25 April 2025
EMA/170310/2025
Committee for Medicinal Products for Human Use (CHMP)

Consultation procedure Public Assessment Report (CPAR)

Consultation on an ancillary medicinal substance incorporated in a medical device

Medical device: XVIVO Heart Solution

Ancillary medicinal substance: Human serum albumin

Procedure No.: EMEA/H/D/006540

Applicant: DNV Product Assurance AS

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

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Administrative information

Invented name of medical device:	XVIVO Heart Solution
INN (or common name) of the ancillary medicinal substance:	Human serum albumin
Applicant for medical device CE certification:	XVIVO Perfusion AB
Notified body:	DNV Product Assurance AS Veritasveien 1 1363 Høvik Norway
Applied intended purpose of the device:	XVIVO Heart Solution is intended for use in cold flushing and continuous non-ischemic, hypothermic machine perfusion preservation of an isolated donor heart during retrieval, storage, and transportation, until eventual transplantation into a recipient.
Intended purpose of the ancillary medicinal substance in the device:	Human serum albumin provides a slightly hyper-oncotic solution, generating oncotic pressure across the capillary walls of the heart microcirculation to prevent loss of intravascular fluid into the extravascular space to avoid oedema formation during perfusion.
Pharmaceutical form(s) and strength(s) of the ancillary medicinal substance:	Extracorporeal solution 250 mg/ml

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List of abbreviations

AE	Adverse event
CAV	Cardiac allograft vasculopathy
CE	Conformité Européenne
CFU	Colony forming units
CKMB	Creatine kinase muscle brain type
CoA	Certificate of Analysis
DP	Drug Product
DS	Drug Substance
ECHO	Echocardiogram
FAC	Fractional area change
GMP	Good manufacturing practice
HSA	Human serum albumin
ICSS	Ischemic cold static storage
IFU	Instructions for use
IPC	In-process control
Ph Eur (EP)	European Pharmacopoeia
PMF	Plasma master file
MACTE	Major adverse cardiac transplant event
MCS	Mechanically circulatory support
MD	Medical device
MDR	Medical Device Regulation
mITT	Modified intention-to-treat
MoS	Margin of safety
NB	Notified Body
NIHP	Non-ischemic heart preservation, Hypothermic oxygenated perfusion
NtA	Notice to Applicants
PGD-LV	Primary graft dysfunction of the left ventricle
PGD-RV	Primary graft dysfunction of the right ventricle
ProBNP	Pro-brain natriuretic peptide
QOS	Quality overall summary
SADE	Serious Adverse Device Related Event
SCS	Static cold storage

SAE	Serious adverse event
SGD	Secondary graft dysfunction
T3	Triiodothyronine
TAPSE	Tricuspid annular plane systolic excursion
TnI	Troponin I
VSI	Validation supplementary information
USP	United States Pharmacopoeia
XHS	XVIVO Heart Solution
XHPS	XVIVO Heart Preservation System

Not all abbreviations may be used.

1. Background information on the procedure

1.1. Submission of the dossier

The notified body DNV Product Assurance AS submitted to the European Medicines Agency (EMA) on 12 June 2024 an application for consultation on Human serum albumin incorporated as ancillary medicinal substance(s) in the medical device XVIVO Heart Solution, pursuant to Article 52(9) of Regulation (EU) 2017/745, as amended.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus

The application was received by the EMA on	12 June 2024
The procedure started on	18 July 2024
The Rapporteur's first Assessment Report was circulated to all CHMP members on	7 October 2024
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	7 October 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 November 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 December 2024
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	3 February 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	27 February 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 March 2025
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	9 April 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for quality and safety including the clinical benefit/risk profile of Human serum albumin as ancillary medicinal substance(s) used in XVIVO Heart Solution on	25 April 2025

1.3. Manufacturers

1.3.1. Manufacturers of the active substance used in ancillary medicinal substance

Octapharma Pharmazeutika Produktionsgesellschaft mbH

Oberlaaer Strasse 235

1100 Vienna

Austria

Octapharma AB

Lars Forssells gata 23

112 51 Stockholm

Sweden

Grifols Therapeutic LLC

8368 U.S 70 Bus Highway

West Clayton, North Carolina

USA

Instituto Grifols, S.A.

Poligono Levante

c/Can Guasch, 2

Parets del Valles

08150 Barcelona

Spain

1.3.2. Manufacturers responsible for batch release

Instituto Grifols, S.A.

Poligono Ind. Levante

c/Can Guasc 2

Parets del Valles

08150 Barcelona

Spain

Octapharma AB

Lars Forssells Gata 23

112 75 Stockholm

Sweden

Octapharma Pharmazeutika Produktionsgesellschaft mbH

Oberlaaer Strasse 235

Favoriten

1100 Vienna

Austria

1.3.3. Manufacturer of the medical device

XVIVO Perfusion AB

Entreprenörsstråket 10

431 53 Mölndal

Sweden

1.4. Remarks to the notified body

Labelling

Following request, the applicant updated the instructions for use and added the concentration of human serum albumin and triiodothyronine. Additionally, as no data in xenogeneic settings was provided, the instructions for use and the intended use were requested to be amended, restricting the use of XVIVO Heart Solution on human hearts only.

The information in the instructions for use related to human serum albumin is considered acceptable.

1.5. Recommended measures to the notified body

As discussed at CHMP, it would be recommended that the notified body requests the following from the medical device manufacturer for device approval:

Area[1]	**Description**
Clinical	The instructions for use states that "the heart may be stored in the XVIVO Heart Assist Transport System at least 8 hours." It is recommended that the notified body considers whether this statement is supported by clinical data.

[1] Areas: quality, safety, including clinical benefit/risk profile.

2. Scientific overview and discussion

2.1. General information

Human Serum Albumin (HSA) is present as an ancillary substance in the XVIVO Heart Solution, which is considered as a medical device with an ancillary substance according to Article 1(8) of the Medical Device Regulation (MDR) 2017/745/EU. The Notified Body DNV Product Assurance AS in conjunction with their assessment of the medical device XVIVO Heart solution requested a consultation procedure to EMA for the assessment of human serum albumin as an ancillary medicinal substance incorporated in a medical device.

