetic testing not done: 80 (34%)
Baseline GI AVM and prior treatments	Known upper GI AVM: 148 (62%) Known lower GI AVM: 47 (20%) Received local endoscopic hemostatic treatments: 119 (50%)
Baseline comorbidities relevant to bevacizumab treatment	Hypertension: 67 (29%) Chronic kidney disease: 14 (6%) Diabetes mellitus: 20 (9%) High-output heart failure: 32 (14%) Prior venous thromboembolism: 27 (11%)
Primary bleeding source	Epistaxis: 99 (42%) GI bleeding: 46 (19%) Both epistaxis and GI bleeding: 93 (39%)
Mean baseline hemoglobin (95% CI)	Treated for anemia (baseline Hb <11) (N=197): 8.6 g/dL (8.4, 8.8) All patients (N=232): 9.1 g/dL (8.9, 9.4)
Mean baseline epistaxis severity score (95% CI)	Treated for epistaxis (N=175): 6.75 (6.52, 6.99) All patients (N=213): 5.92 (5.60, 6.24)
Prior local hemostatic treatments for epistaxis	Any treatment: 182 (77%) Laser cautery: 118 (50%) Electrical or chemical cautery: 112 (47%) Nasal septodermoplasty: 38 (16%) Nasal sclerotherapy: 58 (24%) Nasal embolization: 21 (9%) Bevacizumab nasal spray: 26 (10%) Septal bevacizumab injection: 23 (9%) Nasal closure (Young's procedure): 9 (4%)
Prior nasal septum perforation (%)	32 (13%)

[a]The Curaçao criteria are used to establish the diagnosis of hereditary hemorrhagic telengiectasia (HHT); the presence of three or four out of four criteria denotes "definite HHT", while the presence of two out of four criteria signifies "possible HHT". Genetic testing is not required for a diagnosis of HHT but is done to identify HHT subtype. 95% CI: 95% confidence interval; GI, gastrointestinal. AVM, arteriovenous malformation. JPS, juvenile polyposis syndrome.

Two hundred twenty-one patients (93%) began treatment by receiving 4-6 induction infusions of bevacizumab 5 mg/kg administered every 2 weeks; 46 (19%) also received an additional four induction infusions administered every 4 weeks. Induction courses typically lasted 2-4 months but never extended beyond 6 months.

A total of 181 patients received maintenance treatment, which was defined as additional bevacizumab doses administered to prevent or treat recurrent bleeding after completion of the initial induction infusion course. These maintenance doses were administered using one of two different protocols. The majority of patients (n=136) received continuous maintenance, defined as bevacizumab administered on a regular schedule every 4-12 weeks. The remainder (n=45) received intermittent maintenance, defined as retreatment only following recurrence or worsening of bleeding symptoms or anaemia, with one to four doses administered every 2 weeks once the need for maintenance was triggered. Ninety-two percent of patients were given maintenance doses of 5 mg/kg per infusion (regardless of maintenance schedule) but doses of 1, 2.5, 3, and 7.5 mg/kg were also used occasionally. Compared with the relatively universal induction dose intensity of 10.0 mg/kg/month, mean maintenance dose intensity was 4.0 mg/kg/month in patients receiving continuous maintenance and 3.0 mg/kg/month in patients receiving intermittent maintenance.

Outcomes and estimation

Effect on haemoglobin concentration

Of the 197 anaemic (Hb <11 g/dL) patients treated, 185 patients had been treated for ≥3 months and were included in the haemoglobin analysis (Table). In the evaluation of on-treatment mean haemoglobin, freedom from anaemia (Hb ≥11 g/dL) was observed in 67% (n=123/185) of patients. In the evaluation of haemoglobin values at each time point, freedom from anaemia was observed in 64% of patients at 3 months, 73% at 6 months, 76% at 9 months, and 71% at 12 months.

Effect of bevacizumab on Epistaxis Severity Score

Of the 175 patients treated for epistaxis with complete ESS data available, 146 patients had been treated for ≥3 months and were included in the ESS analysis (Table).

Effect of bevacizumab on red blood cell transfusion

A total of 191 patients who had been treated for ≥6 months had complete RBC transfusion data available and were included in the RBC transfusion analysis. (Table).

In an analysis of only those patients who required RBC transfusion in the 6 months prior to treatment (n=137), the median number of RBC units transfused decreased from 9.0 (IQR, 5.0-16.0) in the 6 months before treatment to 0.0 (IQR, 0.0-2.0) in the first 6 months after treatment (P<0.0001); 80/137 patients (58%), were RBC transfusion- free. There was maintained and continued reduction into the second 6 months of bevacizumab treatment (median of 0.0 units, IQR 0.0-0.0; P=0.0005), with 97/121 (80%) being RBC transfusion-free.

Effect of bevacizumab on iron infusion

A total of 183 patients who had been treated for ≥6 months had complete iron infusion data available and were included in the iron infusion analysis. (Table 44).

In the analysis of only those patients who received iron infusion in the 6 months prior to treatment (n=155), median number of iron infusions decreased from 8.0 (IQR, 3.0-20.0) in the 6 months before treatment to 2.0 (IQR, 0.0-5.0) in the first 6 months after treatment (P<0.0001); 48/155 (31%) patients were iron infusion-free. There was a maintained and continued reduction into the second 6 months of bevacizumab treatment (median of 0.0 units, IQR 0.0-3.0), with 84/138 (61%) patients being iron infusion-free.

Table 44. Impact of bevacizumab on hemoglobin, Epistaxis Severity Score, red blood cell transfusions, and iron infusions over the first year of treatment.

Outcome	Hemoglobin and Epistaxis Severity Score Baseline	3 months	6 months	9 months	12 months	Mean on treatment	Baseline vs. mean on treatment, mean difference (95% CI)
Hemoglobin (g/dL), mean (95% CI), baseline anemia (Hb<11 g/dL) (n=185)	8.6 (8.5, 8.8)	11.6 (11.3, 11.9)	12.1 (11.8, 12.4)	12.0 (11.7, 12.4)	12.1 (11.7, 12.4)	11.8 (11.5, 12.1)	+3.2 (2.9, 3.4) *P*<0.0001*
Epistaxis Severity Score, mean (95% CI), treated for epistaxis (n=146)	6.81 (6.56, 7.06)	3.84 (3.49, 4.18)	3.02 (2.73, 3.31)	3.07 (2.70, 3.45)	3.22 (2.81, 3.62)	3.44 (3.17, 3.71)	-3.37 (-3.69, -3.05) *P*<0.0001*

Outcome	RBC transfusion and iron infusion 6 months pretreatment	First 6 months on treatment	Second 6 months on treatment	Pretreatment vs. on treatment, median difference (95% CI)
RBC transfusions, units, median (interquartile range) (N=191)	6.0 (0.0-13.0)	0.0 (0.0-2.0)	0.0 (0.0-0.0)	6 months pretreatment *vs.* 1st 6 months on treatment: -4.0 (-6.0, -3.0), *P*<0.0001† 1st 6 months on treatment *vs.* 2nd 6 months on treatment: 0.0 (0.0, 0.0), *P*=0.0005†
Iron infusions, median (interquartile range) (N=183)	6.0 (1.0-18.0)	1.0 (0.0-4.0)	0.0 (0.0-2.0)	6 months pretreatment *vs.* 1st 6 months on treatment: -4.0 (-6.0, -1.0), *P*<0.0001† 1st 6 months on treatment *vs.* 2nd 6 months on treatment: 0.0 (0.0, 0.0), *P*<0.0001†

*By a paired *t*-test. Normality for hemoglobin and Epistaxis Severity Score data confirmed with the D'Agostino and Pearson test. †By the Wilcoxon signed-rank test. 95% CI: 95% confidence interval; ESS: Epistaxis Severity Score; RBC: red blood cell.

5.3.4. Clinical studies in special populations

Not applicable for biosimilars.

5.3.5. In vitro biomarker test for patient selection for efficacy

Not applicable.

5.3.6. Supportive studies

None

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

Not applicable

5.3.8. Observational data/Data from registries

The Cobevaro and the Inhibit Bleed registry studies are presented under 6.3.2 and 6.3.3 in relation to the other studies for the respective sought indications.

5.3.9. Overall discussion and conclusions on clinical efficacy

5.3.9.1. Discussion

The application is based on efficacy data from three proprietary clinical studies; the phase II HHT-PS1/Metafore study, a single arm study in patients with severe hepatic forms of haemorrhagic telangiectasia (HHT), the phase II HHT-PS2/BABH study, a randomized study in patients with haemorrhagic form of HHT and the HHT-RS1/Cobevaro study, a retrospective registry study on

patients with HHT. In addition, the proposed SmPC contains data from two scientific publications. The study by Chavan et al 2017 reports data from a single-arm prospective study in patients with hepatic form of HHT whereas the study by Al-Samkari et al 2021 reports data from a retrospective registry study in patients with haemorrhagic forms of HHT. Orblid contains the same monoclonal antibody as an authorized biosimilar to Avastin, and biosimilarity between these products were supported by the Phase 3 CT-P16 randomized controlled study. This study was included in the current application but given that it has been previously assessed within the MAA, it is not further assessed in the current application.

The proposed SmPC aims at two separate sub indications for patients with HHT:

(i) severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnea despite well-conducted cardiological medical treatment and/or

(ii) a severe hemorrhagic form (epistaxis and/or digestive bleeding) of the disease with dependence on transfusions and/or intravenous iron.

The two main clinical studies, BABH and METAFORE, was conducted with Avastin. However, as Orblid contains the same monoclonal antibody as an already authorized biosimilar to Avastin (in the treatment of various solid tumours in adult patients), the use of Avastin in these studies is considered acceptable, and that results can be extrapolated to Orblid.

Dose selection

No dose finding studies have been conducted for the applied indication. During previous CHMP advice it was concluded that in the absence of dedicated dose finding studies in the target indication, a clear benefit for patients should be evident from the data available from both clinical studies as well as bibliographic data in support of the desired dosing schedule in HHT patient. As previously discussed in this report, no additional support is available from PKPD modelling.

Concerning the induction dose, the scheme used in the Metafore and the BABH studies is in line with the proposed posology, i.e. 5 mg/kg per infusion, every two weeks for a total of 6 infusions (total duration 12 weeks). Data reflecting clinical practice is available from the registry studies. In the Cobevaro study, a full induction dose was defined as 4-6 injections with a duration of 10-16 weeks. 92% of doses administered in the study was 5 mg/kg. In the Inhibit bleed study, 93% of participants received an induction dose of 4-6 administrations of 5 mg/kg every 2 weeks. This proposed posology is also in line with the guidelines from the European Reference Network for Rare Vascular Diseases (VASCERN) which states that based on published data, a dosage of 5 mg/kg body weight at 14 day–21 day intervals is recommended.

For the maintenance dose, the rationale is not fully clear, and the applicant is requested to justify the proposed dosing scheme.

According to the CHMP Scientific Advice dated 2015 (EMEA/H/SA/3153/1/2015/PA/II) on the BABH study design, the Applicant intended to investigate the efficacy of the induction phase and the maintenance phase by including two distinct parts in the study.

As stated by the CHMP in the Scientific Advice dated 2023 (EMA/SA/0000133895), available data at that time suggest that most HHT patients relapse 9 months to 2 years after the end of treatment. Considering also the safety profile, there is a need on one hand to demonstrate the maintenance of the efficacy and on another hand to search for a dosing strategy allowing a minimal exposure compatible with the maintenance efficacy and an acceptable safety profile.

In the Cobevaro study, among the 140 patients receiving maintenance doses of bevacizumab, 25 patients received more than 1 induction course before starting on maintenance, and 44 still needed

induction doses after starting on maintenance. This tends to show heterogeneity in the maintenance of the clinical response. It is acknowledged that Bevacizumab maintenance dosing in HHT has evolved as clinical experience has grown. As a result, the multiplicity of possible induction and maintenance schedules (and their dosages) in the Cobevaro study makes the analysis very complex and unclear. If the maintenance phase therapy is necessary to sustain the treatment effect over time, the dose as well as frequency of the injections (between once a month or every 2 or 3 months) need to be further characterized (MO).

The proposed dose for maintenance phase relies mainly on the InHIBIT-Bleed study (Al-Samkari and al. 2021) and the BEST study (Dupuis-Girod and al. 2025). The InHIBIT-Bleed study was conducted in 9 centres in the USA and one centre each in Argentina, France and Israel. The majority of patients (136) received continuous maintenance defined as bevacizumab administered on a regular schedule every 4-12 weeks. The remainder (45 patients) received intermittent maintenance defined as retreatment only following recurrence or worsening of bleeding symptoms or anaemia, with one to four doses administered every two weeks once the need for maintenance was triggered. Ninety-two percent of patients were given maintenance doses of 5 mg/kg per infusion. Results suggest no significant differences in RBC transfusions between patients receiving continuous scheduled bevacizumab maintenance and those receiving intermittent (as-needed) bevacizumab maintenance.

The BEST study, conducted in France, was a descriptive study regarding a one-year follow-up of the BABH study. In the BABH study, patients received six infusions of treatment 14 days apart and then stopped the treatment and had a 3-month follow-up before their inclusion in the BEST study. The treatment modalities for the BEST study were decided by each centre, but the national consensus is 5 mg/kg every month or 2 months as maintenance therapy in most patients. In total, 22 patients were included in the BEST study; six of the 11 patients initially in bevacizumab group and nine of the 12 patients who received the placebo in the BABH study were treated with bevacizumab alone in the 12-month follow-up period (15 in total). Of these 15 patients, only 3 subsequently received at least one injection of maintenance treatment (initially every 2 months, with frequency adapted to clinical improvement).

Overall, the InHIBIT-Bleed study and the BEST study remain purely descriptive cannot allow to conclude on long term efficacy and dosing and frequency strategies, and thus cannot support the proposed posology in the SmPC. Moreover, there are questions on the need of dose adjustments based on the measure of residual concentrations of bevacizumab (**MO**). Furthermore, the applicant is requested to clarify the statement in the SmPC concerning "minimum" dose of 5 mg/kg every two months, as well as clarify to the prescriber how the frequency of administration could be increased in patients with inadequate response as proposed in the SmPC. (**OC**)

The clinical study data concerning each indication is discussed separately under the respective sections below.

HHT with severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnea despite well-conducted cardiological medical treatment

HHT-PS1 / Metafore Study

The Metafore study is a single centre, phase 2, prospective, uncontrolled, open label study evaluating bevacizumab in patients with hepatic arteriovenous malformations (AVM) and cardiac repercussions of high output cardiac failure (HOCF), a known comorbidity in HHT. HOCF is a complication in HHT leading to invasive interventions such as hepatic artery embolization or liver transplantation. Medical management to postpone or elude such procedures are desirable goals. Previous studies show

significant variations in the clinical picture over time due to natural variations as well as guideline recommended common treatments (Garcia-Tsao, NEJM, 2000)

The study is composed of a treatment period of 3 months followed by 9 months of follow-up. The screening visit could occur from 2 days to 60 days before inclusion. Bevacizumab was administered within the hospital departments as an intravenous infusion at the dose of 5 mg/kg once every 14 days, with a total of 6 injections.

Results

25 patients were included and received the first dose of bevacizumab, and 24 completed the whole study protocol. 1 patient left due to personal reasons after the first injection but were retained in the analysis and considered a failure. The female to male ratio is 24/1, which does not reflect the prevalence of quite equal distribution among sexes in HHT and might impact the generalisability of the study data. As patients according to guidelines should receive optimal heart failure medication, the applicant should provide medications at baseline, as well as medications started during the study (**OC**).

The primary objective of the study was to test the efficacy of bevacizumab on decreasing cardiac output in patients with severe hepatic involvement in HHT. The applicant considers the treatment to be effective if a partial (decrease without normalization of the cardiac index) or complete (decrease with normalization of the cardiac index) response is observed at 3 months after the start of the study. 80% (20/25) of the population displayed either a partial or complete response (reduction of cardiac index) at 3 months. 12% (3/25) of patients displayed complete response and 68% (17/25) partial response. Mean values for cardiac index (CI) was lower than pre-treatment throughout the study but was slightly higher at the last measurement (12 months). The protocol however lacks definitions of partial and complete responses, which is problematic as set criteria of elevated level in many circumstances would be considered normal as well as due to the natural variation in the measurements. As the normal values of CI is accompanied with a wide variation due to factors not associated with pathologic conditions, and the set limits in the study are not justified by international consensus for pathologic circulation, its validity in determining treatment success is questioned (**MO**).

The majority of patients were in NYHA class II at baseline (64%), 4% in class I and 32% in class III. In general, the NYHA class improved slightly during the study. The most pronounced response was noted 6 months after administration where 64% patients displayed an improvement compared to baseline. Cardiac doppler evaluation of the hearts were in general consistent during the study.

As increased CI is not an established endpoint for high output heart failure, HHT guidelines recommend invasive investigations to establish pathological conditions. In these trials, no validations have been made to confirm established heart failure.

The secondary endpoint on BNP change is not reported. No significant changes were seen on hepatic CT or ultrasound nor in hepatic blood samples.

The number of episodes of epistaxis and their duration were reduced during the study, the effect was most pronounced at month 6 where 75% of patients displayed an improvement of 30%. The total average monthly duration was 57 vs. 252 minutes. There was no effect on transfusions compared to pretreatment. The study did not specially recruit anaemic patients. Mean haemoglobin values were stable during the study.

In a single arm study, the primary endpoint cannot be reached due to natural variations or concomitant treatments other than the one studied according to the EMA reflection paper on single arm trials. In this case, it is not clear whether concomitant heart failure medications were present, optimised or changed during the study. It is also not clear if the changes in measured CI could be an

effect of natural variations in the underlying condition. This makes it impossible for to assess the effect of bevacizumab in the present study (**MO**).

Statistical considerations

Partial response for the primary endpoint cardiac index (CI) is defined as any decrease in CI. According to the EMA Reflection paper on establishing efficacy based on single-arm trials (EMA/CHMP/458061/2024), observations of the desired outcome should be known to occur only to a negligible extent in the absence of an effective treatment. The applicant has not defined a size of the decrease, why a response for the primary endpoint may occur due to the variability mentioned above **(MO)**.

The primary endpoint of the success rate at 3 months was presented together with a 95% exact confidence interval (Fleiss). Additional secondary endpoints were also presented descriptively. Comparative tests (paired Wilcoxon test or mixed models) were carried out to study evolution of these parameters over time. The p-values for these tests are considered nominal, since the study lacks type I error-control for both primary and secondary endpoints (See below).