The XVIVO Heart Assist Transport System is a system for preservation of donor hearts during transportation using hypothermic non-ischaemic perfusion. In addition to the mechanical perfusion and transportation parts, the system consists of two different solutions. The XVIVO Heart Solution, which is the scope of the present consultation procedure, is a perfusion solution consisting of electrolytes, nutrients, human serum albumin and other additives. The product also contains the medicinal product triiodothyronine (T3) which will be assessed in a separate national consultation procedure. The XVIVO Heart Assist Transport System also encompass the XVIVO Heart Solution Supplement (a medical device incorporating additional medicinal products) which is added to the XVIVO Heart Solution prior to perfusion. The XVIVO Heart Solution Supplement will also be assessed in the national consultation procedure.

XVIVO Heart Solution

XVIVO Heart Solution is a sterile, clear, slightly yellow coloured, hyper-oncotic perfusion solution containing electrolytes, HSA, dextran, glucose and T3. It is intended for use in cold flushing and continuous non-ischemic, hypothermic machine perfusion preservation of an isolated donor heart during retrieval, storage, and transportation, until eventual transplantation into a recipient.

XVIVO Heart Solution is intended to be used with the XVIVO Heart Assist Transport, XVIVO Heart Assist Transport Perfusion Set and the XVIVO Heart Solution Supplement. Additives and drugs (i.e. sodium bicarbonate, heparin, insulin, potassium, imipinem or equivalent broad-spectrum antibiotic, 300 - 500 ml compatible, red blood cells from the blood bank) are also added when preparing the perfusion solution for the heart preservation. According to the instructions for use (IFU), the heart may be stored in the XVIVO Heart Assist Transport System for at least 8 hours.

XVIVO Heart Solution is supplied in 1000 mL Big Bore Infusion Bags with Permanent Clamp.

2.2. Quality documentation

2.2.1. For the ancillary medicinal substance or the ancillary human blood derivative itself

2.2.1.1. Active substance

2.2.1.1.1. Nomenclature and structure

XVIVO Heart Solution is a sterile, clear, slightly yellow coloured, hyper-oncotic perfusion solution containing electrolytes, human serum albumin (HSA), dextran, glucose and triiodothyronine (T3).

HSA is a globular single chain of 585 amino acids, crosslinked by 17 disulfide bridges. A single cysteine occurs at position 34. Albumin has a high percentage of ionic amino acids, glutamic acid and lysine, which confer a relatively high solubility to the protein.

HSA is the most abundant protein in human blood plasma. XVIVO uses human albumin solution manufactured by Grifols and Octapharma. Human Albumin solution is manufactured from human plasma for fractionation as starting material.

Human Albumin 25% is a clear, slightly viscous, pale yellow to amber coloured solution. The active substance is human albumin. The albumin content in the product is not less than 96% for Octapharma, not less than 95% for Grifols.

2.2.1.1.2. Manufacture, characterisation and process controls

Valid manufacturing authorisations and GMP certificates for the albumin manufacturing sites, listed in section 1.3 of this report have been presented. The manufacturing sites for the Human Albumin 25% are subject to routine GMP inspections. Therefore, compliance of the manufacture of the ancillary substances with cGMP is confirmed. Both sources of HSA are supported by a valid Plasma Master File certificate: EMEA/H/PMF/000002/04/IB/040/G for Grifols and EMEA/H/PMF/000008/05/II/33/G for Octapharma. HSA complies with Ph. Eur. monograph 0255 "Human Albumin Solution".

The manufacturing process of HSA consists of two steps, fractionation and purification, from plasma pooling to the sterile bulk.

The documentation provided by the Notified Body initially was considered insufficient as it did not present relevant parts of the CTD Module 3 Drug Substance or Drug Product sections. Only a Module 2 Quality Overall Summary of the human albumin solutions supplied by Instituto Grifols and Octapharma was provided. Respective Module 3 information was needed as part of the submission, following EC guidance on medical devices incorporating, as integral part, an ancillary medicinal substance or an ancillary human blood derivative MEDDEV 2.1/3 rev3, section C3, 2a and EMA guidance EMA/CHMP/578661/2010 rev 1.

In the responses to the questions raised by CHMP, the medical device (MD) manufacturer updated the 2.3.S Quality Overall Summaries and provided complete Module 3 Drug Substance and Drug Product dossiers for both sources of human albumin.

The MD manufacturer clarifies that the human albumin solutions supplied by Instituto Grifols and Octapharma are identical to the EU-approved Human Albumin finished products Plasbumin 25 and Albunorm 25%. Respective manufacturing authorisation numbers are provided (Plasbumin 25: 10537a/96; Albunorm 25%: DCP number DE/H/480/04). All albumin batches supplied to XVIVO are accompanied by EU/EEA OCABR batch release certificates. Therefore, the level of details on the two albumins used as ancillary substances is in line with the guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010).

Beside recent PMF certificates, with the response to CHMP questions, complete plasma master file (PMF) dossiers, confidential and non-confidential parts, have been provided to the MD manufacturer. The level of details on the quality and safety of the plasma used for the manufacture of the human albumins that is available to the MD manufacturer is now in line with the Medical Device Directive MDR 2017/745.

2.2.1.1.3. Specifications

HSA complies with Ph. Eur. monograph 0255 "Human Albumin Solution".

For Grifols, the active substance (the final sterile bulk) is tested for protein composition by capillary zone electrophoresis (CZE). The specification for the bulk has been set at not less than 95% albumin. This specification will ensure that the final container will meet specification prior to filling. The protein composition method, CZE, has been validated for Albumin (Human) products and a summary of the validation is presented in the QOS demonstrating its suitability. All other control tests are performed on the finished product level.

For Octapharma, in-process controls (IPC) and their acceptance criteria during the different steps of manufacture of Albunorm active substance are presented from plasma pool until the UF/DF final bulk. A separate active substance testing is not specified, as testing is performed at the finished product stage.

2.2.1.1.4. Stability

For Grifols, evaluations were performed to establish both the shelf-life and storage conditions for the drug substance. Batches for drug substance stability studies were manufactured at the production facility in Clayton, North Carolina, USA with a scaled-down model of the container/ closure system used with the commercial product. All data for the active substance met the established acceptance criteria for pH and aggregates throughout the duration of the studies. No significant changes in molecular weight distribution for the active substance bulk samples were observed through 30 days of storage at 2-8 °C, followed by NMT 72 h at 25°C, which is designated as the shelf life and storage conditions of the product.

For Octapharma, the current stability study report comprises data of selected stability parameters obtained over the period of 28 days carried out at +5 °C and +25 °C/60 % RH for four batches of Albumin 25 % bulk. The results demonstrate the stability of the bulk product for up to 28 days at NMT 25 °C which is designated as the shelf life and storage conditions of the product. All data are in accordance with the limits given in the relevant product specification and prove the stability of Albumin 25 % bulk.

2.2.1.2. Finished product

2.2.1.2.1. Description of the product and pharmaceutical development

The finished product for Albumin 25%, Albunorm 25% and Plasbumin 25%, is defined as the packaged final container (glass vials).

The applicant initially applied for complete omission of the "Drug product" sections (Modules 2.3.P and 3.2.P) because the sterile albumin bulk solution is defined as the active substance, which is not further formulated into a finished product before filling into the glass vials. This position was not endorsed by CHMP because the flow charts of the human albumin manufacturing processes at Grifols and Octapharma describe typical albumin finished product manufacturing steps. With the response and in line with MEDDEV 2.1/3 rev 3, separate Module 3 Drug Substance and Drug Product sections are made available to the MD manufacturer.

Remaining uncertainty regarding the final manufacturing steps of the human albumin solutions are now resolved, as the albumin manufacturers clearly indicate that the albumin solutions in glass vials supplied to XVIVO Perfusion AB are identical to the EU-licensed finished products Albunorm 25% (Octapharma) and Plasbumin 25 (Instituto Grifols). Regarding control of the active substance or finished product, with complete Module 3 dossiers submitted in the response, the supplier now also provided the release specifications for the albumin solutions to the manufacturer of the medical device,

including details on the release tests and their validation. The level of details on the finished product section is now in line with the guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010).

In conclusion, in line with MEDDEV 2.1/3 rev 3, the MD manufacturer has full access to all relevant documentation on the manufacture and control of the Human Albumin solutions used as ancillary substances in the XVivo Heart Solution. The documents confirm that both human albumin 25% solutions are EU-approved albumin products that comply with the requirements of Ph. Eur. monograph 0755 Human Albumin Solution. Each batch of albumin provided to the MD manufacturer is quality-controlled by EU/EEA OCABR batch release and respective certificates are made available to the MD manufacturer.

The MD manufacturer has also full access to all relevant information on the plasma used as starting material in the albumin manufacturing process, as laid down in the supplier's PMF documentation. It is also confirmed that quality agreements between both albumin suppliers and XVIVO Perfusion AB as customer are in place to inform the MD manufacturer on any relevant quality or safety issues associated with the human albumins.

2.2.1.2.2. Manufacture of the product and process controls

The finished product manufacture is standard for this type of product. Manufacturing process flow charts are provided.

2.2.1.2.3. Control of excipients

N-Acetyl-*DL*-tryptophan and sodium caprylate are the excipients for both Albumin 25%. The specifications for both excipients N-Acetyl-DL-Tryptophan and Sodium Caprylate comply with those set out in the current version of the applicable compendia (i.e., Ph. Eur. and USP).

2.2.1.2.4. Product specifications

Both finished product specifications comply with Ph. Eur. 0255 monograph Human Albumin solution.

2.2.1.2.5. Container closure system

For Grifols, the sterile albumin solution is aseptically filled into sterile 50 mL, 100 mL clear glass vial (USP/Ph. Eur. Type II). The bottles are closed with butyl stoppers and has an aluminium seal, lacquered with plastic flip off top.

For Octapharma, the container consists of colourless glass bottle of type II quality (Ph. Eur.). The bottles are closed with type I bromobutyl rubber stoppers (Ph. Eur.).

All containers comply with Ph. Eur. requirements. The container closure system choice has been validated with stability studies.

2.2.1.2.6. Stability of the product

For Grifols, the stability study was designed for evaluating the stability of Albumin 25% final container process validation conformance batches. The batches for this stability study were manufactured in Clayton, North Carolina, USA. Data are available for these batches through up to 30 months for the 30

± 2 °C storage condition and through up to 12 months for the 40 ± 2 °C storage condition. All testing followed the established protocol.

These batches will continue to be evaluated on stability at the licensed storage condition of 30 ± 2 °C through 36 months and at the accelerated storage condition of 40 ± 2 °C through 12 months. The results obtained to date for the stability study of the Albumin 25% final container process validation conformance batches support the stability of this product through 36 months when stored at the licensed storage condition of NMT 30°C (freezing should be avoided). This is the approved shelf life.

For Octapharma Albunorm 25% finished product: Based on the stability reports and the former long-lasting experience with albumin 25% finished product, the following shelf life has been approved: 36 months at 2 °C to 25 °C, not to be frozen and protected from light.

Stability data from both suppliers support the proposed shelf life.

2.2.1.2.7. Adventitious agents

The relevant information on the virus and prion reduction capacity including study reports has been provided for both albumins (i.e. from Octapharma and from Grifols).

A virus risk assessment is provided in relation to the usage of the medical device incorporating human albumin as ancillary substance.

No animal derived materials are used in the manufacture of Albumin (Human) of both albumin manufacturers.

Information related to adventitious agents is satisfactory.

2.2.2. For the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device

2.2.2.1. Qualitative and Quantitative particular of the constituents

The composition for XVIVO Heart Solution is as follows:

Glucose
Sodium Chloride
Potassium Chloride
Sodium dihydrogen phosphate
Magnesium chloride
Calcium chloride
Dextran 40
Human serum albumin
Triiodothyronine
Ethanol
Water for injection

The complete qualitative and quantitative composition has been provided.

2.2.2.2. Description of method of manufacture

The medical device XVIVO Heart Solution is manufactured in a plant designed for production of sterile products. Manufacturing is operated according to GMP regulations.