The applicant states that the sample size calculation was based on the assumptions of treatment effect of 30% and a power of 90%. Gehan's design was applied in the study, meaning that the outcome was planned to be evaluated at two stages. In the first stage futility was evaluated. This step was planned to be performed for the first 7 patients included in the study. Given that the first stage did not conclude futility based on the pre-determined criteria, the result from the first stage was used to inform the sample size for the final analysis. This approach might result in overestimation of the treatment effect and an inflated type I error **(MO)**. The first stage was evaluated in terms of futility for the first 5 patients instead of for the first 7 patients as pre-defined. However, it appears that the second stage was informed from the result of the analysis of the first 7 patients. Besides the above-mentioned assumptions for the sample size calculations, the precision percentage (standard error) retained (10%) and the number of successes observed during the preliminary phase was used to determine the sample size for the second stage. However, since the primary endpoint is a descriptive measure, the applicant is not asked to provide any additional information regarding the methods and assumptions related to the determination of the sample size for the final analysis.

The primary endpoint is descriptive, and no statistical hypothesis is formulated. Furthermore, all secondary endpoints were not explicitly stated in the statistical methods section. The secondary endpoints were not hierarchically ordered or type I error controlled. The mixed models applied were not pre-defined and are therefore considered exploratory. Hence, the results are considered descriptive and any presented p-value nominal.

Missing data were not replaced. However, the one patient who withdrew from the study after the 2nd injection for personal reasons was imputed as a failure in the analysis. This approach is considered conservative and hence accepted.

The study protocol was only provided in French, as was the statistical analysis plan, which was included as a statistical methods section in the protocol. If a separate Statistical Analysis Plan (SAP) exists, the applicant is asked to submit (all versions) of this document in English **(OC)**.

HHT-RS1 / CoBevaRo study

The HHT-RS1 /CoBevaRo is a retrospective study of data from the CIROCO registry of French HHT patients treated with Avastin or biosimilars between 2009 and 2023. This study is based on the secondary use of real-world data originally collected in routine clinical practice, not specifically for research purposes. Among the 6,351 patients recorded in the CIROCO database, 249 patients were identified as having received bevacizumab. Subsequently, twelve patients were excluded from analysis

as they met exclusion criteria. Out of the remaining 237 patients, 203 had received at least one full induction course and were retained for analysis.

It is noted that the data from the CoBevaRo study that is used by the applicant to support efficacy claims were secondary endpoints, whereas the primary endpoint of the study was to provide descriptive data on bevacizumab prescriptions.

The cutoff in CI is set to > 3.9 l/min/m² in men and 3.6 l/min/m² in women. There is no international consensus on the normal range of CI, but 3.5 L/min/m2 with a SD of 0.7 is a common estimate. This means that the cut-off values in this study may well fall within the normal range. There is also no definition set in terms of size of decrease in cardiac index that is considered beneficial partial decrease. The applicant is requested to clarify and also discuss the validity of measurements of CI in this retrospective registry study as many factors, such as sonographer and settings, are known to greatly influence the results (**OC**).

The data indicates an effect on lowering CI during the initial 6 months after treatment, but a relapse with increasing CI from assessment month 6 to month 12. As the definitions of treatment success on outcome variables are questioned and the efficacy populations are highly selected, no clear conclusion can be drawn on a possible treatment effect. The non-controlled evaluation of cardiac index measurements inflicts on the results as echocardiography is heavily dependent of the examiner/interpreter.

As previously discussed in relation to the Metafore study, the cardiac index, used to evaluate high output cardiac failure is not a validated endpoint for cardiac morbidity and is associated with high variability. The treatment success, as determined by changes in cardiac index, is therefore questionable (**MO**). Additionally, the non-blinded and non-controlled nature of the studies, with a single arm-design, makes it difficult to isolate the treatment effect of bevacizumab from other therapeutic interventions that may have occurred during the studies. (**MO**)

Statistical considerations

No statistical hypotheses are defined. The applicant claims to account for the Type I error inflation due to the multiplicity of comparisons by adjusting p-values using the Holm method. However, this is performed for the mixed model analyses only. The specifications, in terms of included variables, for the mixed effect models are not stated in the protocol. Hence, these analyses are considered exploratory.

Registry-based studies are associated with certain limitations in terms of the ability to isolate a possible treatment effect. Patients are considered likely to have received bevacizumab treatment when they had an increase in symptoms. Due to the likely increase in symptoms before initiating treatment, a regression towards the mean in the outcome is expected **(MO)**.

Further, the efficacy analysis populations are highly selected. The database, on which the study is relies, is according to the applicant estimated to cover 52.5% of the HHT population in France. Of 6,351 records screened, 249 adults received at least one dose of bevacizumab for HHT. Twelve were excluded, yielding a final cohort of 237 patients. From the 237 identified patients, the ones included in the efficacy analyses are limited to the 203 with at least one full induction course. The number of patients included in the different analyses varied depending on the availability of relevant baseline and post-treatment data for each endpoint, which resulted in the following number of patients evaluated for the different efficacy endpoints: 135 (red blood cell transfusion), 154 (IV iron supplementation), 143 (haemoglobin concentrations), 63 (cardiac index measurements), 95 (epistaxis frequency). However, 26 out of 237 (11%) patients in the cohort, and 26/63 (40%) of patients with a CO measurement after treatment is evaluated for the effect of bevacizumab on high output cardiac failure.

For the twelve months evaluation, 13/237 (5%) was included in the analysis. This lapse of subjects cannot be controlled nor adjusted for in the analysis. **(MO).**

The statistical methods used in the study are summarised in the clinical study report. However, no Statistical Analysis Plan (SAP) has been provided by the applicant and the statistical considerations as outlined in the study protocol are very limited. The applicant is asked to submit the SAP (all versions) if a SAP exists **(OC)**.

HHT-PS4 (CHAVAN et al. 2017)

The HHT-PS4 /Chavan et. al is a single-centre, non-blinded and non-controlled prospective study of 21 patients conducted between October 2010-April 2016. The study was included in the submission as a scientific article and not further presented in the application but data from the study is presented under section 5.1 of the SmPC.

All HHT patients with symptomatic hepatic involvement requiring invasive therapy were considered eligible. The hypothesis is that systemic bevacizumab therapy alleviates liver related pain and cardiac overload, thus obviating the need for invasive treatment of liver damage.

The primary objective in HHT-PS4 /Chavan is to evaluate changes in the grade of abdominal pain, cardiac output and the New York Heart Association (NYHA) stage before and three months after bevacizumab treatment, which we consider is of an exploratory kind. The secondary endpoints included the epistaxis response to therapy, the change in haemoglobin after therapy, the necessity for repeated therapies, and the safety and tolerability of bevacizumab.

In HHT-PS4 /Chavan, cardiac output is used instead of indexing to body surface (cardiac index), which imputes further difficulties in interpretation and generalisability. Two patient reported outcomes (PRO´s) are used as primary study endpoints (NYHA and NRS), which are questionable methods in an uncontrolled study. No statistical cut-off on treatment effect on any of the outcomes are predefined. It is not stated in the eligibility criteria that patients should be optimised in heart failure medication before inclusion.

There are also no clear definitions on what treatment effects are regarded as endpoints valid to confirm the hypothesis.

In this prospective, single-arm, non-blinded trial, no presentation on participant flow, planned assessments or duration of treatment is presented. Baseline data are generally lacking in individual characteristics at baseline. No data on concomitant medications is provided.

Abdominal pain was a presenting symptom in 15 patients. The NRS grades pretherapy and post-therapy were 2–7 and 0–3 respectively. Mean pain grade improved from 3.0 ± 2.2 (95% CI 1.99–3.91) pretherapy to 0.9 ± 1.0 post-therapy (95% CI 0.48–1.33) ($P < .001$).

Cardiac output pretherapy ranged between 4.9 L/min and 19 L/min (mean 8.7 L/min ± 3.5) (95% CI 7.25–10.24). Following therapy, the mean value fell significantly to 6.5 L/Min ± 1.8 (95% CI 5.73–7.24) (range 4.3 L/min-10.0 L/min) ($P < .0008$). The fall in cardiac output was considered associated with an improvement in the signs and symptoms of cardiac decompensation as signified by the mean NYHA stage improving from 2.8 ± 0.7 (95% CI 2.49–3.13) pretherapy to 1.6 ± 0.9 (95% CI 1.25–1.99) post therapy ($P < .0001$). The authors conclude that these results demonstrate that abdominal pain as well as cardiac overload in HHT patients with severe hepatic involvement respond well to bevacizumab.

There are three endpoints, whereof 2 PRO´s, in this paper presented to prove efficacy of bevacizumab on liver damage.

According to the EMA reflection paper on single-arm trials, SAT, (EMA/CHMP/458061/2024) *If in a SAT individual outcomes for the planned endpoint are observed that could not occur without effective treatment within the designated follow-up period for any trial participant, the SAT is able to isolate the treatment effect on that specific endpoint.*

Three out of 21 patients needed hepatic arterial embolization and one of them additional liver transplantation during the trial. This indicates rejection of the trial hypothesis that bevacizumab in this cohort refutes from invasive treatment.

Statistical considerations

According to the applicant, the Chavan study lacks study protocol since the study is published as a letter to the editor. Hence, the study must be regarded explorative since no pre-planned analyses are defined. Further, the presentation of statistical considerations is very limited in the publication. Data is presented descriptively in terms of means and confidence intervals. A p-value is also presented for each endpoint, but no information regarding statistical test used. In addition, the use of patient-reported outcomes as primary endpoints is questioned as well as the lack of predefined cut-off for clinically relevant treatment effects and that no optimization of heart failure medication for patients before inclusion was performed. The trial's design and methodological limitations raise concerns about its ability to provide adequate evidence of efficacy, as stated by the EMA reflection paper on establishing efficacy based on single-arm trials (EMA/CHMP/458061/2024). These limitations challenge the ability to fully examine this study for evidence claims in the SmPC. (**OC**)

A severe hemorrhagic form (epistaxis and/or digestive bleeding) of HHT with dependence on transfusions and/or intravenous iron

HHT-PS2 / BABH Study

The BABH study was a prospective, multicentre, randomized, placebo-controlled, double blind phase II study. Six doses of bevacizumab (5 mg/kg) or placebo was administered every 14 days. The study, which was conducted in four expert centres in France, recruited HHT patients having required blood transfusions related to nosebleeds or digestive bleeding (at least 4 units of RBC in the 3 months preceding inclusion). The study is the sole controlled study supporting the application and is considered pivotal.

Methods

The treatment period consisted of a 6-month screening period and a double-blind 6-month period, including 10 weeks of treatments and 3.5 months of follow-up. The long screening period was designed to assess transfusion needs at baseline (see selection criteria), which appears appropriate as number of transfusions may be highly variable across patients (from less 1 time per months to more than 10-15).

In order to assess persistence of the effect and/or rebound effect, the double-blind period was prolonged 3 months after treatment termination. This 3-month duration is considered short given that the relapse after the treatment termination varies between patients (from a few months to a few years). It is noted that only efficacy of induction has been investigated in this study. However, a one-year follow-up study (BEST) have been conducted allowing patients from the placebo group to be switched to bevacizumab (please see further below the discussion on the BEST study) but no controlled maintenance study was conducted (**MO**).

There was no definition of a level of epistaxis severity score (ESS) in the inclusion criteria. However, considering that selection criteria required repeated blood transfusions related to nosebleeds or

digestive bleedings with at least 4 units of RBC in the 3 months preceding inclusion, the enrolled population can be reasonably defined as patients with severe HHT because they required repeated transfusions. It is however emphasized that patients with dependence to intravenous iron but without need of transfusion were not part of the study population. In that perspective the proposed indication appears too wide (**MO**).

While not clearly specified in the definition of the population, based on the selection criteria, naïve as well as already treated patients by Avastin were enrolled. Regarding this last subset, a 6-months washout following the last injection of Avastin was applied. The inclusion of already treated patients is understood; as it is a life-long disease, re-induction treatment phase or long-term treatment (if sufficiently demonstrated, see further below) can be expected in medical practice. As the persistence of the clinical effect to justify the duration of the washout from prior use of bevacizumab is not sufficiently discussed; this could impact the baseline frequency of haemorrhages calculated on the last 3 months before inclusion in the BABH study. The applicant is asked to discuss this point. Furthermore, the applicant is asked to justify the absence of wash out period regarding other prior therapies potentially used during the screening period in the BABH study (e.g. antifibrinolytics and anti-angiogenic treatments). No data on the history of treatment in the study was provided. The number of patients who received an anti-angiogenic treatment in the 6 months prior to inclusion in each group, and also individually, should be provided. (**OC**)

Also during the study, concomitant treatments necessary for management were allowed during all the study. Although this can be understood from an ethical point of view, the absence of criteria and guidance may challenge the interpretation of the efficacy results. Indeed, other anti-angiogenic treatment (e.g. pazopanib and nintedanib) or treatments for bleedings (e.g. tranexamic acid), anaemia or iron deficiency can have an impact on the risk of bleedings, haemoglobin and ferritin concentrations and iron perfusions. While the protocol mention that information was collected, no data are presented in the BABH study report. The use of concomitant medication during the treatment period and during the efficacy assessment period should be presented, and the impact on the interpretation of the efficacy outcomes need to be discussed. (**OC**)

The primary endpoint was the proportion of patients with a decrease by at least 50% of the number of red blood cell transfusions between the 3 months-period before treatment and the period from the 3rd to 6th months (N2) after the beginning of treatment. Interpretation of the reduction may vary depending on the severity of the patient's illness before treatment (the number of red blood cell transfusions in the 3 months before treatment varied between 4 and 52 across subjects).

The secondary endpoints include the assessment of the haemoglobin levels and the monthly epistaxis duration and frequency at Month 3 and 6. These two secondary endpoints are clinically relevant, but the epistaxis duration and frequency are assessed by the patients themselves and thus less objective.

The quality of life was also assessed with SF-36 score and ESS questionnaire. The choice of these PRO was supported in Scientific Advice (EMEA/H/SA/3153/1/2015/PA/II).

The provided study protocol for the BABH study mentions that data quality assurance is in place. However, no information on quality assurance step in place during and after the conduct of the study is provided, e.g. training, monitoring, data collection and analyses, and audits. The applicant is requested to provide additional information. (**OC**)

Amendment 1 was conducted during the study and included more precise definitions of the rules for counting the number of transfusions per period. The applicant is requested to provide more information on the change and discuss the possible impact on the assessment of the primary endpoint. (**OC**)

Results

80 patients were screened, and 24 patients were enrolled in the study (12 + 12 in the bevacizumab and the placebo group, respectively). More than 50% of screened failure may raise questions on the selection of the study population and how the results can be extrapolated to the general population. 35 of the 56 exclusions were due to met exclusion criteria. However, no further details are provided in the study report.

Patients were recruited in one country and 4 centres only which remains a limitation as the management of patients may vary across centres and countries.

The ITT analysis included 23 patients (12 in the placebo arm, 11 in the bevacizumab arm) instead of 24 patients, as initially defined (See statistical considerations below). The analysis should have included all randomized patients and the patient in the bevacizumab arm who exited the study prematurely because he was no-compliant (patient cancelled the 6-month visit and the replacement visit) should not have been withdrawn from the ITT analysis.

The PP (per protocol) population includes all patients who received at least 5 perfusions of the treatment being studied and who attended the end of protocol visit. In addition, to be analysed in this population, the patients had to have respected the perfusion protocol (14 days between two perfusions over a duration of 70 day +/- 14 days). Patients who underwent nasal or gastrointestinal surgery were excluded from this population. Overall, the PP analysis included 19 patients (11 in the placebo arm, 8 in the bevacizumab arm).

The baseline characteristics are overall well-balanced between the treatment groups; however GI bleedings were less frequent in the bevacizumab compared to the placebo group at baseline (17% [2 patients] vs. 67% [8 patients]). Data concerning nosebleeds and transfusion are scattered but may instead indicate more severe bleedings in the bevacizumab group. The applicant is requested to discuss the impact of these imbalances on the BABH study results. (**OC**)For the primary endpoint of treatment success, no significant difference was found between the bevacizumab and the placebo group (63.6% [7 patients] vs. 33.3% [4 patients], p=0.1451) in the ITT population. Also in the PP population there was no difference between the groups (62.5% [5 patients] vs. 36.4% [4 patients], p=0.3698). Explorative comparisons between the number of units transfused 3 months after the treatment revealed no significant differences between the groups.

The secondary endpoints were comparisons of haemoglobin and ferritin, comparisons of the durations and episodes of nosebleeds, the epistaxis severity score (ESS), the comparison of SF-36 scores, and the description of digestive bleeding and were conducted in the ITT population. No clear estimand were defined, and several statistical comparisons were conducted for each endpoint.

At 3 months after treatment, haemoglobin was higher in the bevacizumab vs. the placebo group (99.82 vs. 85.25 g/L, nominal p=0.0180). However, as most of the patients received blood transfusion during the study, the results on secondary endpoint of Hb levels are considered confounded. Furthermore, it not clear whether blood transfusions and iron administration followed defined rules, the applicant is requested to comment (**OC**). For ferritin, the scatter was high and there were no significant differences in ferritin between the groups.

For nosebleeds, there were no differences between the treatment arms in either duration or the number of episodes. The endpoints assessing the duration of epistaxis (total duration, mean duration) is not fully defined and the applicant is requested to clarify. (**OC**) Also, there were no differences in the ESS between the groups.

The data on the secondary endpoint concerning "The presence of digestive bleeding 6 months after the start of the treatment in patients who had such bleeding before inclusion" should be clarified and

provided in a summary table. The applicant should also discuss the reason for the imbalance regarding GI-bleedings prior to inclusion, with more bleedings in the placebo group. (**OC**)

The applicant has provided an explorative analysis on the treatment response in RBC units related to bevacizumab exposure below (or equal) or above the median exposure. The analysis indicated a more pronounced response in the small group of five patients with bevacizumab exposure above the median. However, as discussed in the Clinical Pharmacology section of this report, the analysis is highly uncertain and may rather be a chance finding.

In conclusion, the pivotal randomised controlled BABH Study failed to show a significant effect of bevacizumab on the primary endpoint, a reduction of 50% in the number of blood transfusions. Additionally, the results indicated no substantial differences in the number of transfusions between the groups. Given that the majority of patients underwent blood transfusions during the course of the study, the findings related to the secondary endpoint of haemoglobin levels are compromised due to confounding factors. Moreover, the parameters measuring secondary endpoints of nose bleeds did not show any consistent trends in in favour of bevacizumab, either. (**MO**)

Statistical considerations

Participants were randomised in a 1:1 ratio without stratification factors to either active treatment (bevacizumab) or placebo through the intermediary of an IWRS, based on a single randomisation list for all centres. To account for the variability in severity across patients at baseline, a stratification in term of number of transfusions would have been clinically relevant. But considering the very limited sample size, the absence of stratification is understood.

For the sample size calculation, it was assumed that 80% of the patients in the treatment group decreased the number of red blood cell transfusions by at least 50% versus 20% in the placebo group. An exact Fisher test with a bilateral significance level of 0.050 would have a power of 81% to detect the difference between a proportion in group 1 (p1) of 0.200 and a proportion in group 2 (p2) of 0.800 when the sample size in each group is 12. The assumptions of the sample size calculation, which imply an absolute treatment effect difference of 60%, lack empirical evidence or justification.