The manufacturing process is an adding and mixing procedure of ingredients in solution. All components are added in their original form, including the ancillary medical substance human serum albumin (Albumin 25%). In process control (IPC) during preparation of the bulk are specified. It has been clarified that bioburden testing takes place prior sterilization filtration and why control of albumin concentration is not implemented during the manufacturing process.

Prior to aseptic filling in sterile, flexible 1000 ml bags, the bulk solution is filtered through a sterilizing grade filter. The filled bags are inspected, labelled and packed in protective packaging.

Flowcharts have been provided for the manufacturing process and also a more detailed description of the sterilisation procedure.

2.2.2.3. Control of starting materials

The ancillary substance Human Serum Albumin is a starting material for which no separate control testing is performed at receipt. The release at XVIVO Perfusion AB relies on reviewing the EU official batch release results and a certificate of origin. A sample from each batch of bulk and/or finished product of the human blood derivative is tested by an Official laboratory. Each batch is accompanied with the following documentation: EU Official Control Authority Batch Release Certificate, FDA release certificate, CoA for EU, CoA for US, Certificate of Origin. No further testing is performed at incoming inspection. It is justified why no further testing is applied before albumin product enters the medical device manufacturing process.

2.2.2.4. Control test carried out at intermediate stages of the manufacturing process of the medical device

Bioburden testing takes place on the remaining unfiltered bulk solution, at the end of filtration. Bioburden testing as an in-process control takes place immediately prior to the final sterilization filtration. In-process controls were considered acceptable.

2.2.2.5. Final control tests of the ancillary medicinal substance or the ancillary human blood derivative in the medical device.

Extended final release verification testing was performed during process validation including tests with defined limits for included components: glucose, T3, dextran 40 and human serum albumin.

Performed and approved process validation showed reproducibility and consistency in final product testing, therefore analysis of glucose, T3, dextran and HSA have been assessed to be able to be excluded from final release testing. Final release verification testing is performed according to the criteria/test, methods, and limits in product specification for XVIVO Heart Solution, see below.

No specific tests are performed for the ancillary substance. From the results of the process validation and stability studies, the quantity of HSA was assessed as a parameter that could be omitted from the final product specification. The risk analysis has considered the assays and need for control and it has been assessed that no risk exist for inconsistent assays as long as manufacturing is performed according to the established master batch protocol.

The approach to release testing has been found satisfactory.

2.2.2.6. Stability

Stability data for products in the final packaging materials and analysed with the final methods, confirms that all analysed parameters remain within specification, when stored at 5 ± 3 °C/ambient RH for 24 months (and at 25 ± 2 °C/60±5% RH for 6 months). No strong trend can be seen for any of the analysed parameters.

The conclusion of the finalized stability studies, performed according to ICH-guidelines, is that XVIVO Heart Solution, remains within the shelf-life specifications and can be provided a shelf life of 24 months when stored dark at 5 °C ± 3 °C in primary (1000 ml) packaging and additional secondary packaging. Tests contained in product specification for batch release has been defined to turbidity, appearance colour, visible particles, subvisible particles, pH, osmolality, sterility and endotoxins.

The HSA concentration was within specification throughout the stability study.

Container Closure Integrity Test: The results show that all tested samples according to validated methods successfully passed the acceptance criteria for the Container Closure Integrity test both at beginning of and at end of shelf life for samples when stored in real time storage condition 5°C/ambient Rh. In support of baseline packaging validation, samples of XHS in different packaging configurations have been tested for container closure integrity after simulated transportation test with pass result. The requirements regarding integrity for the XHS containers are fulfilled.

In the CCIT report it is stated that the shelf life for XHS is 24 months from the date of manufacturing, but not longer than the shelf life for the Human Serum Albumin used in the product when stored in refrigerated condition.

2.2.3. Discussion and conclusion on chemical, pharmaceutical and biological aspects

2.2.3.1. Ancillary medicinal substance or the ancillary human blood derivative itself

Human albumin solutions 25 % from both suppliers used as ancillary substance in the medical device XVIVO Heart Solution are already licensed in other medical devices as ancillary substances. They are identical to EU-licensed Human Albumin products Albunorm 25% (manufacturer: Octapharma OPG) and Plasbumin 25 (manufacturer: Instituto Grifols). Therefore, with respect to quality and safety, there are no concerns for the use of these two albumin solutions as ancillary substances in the XVIVO Heart Solution.

The available documentation of the ancillary human blood derivative is sufficient to comply with the requirements of the Medical Device Regulation 2017/245 and EC guidance MEDDEV 2.1/3 rev 3. The Module 2 QOS, the Module 3 sections and the contents of the PMF provided to the MD manufacturer include the requested details on the quality and safety of the ancillary substance Human Albumin Solution from two different suppliers and respective details on the starting material "plasma for fractionation" (open and closed parts of the PMFs from both suppliers).

2.2.3.2. Ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device

The provided data supports the quality of the ancillary human blood derivative as incorporated in the medical device.

A nitrosamine risk assessment has been provided at the request of CHMP, which takes into account

considerations including the risk of potential nitrosamine presence from various sources, including incorporation of the ancillary substance into the device. The underlying risk assessment reports are made available to the MD manufacturer for both Human Albumin solutions.

2.3. Non-clinical documentation

The intended mode of action of HSA as a component in the XVIVO Heart Solution (XHS) is to provide a slightly hyper-oncotic solution, generating oncotic pressure across the capillary walls of the heart´s microcirculation to prevent loss of intravascular fluid into the extravascular space, thus avoiding oedema formation during perfusion. The hyper-oncotic pressure is created purely by physical means.

No specific pharmacodynamics or pharmacokinetic studies have been performed for HSA use in XHS, which is considered acceptable. HSA is well-characterised, has been used for decades as a plasma substitute and no differences are anticipated between its effects in XHS and standard *in vivo* applications. The potential dosage that might enter the organ recipient post-transplantation is well within normal dosages administered to patients *in vivo*.

The XHS contains electrolytes, HSA, dextran, glucose, and T3. The composition of XHS closely resembles the electrolyte makeup of plasma, though it contains higher concentrations of magnesium and potassium to keep the heart arrested and sufficient glucose to supply energy during cold preservation. Dextran 40 is added to prevent pathologic interactions with leukocytes, while T3 helps maintaining physiological levels during heart preservation.

Biological evaluation of XVIVO Heart Solution and additional toxicity assessment specifically related to HSA have been performed according to ISO 10993 standard series in the Biological Evaluation Report. Extensive testing, including physical and chemical characterization, cytotoxicity, hemocompatibility, and stability studies, confirmed that no further risk control measures are necessary. The solution and its packaging materials meet ISO standards, and assessments of impurities, contaminants, and material degradation revealed negligible toxicological risk. Exposure to XHS is a single-dose exposure, and among its components, only Dextran 40 has a half-life exceeding 24 hours, thereby minimizing the likelihood of long-term toxic effects.

Conservative calculations for the highest potential impurity amount in the 140 mL solution indicated an adequate margin of safety (MoS), with minimal toxicological concerns even under worst-case exposure. While sodium dihydrogen phosphate contains chromium slightly above the quantification limit, this level was not considered a realistic safety concern based on predicted exposure.

In summary, XHS’s safety profile is supported by extensive testing, historical clinical use of its components, and adherence to pharmacopeia standards, making it approvable from a non-clinical perspective.

Environmental Risk Assessment

Human serum albumin is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, XVIVO Heart Solution is not expected to pose a risk to the environment.

2.3.1. Discussion and conclusion on the non-clinical documentation

HSA is the most abundant protein in human blood plasma. It has been extensively studied and used as a plasma substitute. In the XVIVO Heart Solution, HSA's role is consistent with its natural function in the body. Even if the entire amount of HSA from the solution enters the recipient's bloodstream, it remains within the standard dosage range typically used in medical treatments. No pharmacodynamic,

pharmacokinetic or toxicity data were considered necessary. Based on the quality of the HSA, the nature of the substance, and long history of safe use as a plasma substitute during therapeutic plasma exchanges, the risk of long-term effects due to exposure to HSA in XHS, when used as intended, is concluded to be low and acceptable.

Based on the available information on biocompatibility for the device XVIVO Heart Solution, it is concluded that no further risk mitigation is needed at this stage, the product complies with the requirements in ISO 10993 standard series and is safe from a biocompatibility perspective when used as intended for both adults and children.

2.4. Clinical evaluation

According to the Applicant, the use of HSA in the perfusate is relevant because:

- The HSA provides oncotic pressure to the solution preventing loss of intravascular fluid into the extravascular space so that perfusion can be maintained in the coronary circulation without development of oedema.
- In addition, the HSA is a carrier protein providing hormones and nutrients bound to HSA to the tissue.

HSA is included in the formulation to provide a biocompatible solution and to provide a slightly hyper-physiological oncotic pressure to counteract the hydrostatic perfusion pressure and thereby avoid oedema during hypothermic perfusion.

HSA is classified as a well-known substance used already in the 1940s as a blood substitute to restore and maintain the oncotic pressure in the circulation. The intended function of HSA in XHS is the same as during *in vivo* use.

The intended action of the inclusion of HSA in XHS is to increase the oncotic pressure in the device, to make it similar to that in human blood. The concentration of HSA in blood is 45 g/L and is at that concentration responsible for about 70% of the oncotic pressure in blood. Since all other colloid osmotic components of the serum (e.g., gamma globulin, other proteins) are absent in XHS, the HSA concentration is increased to 64 g/L (45 g/L divided by 70%) to compensate.

A further increase of the HSA concentration to 75 g/L (after buffering and supplementation) is used to reach a slightly hyper-oncotic pressure to counteract hydrostatic pressure during perfusion at hypothermia. The addition of Dextran 40 at low concentration is only marginally contributing to the oncotic pressure.

2.4.1. Usefulness of the ancillary medicinal substance incorporated in the medical device as verified by notified body

According to the provided usefulness report from the notified body, DNV Product Assurance AS (Notified Body 2460) assessed and verified the usefulness of HSA as an ancillary medicinal substance in XVIVO Heart Solution (XHS).

DNV Product Assurance AS assessed the technical documentation submitted by the manufacturer of the device (XVIVO Perfusion AB) which contained data supporting the use of the ancillary medicinal substance in XHS. The following was assessed and confirmed:

The principal intended action of XVIVO Heart Solution is to preserve the explanted heart by cooling and facilitating oxygenated hypothermic perfusion. This is achieved through flushing with pre-cooled heart solution during retrieval followed by machine perfusion. The electrolyte composition of XVIVO Heart

Solution essentially mimics the electrolyte composition of plasma to maintain a normal electrolyte environment for the endothelium.

The HSA has an ancillary function of providing oncotic pressure to the solution preventing loss of intravascular fluid into the extravascular space to avoid oedema formation during perfusion.

Albumin has been extensively used clinically since decades as a colloid for the restoration and maintenance of circulating blood volume in cases of intravascular volume deficiency. The most important physiological function of albumin results from its contribution to the oncotic pressure of the blood. Furthermore, albumin functions as physiological carrier of different endogenous and exogenous substances (e.g. hormones, medicinal products).

The use of HSA in XHS is considered beneficial as it provides a physiological oncotic pressure. Provided that the HSA is produced according to current regulatory standards, the risk for transmission of infective agents via albumin appears negligible. The risk of allergic reaction is also very low as is indicated in instruction for use: when administered systemically, human serum albumin has been associated with rare allergic reactions (<1 in 1000) such as urticaria, fever, chills, pruritus and anaphylaxis. However, no such reactions have been reported with this substance when used for *ex vivo* organ or tissue perfusion or preservation.

Literature data as well as clinical data obtained from clinical investigations of XHS support usefulness of the HSA in the XVIVO heart preservation solution.

Based upon the relevant literature and manufacturer's clinical data, the notified body concluded that use of HSA in the device XHS demonstrates a clinical benefit to the patient. Further, the notified body concluded that the safety profile of the XHS is considered acceptable, and that the benefit/risk profile of the XHS is favourable.

The applicant submitted two clinical studies - NIHP2019 and ANZ-NIHP – described below.