The primary endpoint of number of transfusions in units of red blood cells (RBC) was calculated for the 3-month period prior to the treatment and for the period from the 3rd month to the 6th month after the start of the treatment. Efficacy was considered acquired for a patient if the number of units of RBC decreased by at least 50% between these 2 periods. The primary analysis was to compare the percentage of patients with success in each group using the Chi^2 or the Fisher exact test. It was not clear from the protocol when Fisher exact test was to be used before Chi^2. It appears that the presented results are the result of the Fisher exact test. Changes in the analysis of the primary endpoint are not recommended.

The primary analysis was intended for the intent-to-treat (ITT) population, defined as all randomised patients who started treatment. Initially, the ITT definition included all randomised patients but was modified in Protocol Version 3 to include only those who started treatment. Changes in the analysis population for the primary analysis are in general not accepted. However, as all randomised patients received at least one injection, the point does not raise further concerns. Missing data handling rule for the primary endpoint was not described in the protocol or SAP, but only in the CSR where a patient with a missing response was excluded from the analysis, resulting in a complete-case approach **(OC).**

The statistical methods used in the study are summarised in the clinical study report which is also submitted by the applicant as a separate document named the Statistical Analysis Plan (SAP). The latest version of the SAP (version 1.3) is post hoc and must be regarded as potentially data driven, since it was finalised after unblinding of data. While the list of changes is documented in the SAP

version 1.3, the rationale for these modifications is not explicitly stated. Further, the timing of the amendments relative to the database lock and unblinding is unclear. The applicant is asked to provide all previous versions of the SAP, preferably with tracked changes, together with a rationale and timepoint for all changes **(OC)**. Furthermore, the first version of the study protocol has not been provided by the applicant. The applicant is asked to provide the first version of the study protocol **(OC)**.

The nosebleed grids were reported by the patients. Missing values for one day was replaced by the mean of the 4 values before and the 4 values after. The strategy was applied up to 10 consecutive days over a period of 3 months (84 days). If the missing values were consecutive, more than 10 days and less than 30 days, a daily average was calculated using the data available and multiplied by the number of days in the period. The applicant is asked to report the amount of imputed data for this endpoint separated by type of defined imputation and treatment **(OC).** Furthermore, if the missing data covered more than 30 days, the patient was excluded from the analysis for this nosebleed criterion. It appears patients have been excluded from other analyses as well. The applicant is asked to present the number of excluded patients together with an explanation on why data is missing for each endpoint by treatment **(OC)**.

HHT-RS1 / CoBevaRo study

As previously described in relation to the first indication, the HHT-RS1 / CoBevaRo study identified 203 patients receiving a full induction dose. For the second indication, further analyses in subpopulations are presented according to transfusion need, administration of i.v. iron and Hb during the period of 6 months before bevacizumab administration. The number of patients included in each subpopulation depended on data availability thus introducing selection bias.

For subset of patients receiving at least 1 RBC unit before bevacizumab administration (n=133), the median number of transfusions was lower during the 6-month period following administration compared to the 6-month period before (3 vs. 11 units).

Data on iron transfusions was analysed in the subset of patients either receiving RBCs or IV iron before bevacizumab administration (n=152). The median amount of iron infused was lower during the 6-months period following administration compared to the 6-month period before (2.00 g vs. 3.35 g).

In the subset of patients with Hb below 11g/dL prior to bevacizumab administration (n=139), the haemoglobin values were higher during the 6-month period following administration compared to the 6-month period before (10.4g vs. 8.6g/dL).

In a separate subset, patients with epistaxis before bevacizumab treatment were identified (n=74). The median epistaxis frequency was slightly lower in the 6-month period after treatment compared to the period before (4.25 vs 5).

In conclusion, the CoBevaRo study was a retrospective non-blinded, non-controlled study on data collected in routine clinical practice, not specifically for research purposes. It is considered likely that patients received bevacizumab treatment when they had an increase in the bleeding symptoms. The comparison against pre-treatment values is therefore problematic in the single-arm setting. The contribution of the natural variation of the disease over time is not known and a regression to the mean could have had a substantial influence on the measured outcome. The assessment was only conducted on patients with available data before/after treatment, introducing selection bias. Other therapeutic interventions that may have occurred during the studies to control the excessive bleedings further challenge any reliable estimation of the treatment effect of bevacizumab. Taken together, the possible treatment effect of bevacizumab in the studied HHT population cannot be estimated based on the study results. (**MO**)

Statistical considerations

The results from the CoBevaRo study presented for this indication are subject to the same methodological limitations as for the first indication. See discussion on this study under the first indication.

HHT-RS5 / InHIBIT-Bleed study

The retrospective registry study was conducted on data from nine centers in the USA and one center each in Argentina, Israel, and France. The retrospective study was only provided as a scientific article and was not further presented in the application although data from the study is presented under section 5.1 of the SmPC. The publication contains very limited information on study design. Data was divided into different subsets for the assessment of the endpoints. The number of patients in each subset was determined by data availability for that parameter.

Haemoglobin values (n=185) were higher in the period 3-12 months after bevacizumab administration compared to baseline (mean on treatment 11.8g/dL vs. 8.6 g/dL, nominal $p<0.0001$).

The epistaxis severity score (n=146) were lower during the treatment period 3-12 months after bevacizumab administration compared to baseline (mean on treatment 3.44 vs. 6.81, nominal $p<0.0001$).

The number of RBC transfusions after bevacizumab treatment were compared against the 6-month period preceding administration (n=191). The number of RBC transfusions were considerably lower during the 6 month period after treatment (median 0.0 vs. 6.0) , and was also lower up to 12 months after treatment.

The number of iron infusions after bevacizumab treatment were compared against the 6-month period preceding administration (n=183). The number of iron infusions were considerably lower during the 6 month period after treatment (1.0 vs. 6.0), and was also lower up to 12 months after treatment.

Similar concerns are raised concerning the InHIBIT-Bleed study as for the Cobevaro study. The single-arm setting and comparison to pre-treatment values are problematic, and the natural disease variation and regression to the mean may have significantly influenced the outcome. Data was selected based on availability introducing selection basis. The observed effect may have been confounded by the other treatments or procedures. No conclusions on the treatment effect of bevacizumab on HHT can be drawn from the study. (**MO**)

Statistical considerations

Since no protocol has been provided by the applicant, the pre-specified analyses for this study are not known. Data is presented descriptively in terms of means, confidence intervals and an associated p-value for each endpoint. The statistical tests used are described in the publication, but since no protocol for this study has been provided by the applicant, the validity of the results cannot be examined due to the lack of information regarding pre-planned analyses and other statistical considerations. The applicant is asked to provide the protocol and SAP if accessible **(OC)**.

Missing data were not imputed. For comparisons of means or medians, if the baseline or at least one on-treatment value for a given patient was not available, that patient was omitted from analysis of that particular outcome. Larger amount of missing data impact the possibility to interpret the results. The applicant should address these limitations **(MO)**.

5.3.9.2. Conclusions on the clinical efficacy

HHT with severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnea despite well-conducted cardiological medical treatment

Two proprietary single arm studies, of which one is prospective, and one is retrospective, are presented to support efficacy of bevacizumab to reduce liver damage, which is assessed via the secondary effect of high output cardiac failure. One prospective single arm study (HHT-PS4 / Chavan) provided as a scientific publication is also presented. The MAA states proven efficacy on the endpoints reduced cardiac index and the PRO of NYHA and NRS scale reduction. It is however considered likely that treatment was initiated at or near peak symptoms, as patients in the prospective study were pending liver transplantation and that bevacizumab according to guidelines are a last treatment resort. The presented scientific support is questionable to prove efficacy, and three major issues are identified:

1.The inclusion criteria were poorly defined:

In the present studies, no clear presentation is made on how the heart failure syndrome is validated. The relevance of Cardiac Index in high output heart failure is not well established in literature as the condition is rare. Cardiac output also has a wide normal variability, especially at above resting state. There are no international definitions on pathologic "supra normal" circulation, thus the presence of concomitant heart failure syndrome must be established. The international guidelines on diagnosis and management of HHT from 2020 does not include Cardiac Index as a diagnostic criterion of high output heart failure, but states its importance in clinical follow-up of hepatic AVMs and after heart failure syndrome is established.

The patients had very variable NYHA classification as baseline. NYHA classification is well established in clinical practise as a parameter for follow-up but has a low degree of reproducibility when used as a study outcome (Bennet et al, Heart & Lung, 2002). There are other standardised non-invasive assessments that are considered more valid in studies, such as the Framingham heart failure score or more objective measurements such as ergospirometry or 6-minutes walk test. Other measurements that are stated in the guidelines to evaluate progression of liver damage such as doppler ultrasound on hepatic veins as well as cardiac filling pressures and systolic pulmonary artery pressure failed to show improvement on bevacizumab

2.The chosen endpoints to measure efficacy were not adequate:

The investigation of treatment effects of bevacizumab on liver damage in HHT was evaluated by change in cardiac index.

Cardiac Index is a point estimate of cardiac function limited by a number of factors such as sonographer and interpreter of results, machines used in the investigation and present condition of the patient. A strict protocol and validation are practised when this measure is used in clinical studies, which is not presented in the studies. The studies also do not present definition on what is considered clinically relevant decrease.

Furthermore, little is presented on the natural progression of cardiac index in the condition. The VASCERN guidelines recommends optimised heart failure medication, but data on this at baseline or during the studies are not presented.

3. Methodological limitations

For the primary endpoint of Cardiac Index, partial response was defined as a decrease in CI. According to the above-mentioned reflection paper on single arm trials, observations of the desired outcome should be known to occur only to a negligible extent in the absence of an effective treatment. The

applicant has not defined a size of the decrease, why a response for the primary endpoint may occur due to the above-mentioned variability.

The efficacy estimates are not considered robust and are likely to be biased due to the following limitations. First of all, in the CoBeVaro study, the assessment was only conducted on patients with available data before/after treatment, introducing a selection bias. Additionally, the amount of missing data was large, i.e. the efficacy analysis populations were highly selected. Secondly, in the Metafore study, a sample size re-estimation was conducted, which also might bias the efficacy estimate. Finally, due to the likely increase in symptoms before initiating treatment, a regression towards the mean in the outcome is expected.

A severe hemorrhagic form (epistaxis and/or digestive bleeding) of HHT with dependence on transfusions and/or intravenous iron

The BABH study is the sole randomized study in the application and is considered pivotal. The primary endpoint assessed treatment success, defined as a 50% reduction in the number of units transfused in the period 3 months after treatment compared to the number of units transfused 3 months before the treatment, and no difference was found between the bevacizumab and the placebo group. No other relevant findings from the study support a relevant treatment effect of bevacizumab. (**MO**) The applicant highlights a post hoc analysis indicating a treatment effect in patients experiencing a higher bevacizumab exposure but given the limited dataset, the analysis is considered very uncertain. (**OC**) The single-arm retrospective CoBevaRo and InHIBIT-Bleed studies shows an apparent effect on several parameters during the course of the study. However, it is considered likely that patients received bevacizumab treatment in relation to a period of increased bleeding symptoms and results may be due to regression to the mean. The assessment of endpoints was limited to data availability thus introducing selection bias and the contribution of other treatments and procedures is not known. (**MO**) In conclusion, the provided data is not considered in support for a treatment effect of bevacizumab for severe hemorrhagic form (epistaxis and/or digestive bleeding) of HHT with dependence on transfusions and/or intravenous iron.

5.4. Clinical safety

Please refer to the table of studies in section 6.3.2

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

Two proprietary clinical studies in HTT are presented, HHT-PS1/Metafore and HHT-PS2/BABH with up to one year follow up, as well as one retrospective registry study HHT-RS1/Cobevaro with a median 2.4 years of follow-up (range 0-14 years).

In general, safety evaluations in the studies were designed to specifically include monitoring of the adverse reactions presented in SmPC and AESIs identified for bevacizumab (Avastin) in oncology indications.

Although no marketing authorization of ORBLID® nor any bevacizumab originator or biosimilar was granted in any regions in HHT indication, bevacizumab has been used off-label in HHT patients in various countries, and registry data and some pharmacovigilance data is therefore available.

5.4.2. Patient exposure

Two proprietary clinical studies in HTT are presented, HHT-PS1/Metafore and HHT-PS2/BABH, as well as one retrospective registry study HHT-RS1/Cobevaro. Data from other published prospective and retrospective studies is also presented in the Application, see table below.

Metafore

In Metafore study, 25 patients received at least one dose, 24 having received 6 doses in 12 weeks and 1 receiving only 2 of the 6 scheduled injections. These are very limited data (total 146 doses). Patients were aged from 35 to 68 years old and there were 1 man and 24 women.

BABH study

The only study with placebo-controlled safety data is HHT-PS2/BABH, where 24 patients were randomized in 1:1 ration for induction and 6 months follow-up treatment. Ten received 6 doses and two patients received 3 and 4 doses of bevacizumab. There were 10 women and 14 men, mean age was 60 years old, the patients in the bevacizumab group were aged 50 to 80 years old and were younger in the placebo group, from 42 to 75 years old.

Cobevaro

In Cobevaro retrospective study, data from 237 assessable patients received at least one dose of bevacizumab. There were 140 women and 97 men, with a mean age of 63,6 years old. Among them, 203 (86%) received at least one full standard induction course with 140 of these 203 patients who continued with a maintenance therapy and 63 who received only induction therapy. Among the 63 patients who received only induction therapy, 47 receiving only one induction course and 16 receiving multiple induction courses. Among the 140 patients in maintenance therapy, 121 regularly received maintenance therapy (monthly to quarterly) whereas 19 received intermittent maintenance treatment when necessary. 34 patients did not receive at least one full induction course: 24 received more than 2 maintenance-like administrations and 10 received only sporadic doses. These are very different treatment types but maintenance exposure in 140 patients is seen as satisfying.

The total number of administrations varied among subjects as the length of follow-up was highly variable. The average number of administrations was 21 per patient (from 1 to maximum 148). A total of 4974 bevacizumab administrations have been provided for the analysis, 4565 at the standard induction dose of 5 mg/kg, 240 administrations from 7,5 to 10 mg/kg and 162 from 1 to 4,9 mg/kg.

Following the first infusion, follow-up duration was very variable between patients, with a mean follow-up duration of approximately 1 513 days (4.1 years), but with a mean duration of approximately 1 180 days (3.2 years) when restricting to the period during which patients actively received bevacizumab. Notably, some patients received only the initial administration, while others continued the treatment for over 14 years.

The total number of HHT patients in published prospective and retrospective studies is calculated to 1134 by the Applicant, see table below. Of note, not all studies discuss safety aspects.

Table 45: Number of patients treated with bevacizumab in published prospective and retrospective studies (proprietary studies highlighted in blue)

	Study identifier / short title	number of patients treated with BV
Prospective Studies	CSR HHT-PS1 / Metafore	25
	CSR HHT-PS2 / BABH	12
	HHT-PS3 (Thompson et al. 2014)	6
	HHT-PS4 (Chavan et al. 2017)	21
	HHT-PS5 (Dupuis-Girod et al. 2025)	9
Retrospective studies	CSR HHT-RS1 / Cobevaro	237
	HHT-RS2 (Guilhem et al. 2017)	46
	HHT-RS3 (Al-Samkari et al. 2020)	291
	HHT-RS4 (Epperla et al. 2018)	11
	HHT-RS5 (Al-Samkari et al. 2021)	232
	HHT-RS6 (Vázquez et al. 2020)	20
	HHT-RS7 (Zhang et al. 2021)	27
	HHT-RS8 (Albitar et al. 2020)	57
	HHT-RS9 (Buscarini et al. 2019)	69
	HHT-RS10 (Al-Samkari et al. 2019)	13
	HHT-RS11 (Iyer et al. 2018)	34
Total		1134

5.4.3. dverse events

In single-arm study HHT-PS1/Metafore, 124 adverse events were reported. The most common AE´s were headache (n=53), nausea and vomiting (n=12) and asthenia (n=11). There were 7 episodes of hemorrhage (1 GI bleed, 1 rectorrhagia, 3 epistaxis, 1 throat hemorrhage, 1 hematemesis).

In Study HHT-PS2 / BABH, the only placebo-controlled study, headache (n=4 vs. n=0) and hypertension (n=4 vs. n=0) were more frequent in the bevacizumab group compared to placebo, and pyrexia was more prevalent in the placebo arm (n=7 vs. n=0). Headache and hypertension are known AE´s to bevacizumab. Due to the small sample size and few events, it is difficult to draw any firm conclusions from this study.

In the retrospective registry study Study HHT-RS1 / Cobevaro, 508 of recorded 801 AE´s were analysed. The most common were fatigue, arthralgia, headaches, hypertension, bleeding-related events, proteinuria, diarrhoea and cardiac failure.

The data on AE´s in the total HHT population in published prospective and retrospective studies, per study are summarized in 2 tables below. Of note, many of the studies were small, did not systematically report AE´s and some did not discuss safety at all.