<u>Non-ischemic preservation of the donor heart in heart transplantation (NIHP2019)</u>

The purpose of the clinical investigation was to evaluate if non-ischemic heart preservation with the XVIVO Heart preservation device is safe and superior to ischemic cold static storage of donor hearts.

The study was a single blinded, randomized controlled, multi-center clinical trial. Adult candidates for heart transplantation were randomized in a 1:1 ratio to the non-ischemic heart preservation group using the XVIVO Preservation System (NIHP, treatment arm) and the ischemic cold static storage group (SCS, control arm) that underwent preservation according to standard practices. The patients were followed for 12 months post-transplantation.

The XVIVO Heart Preservation System (XHPS) is a combination of the XVIVO Heart Box, XVIVO Heart Disposable and the Supplemented XVIVO Heart Solution. The XVIVO Heart Box can be described as a portable heart-lung machine. The main components are an automatic pressure/flow-controlled perfusion system, an automatic gas exchange system providing a carbogen gas mix of 95% O_2 and 5% CO_2 from a dedicated gas bottle, a leucocyte/arterial filter, a cooler unit, batteries, and software.

Primary Endpoint

The primary endpoint was defined as time-to-first-event of either cardiac related death, moderate or severe primary graft dysfunction of the left ventricle (PGD-LV) or of the right ventricle (PGD-RV) (according to Kobashigawa et al., 2014), acute cellular rejection ≥2R (according to Stewart et al.,

2005) or graft failure (use of mechanically circulatory support [MCS] or re-transplantation) within 30 days.

Key secondary endpoint

The key secondary endpoint was defined as time-to-first-event of either any cause of death, moderate or severe PGD-LV or PGD-RV (according to Kobashigawa et al., 2014), acute cellular rejection ≥2R (according to Stewart et al., 2005) or graft failure (use of MCS or re-transplantation) or cardiac allograft vasculopathy (CAV) ≥ 1 (according to Mehra, 2010) within 12 months.

Is should be noted that "use of mechanical circulatory support" served 2 different purposes, during determination if primary and/or key secondary endpoint has been reached.

- Any mechanical circulatory support that started in connection with the transplantation surgery, or during the first 24 hours after end of transplantation surgery, was used to determine the PGD endpoint only, even if duration was beyond the first 24 hours.
- Any newly started mechanical circulatory support initiated at 24 hours, or later after end of transplantation surgery, was used to determine the graft failure endpoint only. Use of MCS for indications other than graft failure were recorded but not considered fulfilling the definition of graft failure in the primary or key secondary endpoints.

Secondary Endpoint at 30 days

The secondary endpoints listed below were analysed at 30 days post-transplant on the mITT population.

- Incidence of the individual variables included in the composite primary endpoint at 30 days.
- Length of Stay at Intensive Care Unit.
- Incidence of Major Adverse Cardiac Transplant Events (MACTE).
- Incidence and duration of use of any postoperative mechanical circulatory support.
- Molecular biomarkers CKMB, TnI, and ProBNP at 6 ±2 h, 24 ± 6 h, 48 ± 6 h and 72 ± 6 h after cross clamp removal.
- ECHO data with Left ventricular ejection fraction within 24 hours after transplantation and at 1 week.
- ECHO data with Right ventricular function measured with Fractional area change (RV FAC) within 24 hours after transplantation and at 1 week.
- ECHO data with Tricuspid annular plane systolic excursion (TAPSE) within 24 hours after transplantation and at 1 week.

Results

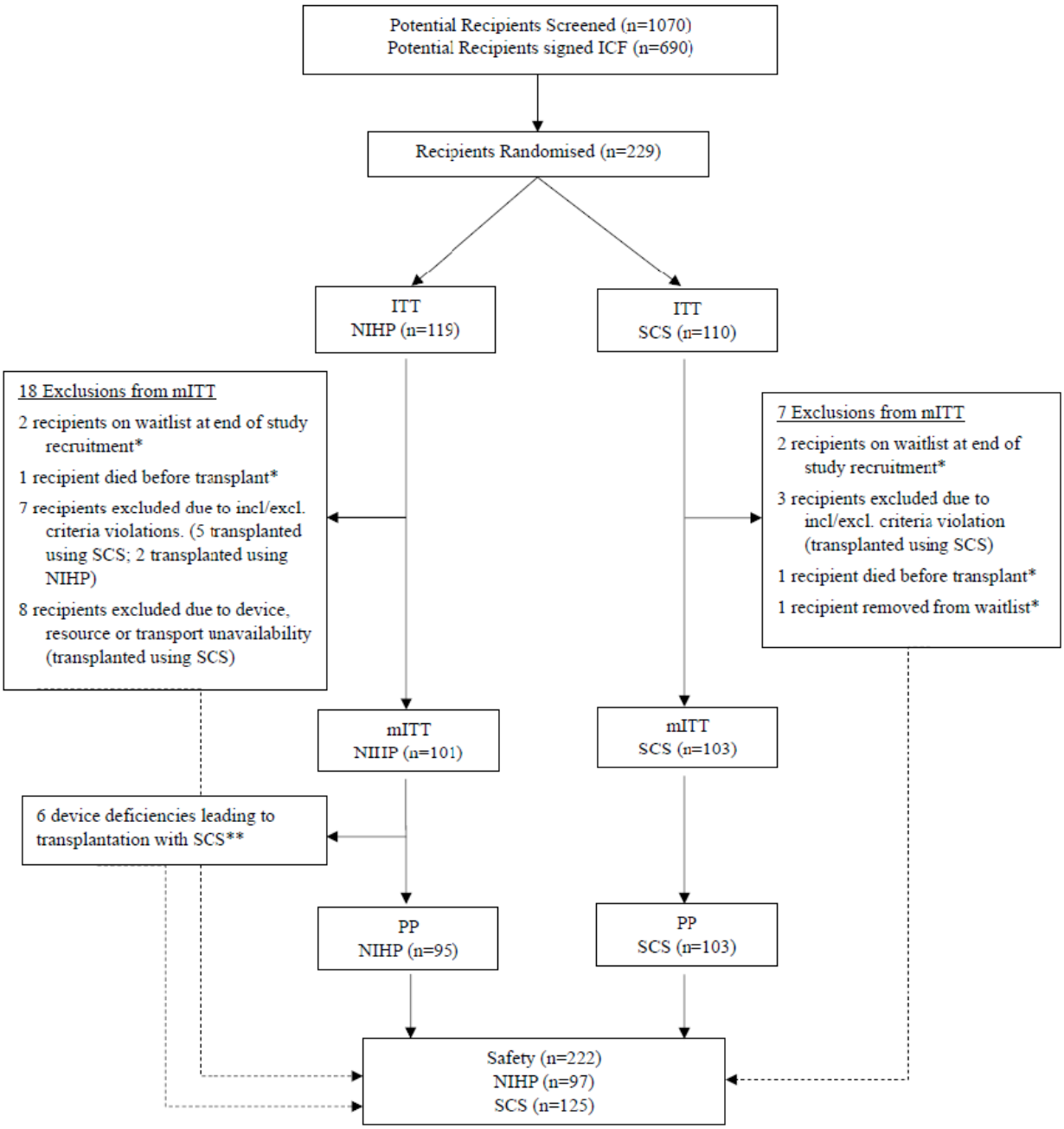

Figure 1. NIHP2019 patient flow consort diagram

**Recipients excluded from safety population due to not being transplanted at the end of the study.*

***All occurring before start of donor heart perfusion.*

Legend
SCS: Static cold storage = ICSS: ischemic cold static storage
NIHP: Hypothermic oxygenated perfusion = NIHP: non-ischemic heart preservation
ITT: Intention-To-Treat = all randomized participants
mITT: modified Intention-To-Treat = all randomized and eligible and transplanted participants
PP: Per Protocol = all transplanted participants without major protocol deviations
Safety: all participants that were randomized and underwent heart transplantation
ITT and mITT were analysed as randomized; PP and Safety were analysed as treated

Twenty-five randomized patients were excluded from the primary analysis, with more patients excluded in the NIHP (non-ischemic heart preservation, 18) arm than in the SCS (static cold storage, 7) arm.

From the mITT population, 6 patients were not included in the per protocol group due to device deficiencies leading to transplantation with static cold storage. The deficiencies were technical problems with the perfusion and were not related to the perfusion solution. Thus, in the per protocol there were 95 patients in the group receiving hypothermic oxygenated perfusion using XVIVO heart solution and 103 patients receiving the control treatment static cold storage.

Primary endpoint

The incidence of primary outcome events was 19 (18.8%) in the NIHP group and 31 (30.1%) in the SCS group, corresponding to a risk reduction of 44% (HR, 0.56; 95% CI, 0.32 to 0.99). The study failed to show superiority of NIHP compared to SCS in the primary analysis (log rank p-value of 0.059, Figure 4).

The predefined sensitivity analysis of the primary outcome adjusting for randomization strata showed a significant 46% risk reduction of the composite primary endpoint in XHPS compared to the SCS (HR, 0.54; 95% CI, 0.30 to 0.96, p=0.035, Table 6).

Most of the primary endpoint events were PGD, which occurred in 11 (10,9%) subjects in the NIHP group and in 29 (28,2%) subjects in the SCS group. Regarding the other components, the incidence was in general low. No graft failure events (use of mechanically circulatory support or re-transplantation) were reported.

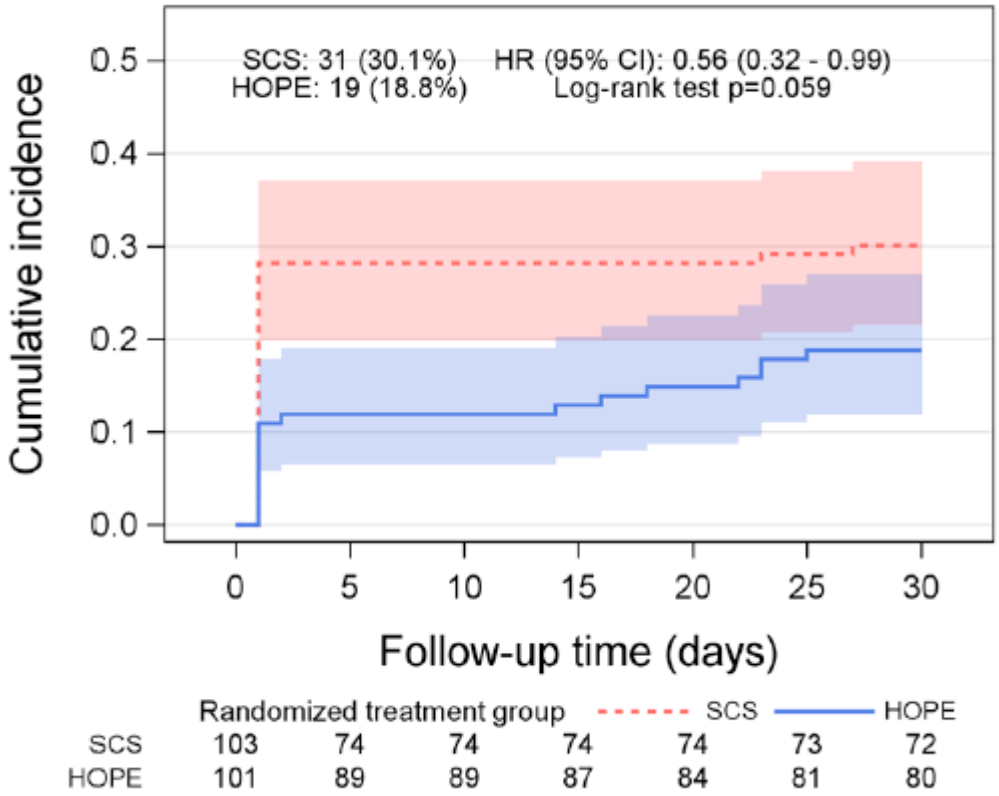

Figure 2. Cumulative incidence of primary endpoint events

Table 6. Primary Endpoint results

	NIHP N=101	SCS N=103	Treatment effect (95% CI)	p-value
Composite endpoint adjusted for randomization strata [1]	19 (18,8%)	31 (30,1%)	0,54 (0,30 - 0,96)	0,035
Unadjusted Composite endpoint [2]	19 (18,8%)	31 (30,1%)	0,56 (0,32 - 0,99)	0,059
Test of PH assumption [3]				0,016
PGD alone [4]	11 (10,9%)	29 (28,2%)	0,39 (0,20 - 0,73)	0,0025
Composite endpoint excl. PGD [2]	9 (8,9%)	9 (8,7%)	1,04 (0,41 - 2,62)	0,93
Composite endpoint including all-cause death [2]	21 (20,8%)	31 (30,1%)	0,62 (0,35 - 1,08)	0,12