5.4.3.1. Overview of AE´s in the total HHT population, per study.

ID	n	Countries	Design	Study population	Dosing	Safety findings
HHT-PS1 / Metafore	24	France	Single center, phase 2, uncontrolled, open label, Gehan design	Clinically confirmed HHT with severe liver involvement related to HHT and NYHA ≥ Class II; Median age (range): 59 (35-68); M/F ratio: 1/23; Baseline avg CI: 5.01 ± 0.67 L/min/m^2	**Induction** (6 doses of 5 mg/kg BV every 14 days)	• **No deaths were observed. No thromboembolic, hemorrhagic, gastrointestinal perforation or leukoencephalopathy events were observed.** • 5 SAEs, possibly related to BV because observed during the treatment phase, were noted. None of the SAE cases were related with any certainty • **The side effects were mild and easily managed** • A total of 6 events classified as grade 3 were reported. Of these events, BV was certainly responsible for 2 (two cases of systemic hypertension). The grade 3 events were limited to complicated cases of systemic hypertension and were easily controlled • Ten grade 2 events were also observed, including 4 for which BV was responsible (atrial extrasystoles (n=1), headaches (n=1), diarrhea (n=1), vomiting (n=1)). • 124 grade 1 events were observed, including 95 for which BV was responsible (including headaches (n=53), nausea and vomiting (n=12), asthenia (n=11), abdominal pain (n=5), muscle pain (n=4), diarrhea (n=4), dental infection (n=3), increased creatinine (n=2), and lymphedema (n=1)), were observed.
HHT-PS4 / Chavan	21	Germany	Single center, phase 2, uncontrolled	HHT patients with symptomatic hepatic involvement requiring invasive therapy; Median age (range): 58 (42-71); Baseline avg CO: 8.7 ± 3.5 L/min	**Induction** (6 doses of 5 mg/kg BV every 14 days) ± **repeated therapies**	• **No arterial embolic episodes in the systemic circulation or proteinuria were noted** • AEs included grade I hypertension (4 patients), grade I epistaxis (1 patient), grade I hematemesis (1 patient), grade III hematemesis (1 patient – who had similar episodes of hematemesis prior to BV) and grade IV pulmonary embolism (1 patient).
HHT-PS2 / BABH	24	France	Multicenter, phase 2, randomized, double-blinded, placebo-controlled (1:1 ratio)	Clinically confirmed HHT with at least 4 RBC units transfused 3 months before enrollment (bleeding related to epistaxis or GI bleeding).; Median age (range): 60 (42-80); M/F ratio: 14/10; Baseline avg Hb: 86.09 ± 14.66 g/L	**Induction** (6 doses of 5 mg/kg BV every 14 days)	• **BV was well tolerated, and toxic effects were low and easy to manage. No deaths were reported. No side effects concerning an increase in the risk of bleeding were observed.** • 22 patients presented AEs. The total number of AEs was 107, of which 10 were SAE in 8 patients, and were similar in the BV group to that of the placebo group - 55 AEs were considered to be related to BV, 30 in the placebo group and 25 in the BV group • Three cases of serious infection were observed in 2 patients (bacteremia) S. epidermis and hominis, S. aureus septicemia and a perianal abscess) in the bevacizumab group, probably related to the treatment, all with favorable evolution • The most frequently reported adverse events related to BV were fatigue,

						headaches, arterial hypertension, abdominal pain, diarrhea and nausea, joint pain, and high temperature
HHT-PS5 / BEST	22	France	Multicenter, observational study Untreated / Treated ratio: 7/15	1 year follow-up of patients from HHT-PS2 / BABH; Avg age (SD): 61.33 (11.82); M/F ratio: 8/7	**Induction** (6 doses of 5 mg/kg BV every 14 days) ± **Maintenance** (5 mg/kg doses every month or 2 months)	• **No serious adverse events occurred** • **No treatment was discontinued prematurely during treatment**
HHT-PS3 / Thomson	6	USA	Single center, uncontrolled, open label	Clinically confirmed HHT with moderate to severe epistaxis refractory to medical management.; Median age (range): 61 (46-67); M/F ratio: 1/1 Baseline ESS: 7.2 ± 2.1	0.125 mg/kg every 4 weeks for 6 infusions	• **Side effects of BV treatment were minimal to none** • The most common AE reported during the trial was headache, followed by change in taste sensation • Only one patient reported having a minor problem with wound healing and one patient reported no negative side effects at all
HHT-RS3 / Al Samkari	291	USA, France, Norway, Netherlands, Israel Argentina	Multicenter (22 North America + 4 International), survey-based to physicians	Patients treated with BV primarily for chronic bleeding in HHT (epistaxis or GI bleed)	**Induction** (4-6 doses of 5 mg/kg BV every 14 days) in most centers, *2/26 reported another induction scheme (4 doses of 5 mg/kg BV every 2 weeks followed by 4 doses every 4 weeks)* ± **Maintenance continuous** (5 mg/kg monthly) or **as needed** (5 mg/kg dosing every 2 weeks for 6 doses)	• **Side effects to BV, including new or worsening hypertension, renal dysfunction, proteinuria, poor wound healing, or other events attributed to BV, were uncommon** • All centres reported adverse event rates <30% and two-thirds of centres reported adverse event rates <10%. • 48% of centres reported that no patient required discontinuation of treatment for adverse events, and 43% reported that such discontinuation was necessary in less than 10% of patients. • Similarly, 57% of centres reported that no patient had discontinuation of treatment for lack of efficacy, and 19% reported that such discontinuation was performed in less than 10% of patients.
HHT-RS4 / Epperla	10	USA	Single center, retrospective, from January 1, 2009, to December 31, 2015	Patients treated with BV for bleeding; Median age (range): 54 (22-79); M/F ratio: 7/3; Median baseline Hb: 87 g/L; 8 epistaxis patients + 2 GI bleeding	**Induction** (6 doses of 5 mg/kg BV every 14 days) + **Re-induction** (n = 7) or **Maintenance** (monthly 5 mg/kg doses, n = 3)	• **No safety findings discussed**
HHT-RS5 / Inhibit Bleed	238	USA, France, Israel, Argentina	Multicenter (9 USA + 3 international), retrospective, from January 1, 2011, to May 1, 2019	Patients treated with BV primarily for chronic bleeding in HHT (epistaxis or GI bleed) Median age (range): 63 (29-91); M/F ratio: 90/148	**Induction** (6 doses of 5 mg/kg BV every 14 days, n = 221) + **Maintenance** (n = 181, 92% with 5 mg/kg doses) continuous (n = 136) or re-treatment (n = 45)	• **No fatal TEAE were observed, and BV was well-tolerated overall** • The only TEAE reported in >1% of patients were hypertension (18%), fatigue (10%), proteinuria (9%), myalgia and/or arthralgia (6%), headache (4%), and venous thromboembolism (VTE, 2%). Overall, 88 patients (38%) experienced at least one TEAE possibly or likely related to BV • The TEAE rate was slightly higher in patients receiving intermittent maintenance (51%) than in those receiving continuous maintenance (32%). • There was no significant difference in number of reported TEAE in patients with long-term exposure to BV (≥2 years) and those with shorter-

						term exposure (<2 years) • Twelve patients (5%) discontinued bevacizumab treatment because of adverse events / Eleven patients (5%) discontinued bevacizumab because of inadequate treatment effect / Discontinuation due to excessive financial cost for patients occurred in two cases (1%).
HHT-RS7 / Zhang	27	China	Single center, retrospective, from December 2016 to December 2019	Patients treated with BV for epistaxis caused by HHT; M/F ratio: 14/13; Age (SD): 55.3 ± 11.2; Baseline Hb: 73.07 ± 23.71 g/L	The dose of bevacizumab was calculated according to the body weight of 5 mg/kg without further scheduling reported.	• Except two female patients who had amenorrhea after the first medication, **all patients had no other adverse reactions and complications**
HHT-RS10 / Al Samkari	13	USA	Single center, retrospective, from October 1, 2015, to April 1, 2018.	Patients treated with BV primarily for chronic bleeding in HHT (epistaxis or GI bleed); Median age (range): 60 (49-81); M/F ratio: 7/13 Baseline Hb: 85 g/L (95%CI: 78-92)	**Induction** (4 doses of 5 mg/kg BV every 14 days) + **Maintenance** (5 mg/kg monthly doses)	• **BV was well tolerated in most patients** • **No patients experienced anaphylaxis, bowel perforation or hemorrhage, wound healing complications or venous thromboembolism. No patients experienced an AE necessitating treatment discontinuation** • Two patients developed grade 3 hypertension necessitating initiation of medical antihypertensive therapy. • One patient was thought to have developed grade 1 proteinuria but repeat urinalysis on the same day, and all subsequent urinalyses were negative. • One patient experienced grade 2 headache.
HHT-RS11 / Iyer	34	USA	Single center, retrospective from June 1, 2013, to January 31, 2017	Patients treated with BV primarily for chronic bleeding in HHT (epistaxis in 15, GI bleed in 4, both in 15); Median age (range): 63 (57-72); M/F ratio: 13/21; Baseline Hb: 91 g/L (IQR: 83-105)	**Induction** (4-6 doses of 5 mg/kg BV every 14 days depending on treatment response) + **Maintenance** (5 mg/kg monthly doses)	• **BV was generally well tolerated** • Three patients during follow-up. **No death could be directly linked to BV treatment.** • Infusion-related chills and fever were noted in 2 patients. • Hypertension was noted in 4 patients • No patient experienced abdominal, brain, pulmonary, or other organ-related bleeding or perforation
HHT-RS1 / Cobevaro	237	France	Multicenter, retrospective, from 2009, to December 31, 2023	Patients with clinically confirmed HHT treated with BV because of HOCF (n = 22, median CI: 4.9 L/min/m^2), severe bleed (n = 135, avg Hb: 85.5 g/L), or both (n = 64, avg Hb: 92.7, median CI: 4.9 L/min/m^2), Median age (range): M/F ratio:	**Induction** (6 doses of 5 mg/kg BV every 14 days) ± **Re-induction** and/or ± **Maintenance** (5 mg/kg monthly, every 2 or every 3 months)	• **26 cases of deaths related to HHT and 33 not related to HHT were reported in the dataset** • 508 AEs (angiogenic drugs + unknown imputation) occurred in 134 patients (57%) between April 12, 2009, and December 31st, 2023, 185 have been imputed to an antiangiogenic drug and 323 have not been imputed. Among these 508 AEs, 255 are represented by 10 types of AEs: - Fatigue emerges as the most common adverse event, reported 37 times, followed closely by arthralgia (joint pain) with 34 instances and headaches with 33 occurrences. Hypertension, a well-known side effect of bevacizumab, was documented 30 times. The list also includes bleeding-related events like epistaxis (25 cases) and general hemorrhage (20 cases), which is possibly mislead due to the intrinsic hemorrhagic nature of HHT. Infections (25 cases) and proteinuria (22 cases) are also notable adverse events. The list rounds out with gastrointestinal symptoms like diarrhea (19 cases) and cardiac-

						related issues such as cardiac failure (10 cases) • The safety profile of bevacizumab in HHT patients shows both similarities and distinct characteristics compared to its general label indications from Genentech, Inc. (2022). While the most common adverse events in HHT patients include fatigue (n=37), arthralgia (n=34), headache (n=33), and hypertension (n=30), largely aligning with the known safety profile, there are notable differences in the haemorrhagic event patterns which lie lies in the higher frequency of epistaxis and various bleeding events, probably reflecting the underlying vascular nature of HHT instead of safety concerns regarding drug's use
HHT-RS2 / Guilhem	46	France	Multicenter, retrospective from March 1, 2009, to May 30, 2015	Patients with clinically confirmed HHT treated with BV for HOCF (n = XX, NYHA ≥ class III, median CI: 5.2 L/min/m^2), severe bleed (n = 20, Hb = 78 g/L) or both (n = 16, Hb = 85 g/L, CI = 5.4 L/min/m^2); Median age (range): 68 (35-83); M/F ratio: 11/12	**Induction** (6 doses of 5 mg/kg BV every 14 days) ± **Re-treatment** (6 doses of 5 mg/kg BV every 14 days) or/and **Maintenance** (no further details)	• **Fifteen (33%) patients died during the follow-up during the follow up, essentially from usual HHT complications.** Seven deaths were related to heart failure, 4 to sepsis and 2 to massive hemorrhages. Three deaths (2 sepsis, 1 ischemic cholangitis) occurred within 6 months after the last injection. Most of these 15 patients were considered as bevacizumab non-responders or had stopped it after an adverse event. • **No case of proteinuria was notified** • The most frequent adverse event was infections (22%) including 3 pneumonias, 1 bacteremia, 1 osteitis, 1 urinary tract infection, 1 epididymitis, 1 ophthalmic infection, 1 herpes zoster, 1 sepsis of undetermined origin. Arterial hypertension and rheumatologic symptoms were less frequent (11% each). Wound-healing complications occurred in 3 patients, 2 of them underwent leg amputation and the third developed of severe bedsores. • Blood pressure elevation has concerned 5 patients (11%). It is an expected side effect of BV and can be most of time easily managed. Arthralgia or arthritis has been reported in 5 (11%) cases • Loss of efficacy under prolonged therapy (maintenance or re-treatment) was reported for 2 patients but no exacerbation of HHT-related symptoms was observed after treatment cessation.
HHT-RS6 / Vazquez	20	Argentina	Single center, retrospective from July 1, 2013, to June 1, 2019	Patients treated with BV because of HOCF (n = 4, median CI: 5.6 L/min/m^2), IDRA (n = 13), or both (n = 3); Median age (range): 63 (49.5-71); M/F ratio: 3/5	**Induction** (6 doses of 5 mg/kg BV every 14 days) ± **Re-induction** or ± **Maintenance** (5 mg/kg BV doses every month, 2 months, or 3 months, depending on clinical response)	• **BV was in general well tolerated** • **No AE was serious enough for considering stopping treatment** • 6 patients died during follow-up, most of them due to severe cardiac failure and/or septic shock (n=4) • Poor wound healing was observed in four patients, worsening of previous hypertension was observed in two, and asthenia/myalgia in four patients • One patient presented an ischemic non-cardioembolic stroked during treatment which was not attributable to BV
HHT-RS8 /	57	USA	Single center, retrospective, from January 1, 2013, to	Patients with clinically confirmed HHT treated with	**Induction** (4-6 doses of 5 mg/kg BV every 14 days	• **No safety findings discussed**

Albitar			July 1, 2019	BV because of HOCF (n = 10, median CI: 5.2 L/min/m^2), severe bleed (n = 47, avg Hb: 95 g/L); Median age (range): 65 (37-89); M/F ratio: 3/7	depending on treatment response) ± **Maintenance** (continuous, 5 mg/kg doses every 4 to 8 weeks)	
HHT-RS9 / Buscarini	69	Italy, Spain, Germany, Denmark, Netherlands, France, UK	Multicenter European (VASCERN), survey-based to physicians	-	Most BV schedules were of: **Induction** (6 doses of 5mg/kg every 2-3 weeks), *followed by* **Maintenance** (5mg/kg every 4-12 weeks)	• **33 AEs in 28 patients treated with BV were reported** - 32 grade 1-3 AEs were reported - Most common reports were joint pain and hypertension - One fatal AE on BV treatment occurred – the patient died from a catastrophic hemoptysis and was deemed possibly related to BV

Table 46: Number of bevacizumab-treated patients experiencing TEAE in prospective and retrospective studies for HHT / total number of treated patients.

		prospective studies				retrospective studies									conclusions
SOC	**TEAE**	**HHT-PS1** (Dupuis-Girod et al. 2012)	**HHT-PS2** (Dupuis-Girod et al. 2023)	**HHT-PS3** (Thompson et al. 2014)	**HHT-PS4** (Chavan et al. 2017)	**HHT-RS1** CoBevaRo	**HHT-RS2** (Guilhem et al. 2017)	**HHT-RS3** (Al-Samkari et al. 2020)	**HHT-RS5** (Al-Samkari et al. 2021)	**HHT-RS6** (Vázquez et al. 2020)	**HHT-RS7** (Zhang et al. 2021)	**HHT-RS9** (Buscarini et al. 2019)	**HHT-RS10** (Al-Samkari et al. 2019)	**HHT-RS11** (Iyer et al. 2018)	
	Median follow-up	12 months	6 months	3 months	33 months		3.5 months	-	12 months	13.2 months	11.23 months	Mean treatment duration : 11 months	13.9 months	17.6 months	
Blood and lymphatic system disorders	Bone marrow suppression								2 / 232						2 / 741
	Thrombocytopenia					4/237									4 / 741
	Anaemia					12/237									12 / 741

	Leukopenia					1/237									1 / 741
	Macrocytosis					1/237									1 / 741
	Neutropenia					3/237									3 / 741
	Pancytopenia					1/237									1 / 741
	Lymphopenia					4/237									4 / 741
Cardiac disorders	Atrial fibrillation					3/237									3 / 741
	Palpitations					2/237									2 / 741
	Sinus arrhythmia					1/237									1 / 741
	Angina unstable					1/237									1 / 741
	Atrial flutter					1/237									1 / 741
	Cardiac failure					8/237									8 / 741
	Acute coronary syndrome					3/237									3 / 741
	Angina pectoris					1/237									1 / 741
Ear and labyrinth disorders	Deafness					2/237									2 / 741
	Tinnitus					1/237									1 / 741
Eye disorders	Eye haemorrhage					1/237									1 / 741
	Visual impairment					2/237									2 / 741
Gastrointestinal disorders	Diarrhoea			1 / 6		20/237			1 / 232			2 / 69 (1 grade 2 and 1 grade 3)			24 / 741
	Constipation					5/237									5 / 741
	Nausea		2 / 12			7/237									9 / 741

	Vomiting					2/237									2 / 741
	Haematemesis				2 / 21 (1 grade 1 and 1 grade 3)	8/237									10 / 741
	Melaena					11/237									11 / 741
	Abdominal pain/gastrointestinal upset/ Gastrointestinal disorder / Abdominal pain upper					20/237			3 / 232						23 / 741
	Pancreatitis acute					3/237									3 / 741
	Ascites					1/237									1 / 741
	Gastro-intestinal bleeding					2/237						1 grade 3 / 69 (resolved completely)			3 / 741
	Rectal haemorrhage					7/237									7 / 741
	Gingival bleeding / Gingival recession					4/237									4 / 741
	Haemorrhoids					3/237									3 / 741
	Haematochezia					1/237									1 / 741
	Faeces discol					1/237									1 / 741

	oured														
	Toothache / Tooth loss / Dental discomfort / Aphthous ulcer					6/237									6 / 741
General disorders	Asthenia/fatigue		5 / 12			33/237			23 / 232	4 / 20		2 / 69 (1 grade 2 and 1 grade 3)			67 / 741
	Wound healing complications / lower extremity venous ulceration			1 / 6		4/237	3 / 46	uncommun	2 / 232	4 / 20					14 / 741
	change in taste			2 / 6											2 / 741
	lower extremity edema / Oedema peripheral					4/237			1 / 232						5 / 741
	Chest pain					6/237									6 / 741
	Pain					4/237									4 / 741
	General physical health deterioration					1/237									1 / 741
	Hyperthermia					1/237									1 / 741
	Injection site extravasation					1/237									1 / 741
	Malaise					5/237									5 / 741

	Pyrexia					2/237									2 / 741
	Ulcer					1/237									1 / 741
Hepatobiliary disorders	Cholestasis / Cholelithiasis / Cholangitis					5/237									5 / 741
Infections and infestation	Infection		6 / 12			22/237	10 / 46		1 / 232						39 / 741
	Abscess					3/237									3 / 741
	Gingivitis					1/237									1 / 741
Injury, poisoning and procedural complications	Fall					6/237									6 / 741
	Epicondylitis					1/237									1 / 741
	Foot fracture / Vertebral fracture / Humerus fracture / Rib fracture / Spinal compression fracture					5/237						1 / 69 (grade 2)			6 / 741
	Tendon rupture					1/237									1 / 741
Metabolism and nutrition disorders	transaminase/ alkaline phosphatase elevation								3 / 232						3 / 741
	Decreased appetite					4/237									4 / 741
	Folate deficiency					1/237									1 / 741
	Hyperammonaemia					2/237									2 / 741
	Hypokalaemia					2/237									2 / 741

	Hyperlactacidaemia					1/237								1 / 741
	Gout					2/237								2 / 741
Musculoskeletal and connective tissue disorders	Arthralgia/arthritis/ Osteoarthritis, myalgia, neck pain, joint pain, facial pain, Musculoskeletal pain, Spinal pain		3 / 12			53/237	5 / 46		14 / 232			9 / 69 (1 grade 1, 6 grade 2 and 2 grade 3)			84 / 741
	Pain in extremity					5/237									5 / 741
	Muscle spasms					5/237									5 / 741
	Tendonitis					3/237									3 / 741
	Osteonecrosis					1/237									1 / 741
	Bone disorder					2/237 (grade 3)									2 / 741
	rheumatologic symptoms, Foot deformity					1/237 (grade 3)	5 / 46								6 / 741
Nervous system disorders	Headaches		3 / 12	3 / 6		38/237			9 / 232			3 / 69 (grade 2)	2 / 13 (grade 2)		58 / 741
	Epilepsy		1 / 12			1/237									2 / 741
	Encephalopathy, Hepatic encephalopathy					6/237									6 / 741
	Amnesia					1/237									1 / 741

	Aphasia					1/237									1 / 741
	Dizziness / lightheadedness			1 / 6		3/237			2 / 232						6 / 741
	Paresthesia, Dysaesthesia, Sensory loss, Burning sensation, Neuralgia, Sciatica		1 / 12			9/237									10 / 741
	Cervical radiculopathy					1/237									1 / 741
	Extrapyramidal disorder					1/237									1 / 741
	Transient ischaemic attack					1/237									1 / 741
	Vascular dementia					1/237 (grade 4)									1 / 741
Psychiatric disorders	Confusional state					3/237						2 / 69 (1 grade 2 and 1 grade 3)			5 / 741
	Insomnia					1/237									1 / 741
Renal and urinary disorders	Proteinuria		1 /12			16/237		uncommun	21 / 232			2 / 69 (grade 2)			40 / 741
	Haematuria					4/237									4 / 741
	Leukocyturia					1/237									1 / 741
	Dysuria					1/237									1 / 741
	Renal failure					1/237									1 / 741
	Acute kidney					2/237									2 / 741

	injury														
	Lupus nephritis		1 /12												1 / 741
Reproductive system and breast disorders	Amenorrhea, Heavy menstrual bleeding					3/237					2 / 27				5 / 741
Respiratory, thoracic and mediastinal disorders	Dyspnoea					9/237			2 / 232						11 / 741
	Cough					5/237									5 / 741
	Rhinorrhoea					2/237									2 / 741
	Haemoptysis					3/237						1 grade 5 possibly related to treatment / 69			4 / 741
	Hoarseness, Dysphonia					7/237			2 / 232						9 / 741
	Epistaxis, Worsened epistaxis				1 / 21	28/237			1 / 232						30 / 741
	Lung disorder					3/237									3 / 741
	Pulmonary embolism					1/237									1 / 741
	Respiratory tract congestion					1/237									1 / 741
Skin and subcutaneous tissue	Rash, Rash popular, Pruritus					8/237			3 / 232						11 / 741
	Hair loss,					1/237						2 grade			3 / 741

disorders	Alopecia											1 / 69			
	Dry skin					4/237									1 / 741
	Eczema					2/237									4 / 741
	Petechiae					1/237									2 / 741
	Skin disorder					1/237									1 / 741
	Skin exfoliation					1/237									1 / 741
	Skin discolouration					1/237									1 / 741
	Ischaemic skin ulcer					1/237									1 / 741
Vascular disorders	Hypertension	2 / 24	2 / 12		4 / 21	28/237	5 / 46	uncommon	41 / 232	2 / 20		5 / 69 (2 grade 2 and 3 grade 3)	2 / 13 (grade 3)	4 / 34[1]	91 / 741
	Haemorrhage					28/237									28 / 741
	Hypotension					9/237									9 / 741
	Venous thrombosis					7/237									7 / 741
	Peripheral ischaemia					1/237									1 / 741
	Raynaud's phenomenon					1/237 (Grade 1)									1 / 741
	Peripheral arterial occlusive disease					1/237									1 / 741
	Peripheral venous disease					1/237									1 / 741
	Aneurysm					1/237									1 / 741

	Arterial thrombosis					2/237									2 / 741
	Venous thrombosis					7/237									7 / 741
	thromboembolism				1 / 21	1/237			5 / 232			1 grade 3 / 69 (unresolved/worsened after treatment interruption)			8 / 741
	enlarged pulmonary arteriovenous malformations											1 / 69 (grade 1)			1 / 741
	Non-cardioembolic stroke								1 / 232	1 / 20, not clearly attribuable to BV					2 / 741

5.4.3.2. Adverse drug reactions

A variety of adverse drug reactions possibly treatment related were reported in prospective/retrospective studies in bevacizumab HHT. The distributions varied between the studies, that may be explained by the different study designs and that some of the studies included a very limited number of patients.

Summary of ADRs in the current bevacizumab SmPC based on the approved oncology indications is presented in the table below.

Table 47: Summary of ADRs in the current bevacizumab SmPC based on the approved oncology indications

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Infections and infestations		Sepsis, abscess[b,d], cellulitis, infection, urinary tract infection		Necrotising fasciitis[a]		
Blood and lymphatic system disorders	Febrile neutropenia, leucopenia, neutropenia[b], thrombocytopenia	Anaemia, lymphopenia				
Immune system disorders		Hypersensitivity, infusion reactions[a,b,d]		Anaphylactic shock		
Metabolism and nutrition disorders	Anorexia, hypomagnesaemia, hyponatraemia	Dehydration				
Nervous system disorders	Peripheral sensory neuropathy[b], dysarthria, headache, dysguesia	Cerebrovascular accident, syncope, somnolence		Posterior reversible encephalopathy syndrome[a,b,d]	Hypertensive encephalopathy[a]	
Eye disorders	Eye disorder, lacrimation increased					
Cardiac disorders		Congestive heart failure[b,d], supraventricular tachycardia				
Vascular disorders	Hypertension[b,d], thromboembolism (venous)[b,d]	Thromboembolism (arterial)[b,d], haemorrhage[b,d], deep vein thrombosis				Renal thrombotic microangiopathy[a,b], aneurysms and artery dissections
Respiratory,	Dyspnoea,	Pulmonary				Pulmonary

thoracic and mediastinal disorders	rhinitis, epistaxis, cough	haemorrhage/ haemoptysis[b,d], pulmonary embolism, hypoxia, dysphonia[a]				hypertension[a], nasal septum perforation[a]
System organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Frequency not known**
Gastrointestinal disorders	Rectal haemorrhage, stomatitis, constipation, diarrhoea, nausea, vomiting, abdominal pain	Gastrointestinal perforation[b,d], intestinal perforation, ileus, intestinal obstructio, recto-vaginal fistulae[d,e], gastrointestinal disorder, proctalgia				Gastrointestinal ulcer[a]
Hepatobiliary disorders						Gallbladder perforation[a,b]
Skin and subcutaneous tissue disorders	Wound healing complications[b,d], exfoliative dermatitis, dry skin, skin discoloration	Palmar-plantar erythro-dysaesthesia syndrome				
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia	Fistula[b,d], muscular weakness, back pain				Osteonecrosis of the jaw[a,b], non-mandibular osteonecrosis[a,f]
Renal and urinary disorders	Proteinuria[b,d]					
Reproductive system and breast disorders	Ovarian failure[b,c,d]	Pelvic pain				
Congenital, familial, and genetic disorder						Foetal abnormalities[a,b]
General disorders and administration site conditions	Asthenia, fatigue, pyrexia, pain, mucosal inflammation	Lethargy				

Investigations	Weight decreased					

When events were noted as both all grade and grade 3-5 adverse drug reactions in clinical trials, the highestrequency observed in patients has been reported. Data are unadjusted for the differential time on treatment.

[a] For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting.'
[b] Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).
[c] Based on a substudy from NSABP C-08 with 295 patients
[d] For additional information refer below within section "Further information on selected serious adverse reactions."
[e] Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.
[f] Observed in paediatric population only

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

Adverse events of special interest included hypersensitivity/infusion related reactions, gastrointestinal perforation/fistulae, wound healing complications, hypertension, encephalopathy, proteinuria, arterial and venous thromboembolism, hemorrhages chronic heart failure and ovarian failure. These events in proprietary studies are summarised below.

There were no deaths in proprietary studies Metafore or BABH. In the registry study Cobevero, 26 deaths related to HHT and 32 deaths related other than HHT occurred. In the Cobevaro, one patient presented with pulmonary embolism and died at age 85 over the course of her maintenance regimen. She had experienced another grade 1 venous thrombosis event prior to this fatal event.

Table 48. Overview of deaths and adverse events of special interest in proprietary studies

Study	HHT-RS1 / Cobevaro			HHT-PS1 / Metafore	HHT-PS2 /BABH			
	Induction Study Period	Maintenance Study Period	Whole Study Period[1]		Bevacizumab	Placebo	Global	p-value
N in safety population	N=203	N=174	N=237	N=25	N=12	N=12	N=24	
Number (%) of subjects with ≥ 1 TEAE leading to death	0 (0)	1 (0.6)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	
Related	0 (0)	1 (0.6)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	
Unrelated	-	-	-	0 (0)	0 (0)	0 (0)	0 (0)	
Number (%) of subjects with ≥ 1 AESI of hypersensitivity/ infusion related reaction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Number (%) of subjects with ≥ 1 AESI of gastrointestinal perforations/ fistulae	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Number (%) of subjects with ≥ 1 AESI of wound healing complications	0 (0)	2 (1)	2 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	
Number (%) of subjects with ≥ 1 AESI of hypertension	13 (6)	11 (6)	25 (11)	2 (8)	4 (33.3) (2 related)	0 (0)	4 (16.7)	
Number (%) of subjects with ≥ 1 AESI of encephalopathy	1 (0.5)	2 (1)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	
Number (%) of subjects with ≥ 1 AESI of proteinuria	8 (4)	7 (4)	14 (6)	1 (0.61) unrelated 1 renal failure (0.61) related	1 (8.3) related	0 (0)	1 (4.2)	
Number (%) of subjects with ≥ 1 AESI of ATE	0 (0)	1 (0.6)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	
Number (%) of subjects with ≥ 1 AESI of VTE	2 (1)	3 (2)	5 (2)	0 (0)	0 (0)	0 (0)	0 (0)	
Number (%) of subjects with ≥ 1 AESI of hemorrhages	8 (4)	9 (5)	16 (7)	1 gastrointestinal hemorrhage (0.61) related	0 (0)	1 (8.3)	1 (4.2)	
Number (%) of subjects with ≥ 1 AESI of CHF	0 (0)	0 (0)	0 (0)	1 (0.61) unrelated	0 (0)	1 (8.3)	1 (4.2)	
Number (%) of subjects with ≥ 1 AESI of ovarian failure/fertility	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	

5.4.5. Discontinuation due to adverse events

In Study HHT-PS1 / Metafore, no treatment was stopped for safety reasons during the study. One patient left the study after only 2 injections due to personal convenience.

In Study HHT-PS2 / BABH, two patients in the bevacizumab group had their treatment discontinued due to the following adverse events: TSAE perianal abscess after 3 injections, very probably related to treatment (1 patient. Complete resolution) and TSAE Epilepsy after 4 injections, possibly related to treatment (1 patient. Complete resolution). Additionally, one patient exited the study early for non-safety reasons (noncompliance).

In Study HHT-RS1 / Cobevaro, among all treated patients (n = 237), 34 (14%) individuals discontinued bevacizumab due to AE´s across 40 discontinuations, suggesting that some patients may have had multiple temporary discontinuations and restarts. Of these 34 patients, 25 indeed resumed treatment after a discontinuation due to an adverse event. Among the 40 episodes, the nature of the AE leading to discontinuation was available in 30 cases. The most common were Polyarthralgia (6 patients) Abscesses, epistaxis, proteinuria, arterial hypertension, and fatigue (2–3 cases each). Other events included osteonecrosis, headache, pulmonary embolism, skin rash, neutropenia, hemoptysis, and tendon rupture.

5.4.6. Safety in special populations

The approved bevacizumab SmPC (Avastin) states in 4.2. that no dose adjustment is required in patients ≥ 65 years of age. The safety and efficacy have not been studied in patients with renal impairment. The safety and efficacy have not been studied in patients with hepatic impairment. The safety and efficacy of bevacizumab in children aged less than 18 years old have not been established. There is no relevant use of bevacizumab in the paediatric population in the indications for treatment of HHT.

No specific tables by age range or special population have been included. The Applicant is asked to provide this. The Applicant is asked to modify the information in the SmPC whether dose adjustment or not, or any restriction applies, depending on the level of impairment in the target population (severe liver damage). The Applicant should also review this section according to the PIP for the proposed indication. **(LoQ, safety OC)**

5.4.7. Immunological events

Please see the PK/clinical efficacy section regarding bioanalytical methods and discussion on ADAs in the target population.

In some clinical trials across indications, the incidence of anaphylactic and anaphylactoid-type reactions in some clinical trials of bevacizumab is common (up to 5% in bevacizumab-treated patients). The Applicant is asked to include specific data in the HHT population in the SmPC **(LoQ, OC SmPC)**. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If a reaction occurs, the infusion should be discontinued, and appropriate medical therapies should be administered. According to the current label of bevacizumab (Avastin), a systematic premedication is not warranted.

5.4.8. Safety related to drug-drug interactions and other interactions

The EPAR for bevacizumab (Avastin) states: No in vitro studies were performed. Formal in vivo drug-drug interaction studies were not performed. However detailed pharmacokinetic data was obtained from several studies in which bevacizumab was administered concomitantly with various other antineoplastic drugs. Avastin is indicated in concomitant with anti-neoplastic therapies. The pharmacokinetics of bevacizumab did not appear to be affected by dosing of concomitant chemotherapies, including doxorubicin, carboplatin/paclitaxel, 5-FU/FA, capecitabine, and IFL. With the exception of irinotecan, the pharmacokinetics of these chemotherapeutic drugs were not affected by bevacizumab. In Study AVF2107g, irinotecan concentrations were not affected when dosed in combination with bevacizumab; however, there was an estimated 33% increase in exposure to SN38, the active metabolite of irinotecan, which could be a cause of the increased incidence of diarrhoea.

In the present studies of bevacizumab in HHT, no detailed data is presented on interactions with concomitant medications. There is a case presentation where simultaneous warfarin has had no interaction.

5.4.9. Vital signs and laboratory findings

Regarding vital signs and physical examinations, no individual measurements were reported as TEAE in studies HHT-PS1/Metafore and PS2/BABH. No vital signs or physical examinations were provided in the HHT-RS1/Cobevaro. No clinically important individual changes in laboratory findings were reported by the Applicant for study HHT-PS1 Metafore and PS2 BABH. HHT-RS1/Cobacvero provides only measurements for haemoglobin and ferritin, and results are presented in effect section.

In contrast, the SmPC for bevacizumab (Avastin) states: Decreased neutrophil count, decreased white blood cell count and presence of urine protein may be associated with Avastin treatment. Across clinical trials, the following Grade 3 and 4) laboratory abnormalities occurred in patients treated with bevacizumab with at least a 2% difference compared to the corresponding control groups: hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, decreased white blood cell count, increased international normalised ratio (INR). Clinical trials have shown that transient increases in serum creatinine (ranging between 1.5-1.9 times baseline level), both with and without proteinuria, are associated with the use of bevacizumab. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with bevacizumab.

In clinical trials in oncology indications, proteinuria has been reported within the range of 0.7% to 54.7% of patients receiving bevacizumab. The Applicant is asked to include specific data in the HHT population in the SmPC **(LoQ, OC SmPC)**.

In clinical trials for oncology indications, the overall incidence of hypertension (all grades) ranged up to 42.1% in the bevacizumab containing arms compared with up to 14% in the control arms. The Applicant is asked to include specific data in the HHT population in the SmPC **(LoQ, OC SmPC)**.

5.4.10. Post-marketing experience

Pharmacovigilance analysis of the EudraVigilance database

In a pharmacovigilance report made by the company *For Drug Consulting* (2024), exploration of the Eudravigilance dataset of reports with bevacizumab concomitant with the diagnose HHT were compared to reports in the "general" population of bevacizumab. Major limitations in the dataset were:

- Limited access to EVDAS information for propre case assessment;
- Possible presence of duplicates;
- Reporting of concomitant conditions, consequences and complications of underlying disease and reactions;
- Small number of cases of HHT possibly due to underreporting in unapproved indication or inappropriate coding of indications.

The database included 87243 cases in the "general population" and 187 cases with concomitant diagnose of HHT. 187 out of those 87243 cases were patients with HHT corresponding to 1165 AEs reported. As in the oncologic population, majority of cases were serious (n=169; 90.4%) however there was less percentage of cases with seriousness criterion of death (n=17; 9.1% vs. 19,2%).

Out of 1165 events, 834 (71.6%) were serious with the highest seriousness criterion death reported for 30 (2.6%) events, life-threatening for 44 (3.8%) events, hospitalization/prolonged hospitalization for 404 (34.7%) events, medically significant for 651 (55.9%) events, 5 disabling AEs represented 0.4%. No AEs of congenital abnormality were reported.

This report concludes: When comparing the overall safety profile of bevacizumab in the general population and in the population of patients with HHT, gender, age, seriousness criteria, outcome, SOC distributions were generally comparable. As expected, more fatal events were described in oncological population, which likely reflects the underlying disease. High relative proportion of haemorrhagic events and nosebleeds was reported in the HHT population.

No new safety concerns specific for HHT population have been identified.

In the HHT-RS1 Cobevaro study, comparisons were made of AE´s between the HHT population with those in the "general" population comprising oncologic indications derived from the Eudravigilance dataset reported by the company *For Drug Consulting* (2024).

Differences are increased relative occurrence in HHT compared to the general population of:

- Vascular disorders (13.4% vs 5.6%)
- Musculoskeletal and connective tissue disorders (13.0% vs 2.8%)
- Respiratory disorders (10.2% vs 6.0%)
- Nervous system disorders (10.2% vs 7.0%)
- Renal and urinary disorders (5.9% vs 3.0%)
- Cardiac disorders (4.0% vs. 2.0%)

These differences in adverse event patterns might reflect both the underlying pathophysiology of HHT and potential differences in monitoring practices in this specific population.

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

5.4.11.1.1. Overall assessment of available safety data

For the new proposed indication of hereditary haemorrhagic telangiectasia (HHT), two clinical studies in HTT are presented, HHT-PS1/Metafore and HHT-PS2/BABH, as well as one retrospective registry study HHT-RS1/Cobevaro. In these trials, the cumulative subject exposure is 247. In general, safety evaluations in the studies were designed to specifically include monitoring of the adverse reactions presented in SmPC and AESIs identified for bevacizumab (Avastin) in oncology indications. Although no marketing authorization of ORBLID® nor any bevacizumab originator or biosimilar was granted in any regions in HHT indication, bevacizumab has been used off-label in HHT patients in various countries, and registry data and some pharmacovigilance data is therefore available. As concluded in section 5.2, immunogenicity data are generally lacking in the proposed indication for both induction as well as maintenance treatment. The development of an antibody response can be different for different therapeutic indications. No immunogenicity data in the target population (HTT) has been submitted. The applicant should discuss, with references to peer-reviewed literature, the potential risks of immunogenicity in the HTT population. Furthermore, compared to the oncologic indications, long-term use is expected to be more frequent when used for the HHT indication. The Applicant is requested to address the uncertainty related to immunogenicity of Orblid during maintenance treatment in HHT patients. (**OC**)

The 37 patients treated in clinical studies HHT-PS1/Metafore and HHT-PS2/BABH received 6 cycles of 5mg/kg infusions, 2 weeks apart, except for 1 patient in HHT-PS1 who withdrew after 1 infusion only, and 2 patients in HHT-PS2 who received 3 and 4 infusions respectively. The length of study in HHT-PS1/Metafore is 12 months and in HHT-PS2/BABH 6 months. In the retrospective study HHT-RS1/Cobevaro, the number of administrations varies greatly among subjects, as length of follow-up is also highly variable. The average number of administrations was 21 per patient (from 1 to maximum 148). A total of 4974 bevacizumab administrations have been provided for the analysis, 4565 at the standard induction dose of 5 mg/kg, 240 administrations from 7,5 to 10 mg/kg and 162 from 1 to 4,9

mg/kg. These very low numbers of administration at both lower and higher doses than the standard 5 mg/kg dose do not allow to compare the safety per administered dose to the standard dose of 5 mg/kg. There was only one patient with HHT in this retrospective trial exposed to the biosimilar product that is subject for this MA application (Orblid).

The total number of HHT patients in all published prospective and retrospective studies is calculated to 1134 by the Applicant. Of note, many of these studies were small, and publications did not systematically report AE´s and some did not discuss safety at all.

Metafore

In the single centre, phase 2, uncontrolled, open label study Metafore with 24 patients, the final clinical report does not provide any assessment of the TEAEs, no narrative is provided, only PTs listings were presented. The numbers are not clearly presented by the actual safety terms, but the Applicant presented a total number of TEAEs of 164 in the 25 patients. The tables from the clinical report lack of precision and clarity, show mean values without showing the total data and it is not always possible to understand what the values relates to. It is stated in the report that the 164 TEAEs are also the ADRs, whereas it seems also that there were 164 TEAEs and that the number of TEAEs assessed by the investigators to be related to bevacizumab was 135 or maybe also 96.

In summary, 5 SAEs possibly related to BV because observed during the treatment phase, were noted. A total of 6 events classified as grade 3 were reported. Of these events, BV was certainly responsible for 2 (two cases of systemic hypertension). The grade 3 events were limited to complicated cases of systemic hypertension and were easily controlled. Ten grade 2 events were also observed, including 4 for which BV was responsible (atrial extrasystoles (n=1), headaches (n=1), diarrhoea (n=1), vomiting (n=1)). 124 grade 1 events were observed, including 95 for which BV was responsible (including headaches (n=53), nausea and vomiting (n=12), asthenia (n=11), abdominal pain (n=5), muscle pain (n=4), diarrhoea (n=4), dental infection (n=3), increased creatinine (n=2), and lymphedema (n=1)), were observed. No deaths were observed.

BABH

In the phase 2, randomized, double-blinded, placebo-controlled study BABH of 24 patients (12 randomised to bevacizumab) The most frequently reported adverse events related to BV were fatigue, headaches, arterial hypertension, abdominal pain, diarrhoea and nausea, joint pain, and high temperature. Three cases of serious infection were observed in 2 patients (bacteraemia) S. epidermis and hominis, S. aureus septicaemia and a perianal abscess) in the bevacizumab group. Two other serious adverse events included glomerulonephritis and epilepsy. No deaths were observed. The Scientific Advice recommendation EMEA/H/SA/3153/1/2015/PA/II, EMA had however also recommended to conduct immunogenicity testings and also to monitor the electrocardiogram and a cardiac ultrasound at the beginning and end of the trial at each visit to verify LVEF since congestive heart failure is an ADR in bevacizumab's SmPC. These monitoring's were not implemented in the study protocol.

Cobevaro

In the multicentre, retrospective study, from 2nd March 2009 to December 31, 2023, Cobevaro with 237 patients who received at least one dose, 508 AEs occurred in 134 patients (57%). 185 have been imputed to an antiangiogenic drug and 323 have not been imputed.

Among these 508 AEs, 255 are represented by 10 types of AEs: Fatigue emerges as the most common adverse event, reported 37 times, followed closely by arthralgia (joint pain) with 34 instances and headaches with 33 occurrences. Hypertension, a well-known side effect of bevacizumab, was documented 30 times. The list also includes bleeding-related events like epistaxis (25 cases) and general haemorrhage (20 cases), which is possibly partly due to the intrinsic haemorrhagic nature of HHT. Infections (25 cases) and proteinuria (22 cases) are also notable adverse events. The list rounds out with gastrointestinal symptoms like diarrhoea (19 cases) and cardiac related issues such as cardiac failure (10 cases). Post-hoc analysis of descriptive clinical safety data is generally not robust enough

for a marketing authorization granting considering the lack of completeness of registered data and the heterogeneity of patient monitoring.

No deaths were observed in the Metafore or BABH studies. In Cobevaro 26 cases of deaths related to HHT and 33 not related to HHT were reported in the dataset. How adjudication on cause of deaths has been made is not fully clear and there are some uncertainties raised from the case presentations.

In summary, the safety database for bevacizumab in proposed indications is considered limited, even considering the orphan status of the condition. The clinical trials in HHT with routine adverse events reporting were too small to exclude even common adverse events. However, the safety profile of bevacizumab in oncology indications adds to the database.

Safety profile of bevacizumab is well-established in oncology indications including over 5 700 patients with various malignancies, predominantly treated with bevacizumab in combination with chemotherapy in clinical trials. In this population, the most serious adverse reactions were gastrointestinal perforations, haemorrhage, including pulmonary haemorrhage/haemoptysis and arterial and venous thromboembolism. The most frequently observed adverse reactions across clinical trials in patients receiving bevacizumab were hypertension, fatigue or asthenia, diarrhoea and abdominal pain. Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with bevacizumab therapy are likely to be dose dependent.

Very common labelled adverse drug reactions include e.g. neutropenia, leucopoenia, thrombocytopenia, epistaxis, GI haemorrhage, hypertension, venous thromboembolism, proteinuria, ovarian failure. Common adverse events include e.g. sepsis hypersensitivity and congestive heart failure. Rare events include necrotising fasciitis and anaphylaxis. Very rare events include hypertensive encephalopathy.

A review of additional literature data (13 studies, of which 3 were prospective, all uncontrolled, and 2 of which did not report safety) repeated the same pattern of generally tolerable adverse events with asthenia, headache, hypertension, proteinuria, and low numbers of infections. Four studies reported deaths up to 33% of the studied population, but only one case was "possibly related to bevacizumab".

The company presents a pharmacovigilance report for bevacizumab based on data from EudraVigilance. Out of a total of 87,243 patients with adverse event reports, 187 were patients treated with bevacizumab for Hereditary Haemorrhagic Telangiectasia (HHT). No adverse events (AEs) were found in HHT that had not been described in the oncology population.

The safety profile of bevacizumab in HHT patients shows both similarities and distinct characteristics compared to its general label oncology indications. While the most common adverse events in HHT patients include fatigue (n=37), arthralgia (n=34), headache (n=33), and hypertension (n=30), largely aligning with the known safety profile, there were differences in the haemorrhagic event patterns which lies in the higher frequency of epistaxis and various bleeding events, probably reflecting the underlying vascular nature of HHT. There is an increased mortality in the oncology population compared to HHT. Gastrointestinal perforations or posterior reversible encephalopathy were not reported in the HHT population, but these rare risks cannot be excluded in HHT due to limited exposure.

Furthermore, there is limited safety and pharmacology data in regards of long-term exposure of bevacizumab. The proposed indication HHT has in off-label been used over longer periods, sometimes even decades, with both repeated inductions as well as maintenance regimens compared to in oncology.

Cobevaro is presented to provide data on safety in long-term exposure. Following the first infusion, follow-up duration was very variable between patients, with a mean follow-up duration of approximately 1 513 days (4.1 years), but with a mean duration of approximately 1 180 days (3.2 years) when restricting to the period during which patients actively received bevacizumab. Notably, some patients received only the initial administration, while others continued the treatment for over 14 years. While mean, median, minimum and maximum durations are presented, the report lacks to

present the detail of the durations of exposure among patients treated by maintenance therapy, as well as information on cumulated exposure/exposure days, these detailed exposure data need to be provided.

The three presented studies do not satisfactory provide strong evidence on the safety risk of repeat dose and long-term use of bevacizumab in HHT.

5.4.11.1.2. Adverse drug reactions (ADRs) in the SmPC

The ADRs proposed by the applicant for inclusion in the SmPC are described in section 6.4.3.2 above. In general, the Applicant proposed SmPC in line with currently approved SmPC for Avastin. This is endorsed. However, the Applicant is asked to include specific data in the HHT population under specific warnings and safety concerns in the SmPC as well as omit some sentences that are specific for specific oncology populations. **(LoQ, OC SmPC)**.

In the section 4.8, the Applicant has kept all the wordings and tables related to oncological patients and added data from HHT patients at the end of the section. It is wondered if the order should not be changed in order to better highlight the indication in HHT patients. The proposed data on HHT patients consist in 9 pages of detailed tables of total TEAEs occurrence in the 3 studies of the application. This is not in accordance with the SmPC template. The Applicant should propose a regular table with the justification for the choice of each ADR and the calculated frequencies. **(OC)**

The following additional contraindications that are not included for other bevacizumab indications are proposed: Thrombosis in the 6 months prior to initiation, Atrial fibrillation, Cerebral AVMs on magnetic resonance angiography, Thrombopenia, Anticoagulant treatment. The Applicant is asked to further discuss the safety issues that justify these contraindications. (**LoQ, OC SmPC)**.

5.4.11.2. Conclusions on clinical safety

The safety database for bevacizumab in proposed indications is considered limited, even considering the orphan status of the condition. Immunogenicity data are generally lacking in the proposed indication for both induction as well as maintenance treatment. The proprietary clinical studies were small with only one very small, controlled study. Safety reporting from registry trials is considered less reliable and most of the published studies did not systematically report adverse events. The clinical trials in HHT with routine adverse events reporting were too small to capture even common adverse events. Most of the studies did not have a control group (Metafore, Cobevaro, literature data) leading to possibly subjective assessments of whether the adverse event is related to treatment or not. **(Safety MO)**

Headache, fatigue, arthralgia were the most observed TEAEs. Hypertension was observed but was easily managed. Venous thromboembolism was not frequently observed, possibly because there was not the risk associated to cancer. Proteinuria was observed but without renal failure. The risks of higher tendency to bleed and of infections could be anticipated to be increased in HHT patients, and while no tendency was detected in the pivotal studies no certain conclusion can be made on this point. Similarly, the risk of poor would healing known with bevacizumab could be hypothesized to be even more problematic in HHT patients who have microcirculation defects, however no intestinal perforation was observed and no particular trend of impaired healing was seen in the pivotal studies, but this concern should however not be disregarded considering the lack of solid data and noting that two limb amputations were described in the Applicant's literature articles (no detail on the patients being available though).

However, the safety profile of bevacizumab in oncology indications is well known. The safety profile has been considered acceptable in oncologic indications but is problematic with several serious identified risks, as listed above. No new safety signals have been identified in the sought HTT indications compared to oncology indications. However, the data is very limited or of poor scientific quality. Long-term risks are also more relevant for HHT patients with a treatment that can extend over longer periods than is typical in oncology indications, but data on long-term exposure is lacking. **(LoQ, RMP)** The Applicant is therefore asked to justify how the benefit of treatment in the proposed indications outweigh these serious identified risks. The Applicant is also asked to modify and include specific data in the HHT population in the SmPC. **(LoQ, OC SmPC)**

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 49: Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important Identified Risks	Gastrointestinal haemorrhage, perforation and fistulae
Important Potential Risks	None
Missing information	None

6.1.2. Discussion on proposed safety specification

Given demonstrated biosimilarity, including safety results in cancer patients, and the absence of new safety concerns identified in the HHT population (performed by MAH EVDAS data analysis confirmed comparable safety profiles in both indications), MAH propagated the known safety concerns of Avastin® and and an authorised biosimilar product in cancer population to use of ORBLID for HHT. Risk minimisation measures based on routine pharmacovigilance activities are currently considered as sufficient by the Applicant.

In the proposed RMP version, the Applicant included one safety concern of gastrointestinal haemorrhage, perforation and fistulae as an important identified risk. While this risk is very important towards the population intended to be treated, it is considered that it is addressed in the SmPC which contains the related information and safety measures. The Applicant has moreover not proposed any additional pharmacovigilance activity to further assess this risk nor any additional risk minimisation measure. It is therefore suggested not to include the risk of gastrointestinal haemorrhage, perforation and fistulae as a safety concern, in accordance with the last version of the GVP Module V regarding RMPs (EMA/838713/2011 Rev 2 – 28 March 2017). Furthermore, the current RMP version 34 dated December 2022 for Avastin, does not contain any risk listed as a safety concern. Unless the Applicant provides relevant additional data to the list of outstanding issues and depending on the CHMP evaluation on the second round of the procedure, it is suggested to add 'long-term data' as a

safety concern (missing information) and to consider further characterisation in the post-marketing setting. Thus, it is suggested to specify the request to the applicant for 'Long term safety' to include all specific concerns to be addressed within a post marketing study.

Proposed heading of new missing information category: 'Long term risk of gastrointestinal haemorrhage, perforation and fistulae, other bleeding events, cardiac failure, infections, poor healing, and immunogenicity in patients with HHT. **(OC)** However, in general and especially the long-term safety data from HHT population is limited. The treatment duration in HHT is potentially longer than in oncology indications where mortality is considerably higher. The Applicant is therefore invited to investigate potential data sources and to propose a study synopsis for a PASS with the scope of investigating long term safety. **(OC)**

Bevacizumab's potential to cross the placenta and inhibit angiogenesis in the foetus have been confirmed and is therefore contraindicated during pregnancy. In addition, a warning in SmPC section 4.8 states that bevacizumab "may impair female fertility (see sections 4.6 and 4.8). Therefore, fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with ORBLID. Since the HHT population may differ from the oncological population on several important aspects, including on the age distribution and treatment duration, and given that the treatment will be administered by other/new specialist domains than the oncology domain, the risks of embryofoetal toxicity and ovarian failure in the context of the HHT indication would benefit from further clarification in context of the RMP. The Applicant is therefore invited to discuss whether embryofoetal toxicity and ovarian failure needs to be included in the RMP as important risks. In addition, the applicant should be requested to update the RMP to transparently reflect the applicant's evaluation of these two risks in context of the HHT indication. **(OC).**

6.2. Pharmacovigilance plan

Risk minimisation measures based on routine pharmacovigilance activities are currently considered as sufficient by the applicant.

The applicant did not propose any additional pharmacovigilance activities.

6.2.1. Discussion on the pharmacovigilance plan

6.2.1.1. Routine pharmacovigilance activities

Additional pharmacovigilance activities could be warranted, as outlined below.

6.2.1.2. Additional pharmacovigilance activities

As highlighted in the discussion of the safety specification, uncertainty remains with regard to the long-term safety of bevacizumab in the HHT indication. Additional pharmacovigilance activities could therefore be warranted. The applicant is asked to investigate potential data sources and to propose a study synopsis for a PASS with the scope of investigating long term safety, including the long-term risk of gastrointestinal haemorrhage, perforation and fistulae, other bleeding events, cardiac failure, infections, poor healing, and immunogenicity, when bevacizumab is used in the HHT population. The applicability of including a comparator in the study design should be discussed, and the overall feasibility of the proposed PASS should be discussed with emphasis on any limitations in data collection, study size and timelines. **(OC)**

6.3. Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 50: Planned routine risk minimisation measures

Safety concern	Routine risk minimisation activities
Important Identified Risk: Gastrointestinal haemorrhage, perforation and fistulae	**Routine risk communication:** **Information presented in the SmPC sections:** **Contraindications in Section 4.3** Thrombopenia Anticoagulant treatment **In section 4.4 "Special warnings and precautions for use", SmPC** Bevacizumab must be used with caution in patients with intrabdominal tumours, previously treated with radiation therapy. ORBLID must be permanently withdrawn in patients who develop gastrointestinal perforation or experience Grade 3 or 4 bleeding during bevacizumab therapy. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. **Listed in section 4.8 "Undesirable effects" SmPC** * Rectal haemorrhage, Mild to moderate GI bleeding (≥1/10) * Haemorrhage, gastrointestinal perforation, intestinal perforation, recto-vaginal fistulae (≥1/100 to <1/10) * Gastrointestinal ulcer, gallbladder perforation (unknown frequency) **Risk outlined in section 2, 3 and 4 of PL** **Other routine risk minimisation measures beyond the Product Information:** None

The applicant did not propose any additional risk minimisation measures.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

For the important identified risk of gastrointestinal haemorrhage, perforation and fistulae, routine risk minimisation measures are considered appropriate.

6.4.2.2. Additional risk minimisation measures

The applicant did not propose any additional risk minimisation measures.

Pending the applicant's discussion in response to the LoQ on whether embryofoetal toxicity and ovarian failure should be considered as safety concerns when bevacizumab is used in the HHT population, additional risk minimisation measures could be warranted for these two risks, possibly by means of a HCP checklist to remind about the need for counselling of the female patient with regard to fertility preservation strategies prior to treatment and the need for effective contraception during and after treatment. Please refer to the question to the safety specification. (**OC**)

6.5. RMP summary and RMP annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

☒The CHMP and PRAC consider that the risk management plan version 0.1 could be acceptable if the applicant implements the changes to the RMP requested in the list of questions

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, having considered the data submitted in the application, was of the opinion that it was not appropriate to conclude on the pharmacovigilance system at this time. See list of questions.

The CHMP 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 first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on [insert date of initial scientific opinion].

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every [insert frequency] until otherwise agreed.

The scientific opinion holder shall submit periodic safety update reports for this product in alignment with the requirements for the centrally authorised product as set out in the list of Union reference dates (EURD list) and any subsequent updates published on the European medicines web-portal.

☒ The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD).

☒ Based on the consideration that the HHT indication differs significantly from the existing oncology indication, the PRAC rapporteur is of the opinion that a separate entry in the list of Union reference

dates (EURD list) for bevacizumab is needed, as it cannot follow the already existing entry for bevacizumab. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did <not> request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is [DD.MM.YYYY]. The new EURD list entry will therefore use the <European birth date (EBD)><IBD> to determine the forthcoming Data Lock Points.

8. Benefit-risk assessment

8.1. Therapeutic context

8.1.1. Disease or condition, proposed therapeutic indication

Hereditary haemorrhagic telangiectasia (HHT) is a rare chronic, progressive vascular disorder with a highly heterogeneous clinical expression, affecting approximately 1 in 5,000 to 10,000 people. It is characterized by the presence of multiple arteriovenous malformations (AVMs) that result in direct connections between arteries and veins. The most common clinical manifestation is spontaneous and recurrent nosebleeds (epistaxis). Telangiectasia (small AVMs) are characteristically found on the lips, tongue, buccal and gastrointestinal (GI) mucosa, face, and fingers. Large AVMs occur most often in the lungs, liver, or brain; complications from bleeding or shunting may be sudden and catastrophic. A minority of individuals with HHT have GI bleeding. This application focusses on two subpopulations of the disease that have a high disease burden, i.e. patients suffering from recurrent and uncontrolled bleeding requiring transfusions and patients developing high cardiac output (HCO) failure due to hepatic arteriovenous malformations (AVMs).

In the bleeding subgroup, patients may experience daily epistaxis with significant blood volume loss and/or occult gastrointestinal haemorrhages that persist over decades, progressively depleting iron stores and leading to severe anaemia, and often results in long-term dependence on iron supplementation or transfusions.

In the high cardiac output subpopulation, AVMs within the liver create abnormal vascular shunts that place a sustained volume load on the heart, leading to progressive cardiomyopathy. Symptoms are often subtle in early stages but evolve into debilitating heart failure, arrhythmias, and ultimately, multi-organ complications.

The proposed indication for Orblid is:

Adult patients with confirmed hereditary hemorrhagic telangiectasia (HHT) presenting

(i) severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnea despite well-conducted cardiological medical treatment and/or

(ii) a severe hemorrhagic form (epistaxis and/or digestive bleeding) of the disease with dependence on transfusions and/or intravenous iron.

8.1.2. Available therapies and unmet medical need

For a detailed description, please see section 3.1 of this document.

Currently, there are no specific therapies approved for HHT which remains a rare disease with a high unmet medical need.

Patients with chronic blood loss due to recurrent epistaxis or gastrointestinal bleeding often require regular intravenous iron supplementation or red blood cell transfusions.

In patients with high cardiac output related to hepatic AVMs, management currently relies on symptomatic treatment with diuretics, beta-blockers, and other heart failure medications aimed at controlling volume overload and stabilizing cardiac function. Patients may be treated with hepatic artery embolization and/or ultimately require liver transplantation.

Bevacizumab is currently used off label for treatment of HHT.

Both groups are associated with considerable morbidity, reduced health-related quality of life, and prolonged healthcare utilization and there is a high unmet medical need.

8.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 6.3.2 of this document.

HHT-PS1 / Metafore Study

HHT-PS1 / Metafore Study is a single centre, phase 2, prospective, single arm, open label study evaluating bevacizumab in HHF patients with hepatic arteriovenous malformations (AVM) and cardiac repercussions of high output cardiac failure (HOCF). 25 patients were included and received the first dose of bevacizumab, and 24 completed the whole study protocol. The primary objective of the study was to test the efficacy of bevacizumab on decreasing cardiac output in patients with severe hepatic involvement in HHT. The treatment was predefined to be effective if a partial (decrease without normalization of the cardiac index) or complete (decrease with normalization of the cardiac index) response was observed at 3 months after the start of the study. Several descriptive secondary endpoints were investigated with no defined testing hierarchy, including heart and liver ultrasound and assessment of epistaxis.

HHT-RS1 / CoBevaRo study

The HHT-RS1 /CoBevaRo is a retrospective study of data from the CIROCO registry of French HHT patients treated with Avastin or biosimilars between 2009 and 2023. This study is based on the secondary use of real-world data originally collected in routine clinical practice, not specifically for research purposes. Among the 6,351 patients recorded in the CIROCO database, 249 patients were identified as having received bevacizumab of which 203 receiving at least one full induction course. From the available data, different subgroups were evaluated depending on data availability. This included cardiac index evaluation, transfusion and iron need, epistaxis and haemoglobin before and after bevacizumab administration.

HHT-PS2 / BABH Study

The BABH study was a prospective, multicentre, randomized, placebo-controlled, double blind phase II study. 24 patients were enrolled in the study (12 + 12 in the bevacizumab and the placebo group, respectively). The study recruited HHT patients having required blood transfusions related to nosebleeds or digestive bleeding (at least 4 units of RBC in the 3 months preceding inclusion). The study is the only controlled study performed in HHT. The primary endpoint assessed treatment success, defined as a 50% reduction in the number of units transfused in the period 3 months after treatment compared to the number of units transfused 3 months before the treatment. The secondary endpoints included comparisons of haemoglobin and ferritin, comparisons of the durations and episodes of nosebleeds, quality of life assessments, and the description of digestive bleeding.

HHT-PS4 (Chavan et al. 2017)

The HHT-PS4 /Chavan et. al is a single-centre, non-blinded and non-controlled prospective study of 21 patients conducted between October 2010-April 2016. The study was included in the submission as a published letter to the editor and not further presented in the application but data from the study is proposed by the Applicant under section 5.1 of the SmPC. HHT patients with symptomatic hepatic involvement requiring invasive therapy were considered eligible. The primary objective in HHT-PS4 /Chavan is to evaluate changes in the grade of abdominal pain, cardiac output and the New York Heart Association (NYHA) stage before and three months after bevacizumab treatment

HHT-RS5 / InHIBIT-Bleed study (Al-Samkari et al. 2021)

The retrospective registry study was conducted on data from nine centers in the USA and one center each in Argentina, Israel, and France. The retrospective study was only provided as a scientific article and was not further presented in the application but data from the study is proposed by the Applicant under section 5.1 of the SmPC. The publication contains very limited information on study design. Data was divided into different subsets for the assessment of the endpoints. The number of patients in each subset was determined by data availability for that parameter.

8.3. Favourable effects

Indication 1: HHT patients with severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnea despite well-conducted cardiological medical treatment

In the Metafore study, the primary objective of the study was to test the efficacy of bevacizumab on normalizing cardiac index in patients with severe hepatic involvement in HHT. 12% (3/25) of patients displayed complete response and 68% (17/25) partial response. No response was seen in 20% (5/25) of patients. The majority of patients were in NYHA class II at baseline (64%), 4% in class I and 32% in class III. In general, the NYHA class improved slightly during the study.

In the Cobevaro registry study, patients with least one abnormal cardiac index value (> 3.6 in women, > 3.9 in men) within the 6 months period prior to first bevacizumab infusion as well as data 6 months after the infusion were included for the analysis of this endpoint (n=26). The data indicates an effect on lowering CI during the initial 6 months after treatment (median 3.8 L/min/m^2 [95% CI 3.6, 4.4] vs. 5L/min/m^2 [95% CI 4.6, 5.2] at baseline).

In the HHT-PS4 (Chavan et al. 2017) study, the mean cardiac output was reduced after bevacizumab treatment compared to baseline (6.5 L/min [95% CI 5.73; 7.24) vs. 8.7 L/min [95% CI 7.25; 10.24]) while the mean NYHA class improved from 2.8 (95% CI 2.49; 3.13) pretherapy to 1.6 (95% CI 1.25; 1.99).

Indication 2: HHT patients with a severe hemorrhagic form (epistaxis and/or digestive bleeding) of the disease with dependence on transfusions and/or intravenous iron

In the BABH study, the primary endpoint treatment success, defined as a 50% reduction in the number of RBC units transfused in the period 3 months after treatment, was 63.6% [7 patients] in the bevacizumab group and 33.3% [4 patients], in the placebo group (p=0.1451). The secondary endpoint haemoglobin at 3 months after treatment was higher in the bevacizumab vs. the placebo group (99.82 vs. 85.25 g/L, nominal p=0.0180).

In the Cobevaro registry study, several subsets of patients with data relevant for the second bleeding indication were analysed.

For the subset of patients receiving at least 1 RBC unit before bevacizumab administration (n=133), the median number of transfusions was lower during the 6-month period following administration compared to the 6-month period before (3 vs. 11 units).

Data on iron transfusions was analysed in the subset of patients either receiving RBCs or IV iron before bevacizumab administration (n=152). The median amount of iron infused was lower during the 6-months period following administration compared to the 6-month period before (2 g vs. 3.35 g).

In the subset of patients with Hb below 11g/dL prior to bevacizumab administration (n=139), the haemoglobin values were higher during the 6-month period following administration compared to the 6-month period before (10.4g vs. 8.6g/dL).

In a separate subset, patients with nose bleeds before bevacizumab treatment were identified (n=74). The median nosebleed frequency was slightly lower in the 6-month period after treatment compared to the period before (4.25 vs 5).

In the Metafore study, the secondary endpoint concerning the number of episodes of nosebleeds and their duration were reduced during the study, the effect was most pronounced at month 6 where 75% of patients displayed an improvement of 30%.

The Inhibit Bleed registry study indicated lower number of RBC transfusions and iron infusions, lower epistaxis severity score and higher haemoglobin values after bevacizumab treatment, compared to baseline values. The study was only provided as a scientific publication, limiting the review.

8.3.1. Uncertainties and limitations about favourable effects

The evidence claims are mainly based on open and uncontrolled studies which makes it challenging to isolate a possible treatment effect in a disease with a high variability in symptoms. Due to the likely increase in symptoms before initiating treatment, a regression towards the mean in the outcome is expected. Furthermore, other therapeutic interventions may have occurred during the studies to control symptoms (e.g. transfusions, diuretics, heart failure medication, treatment of gastroesophageal varices, ascites, surgery).

The number of patients in two main studies (BABH and METAFORE studies) is very limited. Only 23 patients in the BABH study (n=11 in bevacizumab group and n=12 in placebo group) and 28 participants in the uncontrolled METAFORE study.

The results provided from the registry studies were based on data from routine clinical practice and were limited to patients with available data before/after treatment thereby introducing selection bias.

The relevance of cardiac index in high output heart failure is not well established in literature, and it is not validated against clinical heart failure symptoms or pathological haemodynamics. Furthermore, cardiac index is associated with high variability due to both intrinsic and extrinsic factors.

The BABH study is the only controlled study, and it failed to show an effect on its primary objective transfusions. No effect on nosebleeds was observed either.

The proposed posology for the induction dose is based on the lowest dose for the oncologic indications of bevacizumab. The absence of dose-finding study raises uncertainties on the choice of the doses. As commented in Scientific Advices, lower doses (with potentially better safety profile) could have been explored. The rationale for the maintenance dose is not clear, and it is only supported by data from the registry studies. The planned extended second part of the BABH study discussed during the first scientific advice studying the maintenance regimen appears not to have been conducted.

The PK models and real-world data provided do not fully address uncertainties long-term pharmacokinetics and dose optimisation. The selected dose and dosing interval for long-term

treatment in HHT has not been supported. Furthermore, there are uncertainties related to long-term pharmacokinetics and immunogenicity which has not been addressed.

8.4. Unfavourable effects

For the new proposed indication of hereditary haemorrhagic telangiectasia (HHT), two clinical studies in HTT are presented, HHT-PS1/Metafore and HHT-PS2/BABH (N=37), as well as one retrospective registry study HHT-RS1/Cobevaro. In these three trials, the cumulative subject exposure is 247. The total number of HHT patients in all published prospective and retrospective studies is calculated to 1134 by the Applicant. Safety profile of bevacizumab is well-established in oncology indications including over 5 700 patients with various malignancies, predominantly treated with bevacizumab in combination with chemotherapy in clinical trials. The company presents also a pharmacovigilance report for bevacizumab based on data from EudraVigilance. Out of a total of 87,243 patients with adverse event reports, 187 were patients treated with bevacizumab for Hereditary Hemorrhagic Telangiectasia (HHT).

In the HTT population, common adverse events include fatigue, arthralgia, headaches, hypertension infections, proteinuria, gastrointestinal symptoms like diarrhea and cardiac- related issues such as cardiac failure. Bleeding-related events like epistaxis and general hemorrhage are reported frequently, which is possibly partly due to the intrinsic hemorrhagic nature of HHT. It Is difficult to estimate the exact frequency of these events in HHT due to the different data sources but seems to be around 4-10% for each of these 10 groups of events.

In the approved oncology population, very common (≥1/10) labelled adverse drug reactions include e.g. neutropenia, leucopenia, thrombocytopenia, epistaxis, GI hemorrhage, hypertension, venous thromboembolism, proteinuria, ovarian failure. Common (≥1/100 to <1/10) adverse events include e.g. sepsis, wound healing complication, hypersensitivity and congestive heart failure. Rare (≥1/10,000 to <1/1,000) events include necrotising fasciitis and anaphylaxia. Very rare (<1/10,000) events include hypertensive encephalopathy.

8.4.1. Uncertainties and limitations about unfavourable effects

The safety database for bevacizumab in proposed indications is considered limited, even considering the orphan status of the condition. The proprietary clinical studies were small with only one very small, controlled study. Safety reporting from registry trials is considered less reliable and most of the published studies did not systematically report adverse events. The clinical trials in HHT with routine adverse events reporting practices were too small to exclude even common adverse events. Most of the studies did not have a control group (Metafore, Cobevaro, literature data) leading to possibly subjective assessments of whether the adverse event is related to treatment or not.

The safety profile of bevacizumab might not be fully extrapolated from oncology indications. For example, the EPAR for Avastin states: *In most clinical trials of Avastin, patients with pre-existing CHF of NYHA (New York Heart Association) II-IV were excluded, therefore, no information is available on the risk of CHF in this population*. The HHT patients may be at increased risk of cardiac failure and bleeding events due to their underlying disease. Long-term risks are also more relevant for HHT patients with a treatment that can extend over longer periods than is typical in oncology indications **(Safety MO).**

8.5. Effects table

Table 51: Effects Table for Orblid

Effect (short description)	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Favourable effects				
Indication: Liver damage with cardiac repercussions				
No controlled studies conducted				
Indication: Haemorrhages requiring transfusions				
	Treatment n=12	Placebo n=12		
Reduction of 50% in number of units of packed RBC (ITT), n (%)	7 (63.6)	4 (33.3)	**Unc:** statistical significance not achieved (p=0.1451), very few participants	BABH study
Unfavourable effects				
	Oncology indications	Number of events in proprietary studies in HHT	**Unc:** Oncology indications: uncertainty of extrapolation to HHT population due to different underlying disease and concomitant cancer therapies. Metaphore: Uncontrolled small study (n=24) BABH: Very small study (n=12) CoBevaRo: Uncontrolled registry study, highly selected adverse event reporting (n=249)	
Haemorrhage	common	Metafore 1, Cobevaro 16		
Thromboembolism	common	Cobevaro 16		
Infections	common	BABH 6, Cobevaro 22		
Hypertension	very common	Metafore 2, BABH 4, Cobevaro 25		
Proteinuria	very common	Metafore 1, BABH 1, Cobevaro 14		
Chronic heart failure	common	Metafore 1		
Gastrointestinal perforation	common	none		

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence;

8.6. Benefit-risk assessment and discussion

8.6.1. Importance of favourable and unfavourable effects

Efficacy

The proposed indication in *HHT patients with severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnea despite well-conducted cardiological medical treatment* is supported by a single-arm clinical trial, a registry study and a single arm report published as a letter to the editor.

Data provided in support for this indication is solely derived from uncontrolled studies and it is challenging to isolate a treatment effect. In the Metafore study, 17% of patients displayed complete response (normalization of cardiac index) whereas 68% displayed a partial response. A clinical effect size for response was, however, not clearly defined and even a minimal decrease appeared to fulfil the criterion of a partial response. In the Cobevaro study, the effect of bevacizumab in normalising cardiac index was retrospectively assessed from a very small subset of subjects in a patient registry.

In these studies, no clear presentation is made on validation of heart failure and the clinical relevance of cardiac index in high output heart failure is not well established in the scientific literature. The international guidelines on diagnosis and management of HHT from 2020 does not include cardiac index as a diagnostic criterion of high output heart failure but describes it as an important follow-up measure after confirmation of the heart failure syndrome with right heart catheterisation. Cardiac index is associated with high variability (both intrinsic and extrinsic factors), and the assessment appears not strictly defined in the current studies. Other therapeutic interventions (e.g. changes in heart failure medication, transfusions, surgery) during the studies are not described. A primary endpoint for a SAT must be objectively measurable and able to isolate treatment effect and the studied outcome should be known to occur only to a negligible extent in the absence of an effective treatment (Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation application EMA/CHMP/458061/2024). Due to the likely increase in symptoms before initiating treatment, a regression towards the mean in the outcome is expected. The clinical manifestations of liver involvement may fluctuate over time, with spontaneous exacerbations and remissions. It may depend on changes in shunting patterns or on the presence of reversible conditions (e.g., anaemia or atrial fibrillation). In the registry study, the analysis was conducted in a highly selected dataset determined by data availability, thus introducing selection bias. Based in these uncertainties, it is not possible to conclude on the efficacy of bevacizumab for treatment of the proposed indication in HHT patients with cardiac repercussions.

The second proposed indication concerns *HHT patients with a severe haemorrhagic form (epistaxis and/or digestive bleeding) of the disease with dependence on transfusions and/or intravenous iron.* The indication is supported by a randomized controlled trial and two registry studies, of which one has been submitted as a scientific publication.

The BABH study is the only placebo-controlled study supporting the application. Its primary objective, a 50% reduction in the number of units transfused in the period 3 months after treatment compared to baseline would have been considered relevant to patients, but this objective was not met. The secondary endpoint haemoglobin was higher in the bevacizumab vs. the placebo group 3 months after the treatment, but the importance of this endpoint is uncertain given that patients received transfusions that dramatically increase the Hb for a short period. There was also an imbalance in GI bleedings at baseline (16.7% [2 patients] bevacizumab vs. 66.7% [8 patients] in the placebo group) further complicating the interpretation of the results. No significant effect was found on any of the parameters used to measure nosebleeds. The Cobevaro and the Inhibit bleed registry studies showed an apparent effect on several parameters related to bleeding before and after treatment. However, the uncontrolled design makes it challenging to isolate a possible treatment effect. The observed results may be an effect of regression to the mean and selection bias, and the contribution of other treatments and procedures is not known. Given that the randomized controlled BABH study failed and the methodological and statistical limitations identified in the registry studies, it is not possible to conclude on the efficacy of bevacizumab for treatment of the second proposed indication either. Furthermore, no patients with intravenous iron but without dependence on transfusions were included in the clinical program and the proposed indication appears too wide.

The PK models and real-world data provided do not fully address uncertainties long-term pharmacokinetics and dose optimisation. The selected dose and dosing interval for long-term treatment in HHT has not been supported. Furthermore, there are uncertainties related to long-term pharmacokinetics and immunogenicity which has not been addressed.

Safety

The most serious adverse events associated with bevacizumab and included in the SmPC are haemorrhage, gastrointestinal perforations, and arterial thromboembolism. These may have

potentially fatal consequences even with close monitoring. The most frequently observed adverse events across all clinical trials in patients receiving bevacizumab were asthenia, diarrhoea, nausea and pain which can have an impact on quality of life.

Analyses of the clinical safety data in oncology indications suggested that the occurrence of hypertension and proteinuria with bevacizumab are likely to be dose dependent. These risks can be monitored. The hypertension seemed to be reversible. Patients with prior hypertension seem to be predisposed for proteinuria. Hypertension is a well-known cardiovascular risk factor. Proteinuria is associate with risk of kidney function loss over time. Other safety signals observed in different trials across indications were e.g. thromboembolic events and congestive heart failure, which need to be monitored and need medical treatment and may lead to hospitalization.

HHT is generally a more benign condition than cancer, which must be considered when assessing the benefit-risk ratio. The clinical trials in HHT with routine adverse events reporting practices were too small to exclude even common adverse events. A **safety MO** is raised highlighting the serious safety-profile and uncertainties related to the sought indications.

An important issue concerning both efficacy and safety is the lack of data on maintenance treatment. There is a need on one hand to demonstrate the maintenance of efficacy, and on another hand to search for a dosing strategy allowing a minimal exposure compatible with the maintenance efficacy and an acceptable safety profile.

8.6.2. Balance of benefits and risks

The proposed indication in *HHT patients with severe liver damage with cardiac repercussions such as hyper output associated with persistent dyspnea despite well-conducted cardiological medical treatment* is solely based on non-blinded and non-controlled studies. The non-controlled study design is particularly challenging for evidence generation in HHT which is a disease characterised by variability in symptoms over time. Cardiac index, the chosen primary endpoint for effect demonstration, displays a large variability and it is not established as a measure of clinical heart failure symptoms or pathological high flow haemodynamics.

The second proposed indication concerns *HHT patients with a severe haemorrhagic form (epistaxis and/or digestive bleeding) of the disease with dependence on transfusions and/or intravenous iron* is based on three studies; a small RCT considered pivotal, and two registry studies. The non-controlled studies have limitations that question the reliability of the results and the RCT failed to show an effect on the primary endpoint, a reduction of 50% in the number of blood transfusions.

Based on the provided data it is not possible to conclude on an effect of bevacizumab for treatment of any of the sought HHT indications. (**MO**)

The PK models and real-world data provided do not fully address uncertainties long-term pharmacokinetics and dose optimisation. The selected dose and dosing interval for long-term treatment in HHT has not been supported. Furthermore, there are uncertainties related to long-term pharmacokinetics and immunogenicity which has not been addressed (**MO**).

The safety database for bevacizumab in the proposed indications is considered limited, even considering the orphan status of the condition. However, the safety profile of bevacizumab in the oncology indications is well known. The safety profile is problematic with several serious identified risks

from diverse organs systems that can have a considerable impact on quality of life, require medical management, hospitalization or even be fatal. No new safety signals have been identified in the sought HTT indications compared to oncology indications, but the data is limited or of poor quality **(Safety MO)**. On the other hand, there is no convincing data to suggest that the safety profile of bevacizumab is generally more favorable in HHT compared to Avastin in an oncology indication, either. The HHT patients in the sought indications may be at increased risk of cardiac failure and bleeding events due to their underlying disease. Long-term risks are also more relevant for HHT patients with a treatment that can extend over longer periods than is typical in oncology indications **(LoQ, RMP)**. The Applicant is asked to modify and include specific data in the HHT population in the SmPC **(LoQ, OC SmPC)**.

Considering all favourable and unfavourable effects, the benefit-risk balance is currently negative.

8.6.3. At Day 80 - individual rapporteur conclusions

The overall benefit/risk balance of Orblid is negative. The provided clinical data is not in support for the proposed indications is not considered robust and should be further justified.

9. Biosimilarity assessment

9.1. Comparability exercise and indications claimed

Quality

The applicant has provided a 2-way biosimilarity study between the biosimilar candidate CT-P16 and the RMP EU-approved Avastin, evaluating relevant quality attributes by a panel of state-of-the-art and standard analytical methods.

Ten independent CT-P16 DP batches representative of the commercial scale and 10 EU-approved Avastin batches are included in the similarity study. The batches reflect an appropriate range of expiration dates and product ages. The DP material used in the analytical biosimilarity studies is considered representative of the commercial process. The similarity analyses have been performed side-by-side using a qualified in-house reference standard. The overall approaches used for the establishment of the biosimilarity assessment criteria are considered acceptable.

The analytical biosimilarity studies of CT-P16 and Avastin included comparisons of primary and higher order structures, post-translational modifications, glycation, glycosylation, charge heterogeneity, purity/impurity, content, biological activity of Fab and Fc related functions, and comparative forced degradation studies.

CT-P16 is considered to be highly similar to EU-approved Avastin with respect to the presented physicochemical and biological characterisations. Some minor analytical differences are noted but these have all been sufficiently justified by the applicant to have no clinical impact.

In conclusion, the provided data in the analytical similarity study between CT-P16 and EU-approved Avastin demonstrates a high degree of similarity in support of the biosimilarity claim.

Summary of nonclinical comparability data

A supportive four weeks of duration repeated toxicology study with toxicokinetic analysis in cynomolgus monkeys comparing CT-P16 to EU-Avastin of was conducted.

Summary of clinical comparability data

One pivotal PK study (i.e. CT-P16 1.1) was conducted: a single-dose (i.e. 5 mg /kg IV infusion for 90 min) randomised, double-blind, 3-arm, parallel study in healthy subjects comparing CT-P16, EU-Avastin and US-Avastin (N ~ 46-48 subjects administered/group). Supportive PK data was obtained from a study with healthy Japanese subjects (i.e. study CT-P16 1.2) and with nsNSCLC patients in the clinical efficacy and safety study CT-P16 3.1. The main efficacy and safety study CT-P16 3.1 is a double-blind, randomised, active-controlled, parallel group Phase 3 study to compare the efficacy, PK, and overall safety of CT-P16 (15 mg/kg) and EU-Avastin (15 mg/kg) when co-administered with paclitaxel and carboplatin as first-line treatment in patients with metastatic or recurrent nsNSCLC. In general, the clinical programme for CT-P16 was consistent with relevant CHMP Guidance concerning development of biosimilars.

9.2. Results supporting biosimilarity

Quality

The applicant has evaluated the similarity between CT-P16 and EU-approved Avastin, evaluating relevant quality attributes by a panel of state-of-the-art and standard analytical methods. The overall approach to assessing analytical similarity is found acceptable.

The analytical biosimilarity studies of CT-P16 and Avastin included comparisons of primary and higher order structures, post-translational modifications, glycation, glycosylation, charge heterogeneity, purity/impurity, content, biological activity of Fab and Fc related functions, and comparative forced degradation studies.

CT-P16 is considered to be highly similar to EU-approved Avastin with respect to the presented physicochemical and biological characterisations. Some minor analytical differences are noted but these have all been sufficiently justified by the applicant to have no clinical impact.

In conclusion, the provided data in the analytical similarity study between CT-P16 and EU-approved Avastin demonstrates a high degree of similarity in support of the biosimilarity claim.

Nonclinical data

Similarity between CT-P16 and EU-approved Avastin was demonstrated for the functional properties (antiproliferation activity, binding to VEGF-A165 and VEGF-A121, binding to FcγR subtypes, FcRn, C1q, ADCC and CDC activity, Inhibition of VEGFR2 RTK autophosphorylation and binding to other VEGF-A isoforms and VEGF family members). CT-P16 and EU-Avastin did not differ in cynomolgus monkeys on their toxicological and toxicokinetic characteristics.

Clinical data

Pharmacokinetics

In the comparison of PK data (pivotal PK study CT-P16 1.1) for the CT-P16 group with the EU-Avastin and US-Avastin treatment groups, the 90% CIs of the geometric LS mean ratios for the three primary PK parameters (i.e. Cmax, AUC0-last and AUC0-inf) were all within 80% and 125% (including 100.00). The sensitivity analyses supported the PK similarity between CT-P16 and EU-Avastin.

In the supportive PK study in Japanese subjects the 90% CIs of ratios of geometric LS means of Cmax, AUC0-last, and AUC0-inf were entirely contained within the predefined equivalence margin of 80% to 125% which indicated that bevacizumab exposures from CT-P16 were similar to those from EU-Avastin. The mean trough concentrations were comparable between CT-P16 group and EU-Avastin group (PK data up to induction cycle 6) in nsNSCLC patients in the study CT-P16 3.1.

Efficacy

In the clinical efficacy study CT-P16 3.1, CT-P16 and EU-Avastin were compared in a Phase III study in nsNSCLC patients. The design and other general characteristics of the study were considered fit for the purpose of demonstrating biosimilarity. The primary endpoint was ORR (based on BOR as per central review) during the Induction Study Period. For the ITT and the PP populations, the reported CT-P16 – EU-Avastin risk differences of 0.40 (95% CI -7.02, 7.83) and -1.90 (95% CI -9.80, 6.00), respectively, were entirely contained within the pre-specified equivalence margin of -12.5 to 12.5. Also based on the local investigators' response evaluation, the 95% CI for difference between CT-P16 and EU-Avastin in ORR during the Induction Study Period was within the equivalence margin of -12.5 to 12.5 (ITT: 4.87% [95 %CI: -2.53 to 12.26]; PP: 2.90% [95 % CI: -4.99 to 10.79]). The post-hoc analysis of ORR by treatment cycle showed similar response rates between the treatment groups; at Induction Cycle 6, the reported ORR was 42.69% (95% CI 37.45, 47.93) for CT-P16 and 43.52% (95% CI 38.30, 48.73) for EU-Avastin in the ITT population, and 44.97% (95% CI 39.50, 50.44) for CT-P16 and 48.84% (95% CI 43.22, 54.47) for EU-Avastin in the PP population. Also in this analysis, the reported CT-P16 – EU-Avastin risk differences of -0.77 (95% CI -8.21, 6.68) and -3.79 (95% CI -11.69, 4.11), for the ITT and the PP populations respectively. Data on time-dependent endpoints is also supportive of biosimilarity. In the ITT population, median PFS was 7.9 [95% CI: 6.9 – 8.3] months and 7.2 [95% CI: 6.5 – 8.3] months for the CT-P16 and EU-Avastin treatment groups, respectively, with a hazard ratio of 0.92 (95% CI: 0.77 – 1.10). In the PP population, median PFS was 8.3 [95% CI: 7.2 – 8.5] months and 8.1 [95% CI: 6.8 – 8.6] months for the CT-P16 and EU-Avastin treatment groups, respectively, with a hazard ratio of 0.93 (95% CI: 0.76 – 1.12). With respect to the comparison between CT-P16 and EU-Avastin, similar results were observed in additional PFS analyses . In the ITT population, median OS was 17.1 [95% CI: 14.6 – 18.7] months and 15.6 [95% CI: 13.4 - 18.0] months for the CT-P16 and EU-Avastin treatment groups, respectively, with a hazard ratio of 0.95 (95% CI: 0.77 – 1.19). In the PP population, median OS was 17.5 [95% CI: 15.5 - 19.2] months and 17.0 [95% CI: 14.6 – 20.5] months for the CT-P16 and EU-Avastin treatment groups, respectively, with a hazard ratio of 0.96 (95% CI: 0.76 – 1.22).

Safety

The clinical Safety Population includes data from 689 nsNSCLC patients in Study CT-P16 3.1 that received CT-P16 (n=345) or EU-Avastin (n=344). In addition, 187 healthy subjects received a single dose (5 mg/kg) of CT-P16, EU-Avastin or US-Avastin in studies CT-P16 1.1 and 1.2. The design of the clinical studies and the safety assessments were adequate, including AESIs, that were identified based on the known safety profile of Avastin. The safety data for the Phase 3 study CT-P16 3.1 was presented separately for the induction study period (combination with paclitaxel and carboplatin), maintenance study period (monotherapy), follow-up period and whole study period. The safety data was not pooled, but presented separately for the three clinical studies. Overall, the size of the safety population included in the clinical studies can be considered sufficient and the groups. comparable in terms of demographics and baseline characteristics to allow a meaningful comparison of safety between CT-P16 and EU-Avastin in the context of a biosimilar MAA.

In the Phase 3 study CT-P16 3.1, at least 1 TEAE was reported for 96.2% and 93.0%, treatment related TEAEs for 51.6% and 50.6% and ≥ Grade 3 TEAEs for 43.8% and 41.9% of patients in the CT-P16 and EU-Avastin groups, respectively. In terms of common TEAEs by SOC, similar frequencies were reported in several SOCs, e.g. skin and subcutaneous tissue disorders were reported for 67.0% and 65.4% and gastrointestinal disorders for 44.9% and 40.7% of patients in the CT-P16 and EU-Avastin groups, respectively. In terms of most common TEAEs by PT, alopecia was reported for 63.8% and 63.4% of patients in the CT-P16 and EU-Avastin groups, respectively. TEAEs leading to study drug discontinuation was reported for 15.9% and 16.0% of the patients in the CT-P16 and EU-Avastin groups, respectively. The number of deaths (6.7% vs 7.0%), other TESAEs (20.0% vs 21.2%) and

related TESAEs (5.2% vs 6.7%), as well as AESIs were generally comparable between CT-P16 and EU-Avastin treatment groups.

Overall, although some numerical differences in the TEAEs were seen in the single dose PK studies (CT-P16 1.1 and 1.2) between study groups, there were no findings that were considered relevant in the context of similarity assessment of safety.

Immunogenicity

The proportion of healthy subjects who had post-dose ADA positive results was 4.3% in both CT-P16 and EU-Avastin treated subjects in study 1.1. In study CT-P16 1.2 no subject were ADA positive. In the phase III study 3.1 the prevalence of ADA positive patients at each time point was low (< 5%) and in line with historical studies. The overall ADA incidence was 78 [22.6%] and 83 [24.1%] for the CT-P16 and EU- Avastin treatment groups, respectively.

9.3. Uncertainties and limitations about biosimilarity

Quality

The overall approach to assess analytical similarity is found acceptable.

CT-P16 is considered to be highly similar to EU-approved Avastin with respect to the presented physicochemical and biological characterisations. Some minor analytical differences are noted but these have all been sufficiently justified by the applicant to have no clinical impact.

In conclusion, the provided data in the analytical similarity study between CT-P16 and EU-approved Avastin demonstrates a high degree of similarity in support of the biosimilarity claim.

Safety

Overall, the frequency of common TEAEs was somewhat higher in the CT-P16 group compared to EU-Avastin group in the Phase 3 study CT-P16 3.1. At least 5% difference in the number of patients with TEAEs was reported in the CT-P16 vs. EU-Avastin group in SOCs blood and lymphatic system disorders (including neutropenia), general disorders and administration site conditions and nervous system disorders. However, more patients were exposed to the CT-16 + chemotherapy vs EU-Avastin + chemotherapy after the first treatment cycle during the induction phase and the numerical differences were largely driven by the chemotherapy-related TEAEs during the induction period. Importantly, no major differences in the frequency of study drug-related TEAEs were observed in the three SOCs analysed.

The most notable difference between study groups were observed in the number of patients with ≥ Grade 3 dyspnoea which was reported for 7 vs 0 patients in the CT-P16 and EU-Avastin groups, respectively. Six (6) out of the 7 cases in the CT-P16 group occurred during the maintenance period. In a more thorough analysis of these cases, some imbalances in the baseline factors (e.g. presence of dyspnoea already at screening and smoking history) were identified that potentially could explain the differences. Further, pulmonary embolism was reported for 8 (2.3%) vs 3 (0.9%), and ≥ Grade 3 pulmonary embolism for 6 (1.7%) vs 3 (0.9%) patients in the CT-P16 and EU-Avastin groups, respectively, which could not be explained by imbalance of risk factors at baseline. On the other hand, e.g. drug related TESAEs leading to death was reported in 7 (2.0%) patients in EU-Avastin group and in 3 (0.9%) patients in CT-P16 group. Therefore, the numerical imbalances in these individual TEAEs were likely a chance finding.

None of the findings described above are considered to be uncertainties that would have an impact on the conclusion of biosimilarity.

9.4. Discussion on biosimilarity

From a quality perspective, an extensive biosimilarity exercise has been performed between CT-P16 and EU-approved Avastin, evaluating relevant quality attributes by a panel of state-of-the-art and standard analytical methods. The overall approach to assessing analytical similarity is found acceptable.

Overall, the provided data indicates a high degree of similarity between CT-P16 and EU-approved Avastin with respect to the presented physicochemical and biological characterisations. Some minor analytical differences are noted but these have all been sufficiently justified by the applicant to have no clinical impact.

In conclusion, the provided data in the analytical similarity study between CT-P16 and EU-approved Avastin demonstrates a high degree of similarity in support of the biosimilarity claim.

From a non-clinical perspective, the provided data indicates a high degree of similarity between CT-P16 and EU-approved Avastin with respect to the presented biological characterisations. Further, toxicology and toxicokinetic analysis in cynomolgus monkeys did not reveal differences between CT-P16 and EU-Avastin However, these data are not considered supportive of the biosimilarity evaluation.

Clinical

Biosimilarity in the pivotal PK study CT-P16 1.1 using healthy subjects has been formally demonstrated between CT-P16 and EU-Avastin and US-Avastin as in the primary PK parameters Cmax, AUC0-last and AUC0-inf, the 90% CI for the ratio of test-to-reference/comparator fell within the acceptance range of 80.00-125.00%. Also, in the supportive PK study in Japanese subjects in the primary PK parameters (i.e. Cmax, AUC0- last and AUC0-inf), the 90% CI for the ratio of test-to-reference fell within the acceptance range of 80.00-125.00%. The sensitivity analyses support the biosimilarity. Additional support for similarity between CT-P16 and EU-Avastin was obtained in the study in nsNSCLC patients (clinical study CT-P16 3.1). The mean Ctrough concentrations were comparable between CT-P16 and EU-Avastin.

As indicated above, efficacy data from the nsNSCLC study CT-P16 3.1 can be considered to support biosimilarity. The primary endpoint was met, with the risk difference contained within the pre-specified equivalence margin, and available sensitivity analyses support this view. This position is supported by the analyses for relevant time-dependent endpoints (PFS, OS). The safety of CT-P16 was consistent with the known safety profile of Avastin with or without chemotherapy that was used during the induction phase in the Phase 3 study CT-P16 3.1. Some numerical differences were observed in the TEAEs between the study groups, but considering the safety data as a whole, CT-P16 and EU-Avastin can be concluded to be biosimilar in terms of safety and immunogenicity.

9.5. Extrapolation of safety and efficacy

Clinical biosimilarity studies of CT-P16 and Avastin support the biosimilarity claim for approved oncology indications. This data has been assessed in detail previously in Procedure No. EMEA/H/C/005534/0000.