[1] Descriptive data n (%), treatment effect expressed by HR (95% CI) from Cox regression (exact approximation of ties due to many ties), p-value from Cox regression

[2] Descriptive data n (%), treatment effect expressed by HR (95% CI) from Cox regression, p-value from log-rank test.

[3] Due to the proportional hazards assumption not being fulfilled, the analysis was divided into early (PGD alone) and late events (all other components).

[4] Descriptive data n (%), treatment effect expressed by RR (95% CI), p-value from Fisher's exact test

Secondary Endpoints

The number of reported events and corresponding statistics analysis are shown in Table 7. In the primary time-to-event analysis methodology the first occurring event for a subject was used. However, in the secondary endpoint analysis all primary endpoint events were accounted for and included. A subject may also had multiple endpoint events. This explains the numeral difference in the number of PGD events in the primary and secondary analysis.

The incidence of major adverse cardiac transplant events was reduced in NIHP compared to SCS group (7.9% [8 cases] vs. 26.2% [27 cases]) with a RR of 0.56 [95% CI 0.34; 0.92).

Table 7. Components of the primary endpoint

Secondary Endpoints	NIHP N=101	SCS N=103	Treatment effect (95% CI)	p-value
Individual variables of composite endpoint				
Cardiac death[1]	2 (2.0%)	4 (3.9%)	0.52 (0.09 - 2.81)	0.44
PGD severe[2]	5 (5.0%)	21 (20.4%)	0.24 (0.10 - 0.62)	0.0013
PGD moderate[2]	5 (5.0%)	6 (5.8%)	0.85 (0.27 - 2.70)	1.00
PGD right ventricle[2]	4 (4.0%)	9 (8.7%)	0.45 (0.14 - 1.42)	0.25
Cellular rejection[1]	7 (6.9%)	6 (5.8%)	1.21 (0.41 - 3.61)	0.73
Length of stay at intensive care unit (days) [3]	8 (6-14)	8 (5-15)	1·03 (0·79 - 1·42)	0·84
Number of patients still in ICU at day 31	12 (11·9%)	10 (9·7%)		
Incidence of MACTE[2]	18 (17.8%)	33 (32.0%)	0.56 (0.34 - 0.92)	0.023
Incidence of any postoperative MCS[2]	20 (19.8%)	28 (27.2%)	0.73 (0.44 - 1.21)	0.25
Duration of use of any postoperative MCS (days) [4]	8.2±4.7 n=20	8.6±7.5 n=28	-0.44 (-4.25 - 3.37)	0.82
Post-hoc analysis				
Site–reported PGD[2]	8 (7.9%)	27 (26.2%)	0.30 (0.14 - 0.63)	0.0007

[1] Descriptive data n (%), treatment effect expressed by HR (95% CI) from Cox regression, p-value from log-rank test.
[2] Descriptive data n (%), treatment effect expressed by RR (95% CI), p-value from Fisher's exact test.
[3] Descriptive data n (%), treatment effect expressed by HR (95% CI) from Cox regression (exact approximation of ties due to many ties), p-value from Cox regression.
[4] Descriptive data mean ± SD, treatment effect expressed by mean difference (95% CI), p-value from Fisher's non-parametric permutation test

The preservation time was longer in the NIHP compared to SCS group (240 vs. 215 minutes; p<0.003). According with the Applicant, this was in part related to the additional back table surgical preparation. Still, the median time from donor cross clamp to start of perfusion was only 28 minutes (cold ischemic time 1, Table 8). This interval includes the cold flush of the donor heart and the explant surgery. The study data is coherent with previous European data where approximately 40% of donor hearts are subject to more than 4 hours of cold ischemic time.

Table 8. Preservation and transplant duration

	NIHP, N = 101	SCS, N = 103	p-value
Total donor heart preservation time*	240 [194 - 274]; (103-444)	215 [183 - 253]; (63-380)	0·003
Cold Ischemic time 1**	28 [23 - 34]; (0-85)	*Not applicable for SCS*	
Device perfusion time	144 [107 - 177]; (14-284)	*Not applicable for SCS*	
Cold Ischemic time 2***	63 [55 - 79]; (32-154)	*Not applicable for SCS*	
Duration of recipient surgery	339 [273 - 424]; (199-887)	345 [277 - 426]; (165-719)	>0·9
Duration of recipient cross-clamp	81 [69 - 109]; (38-256)	82 [64 - 103]; (32-236)	0·4
ECC wean time	64 [43 - 85]; (0-307)	68 [49 - 95]; (0-196)	0·3
Duration of ECC	168 [140 - 213]; (89-591)	168 [134 - 204]; (70-335)	0·4

Preservation and transplantation durations, in minutes.
*From cross clamp application in donor until reperfusion in recipient. In SCS population this is cold ischemic time. For the NIHP group the different phases of the donor heart preservation time are detailed.
**From cross clamp application in donor until start of NIHP.
***From stop of NIHP until cross clam release in recipient.
Median [IQR], (Minimum-Maximum). [1] Wilcoxon rank sum test.

Key secondary endpoints

In the tables and figures below, the Applicant has alternately used the terms HOPE and NIHP to denote the same group.

The key secondary endpoint at 365 days showed a numerically lower incidence in the NIHP group (33.7%) compared to the SCS group (40.8%), HR 0.73 (95% CI 0.47 - 1.15 log-rank p-value= 0.23). A sensitivity analysis adjusting for randomization strata provided a similar estimate.

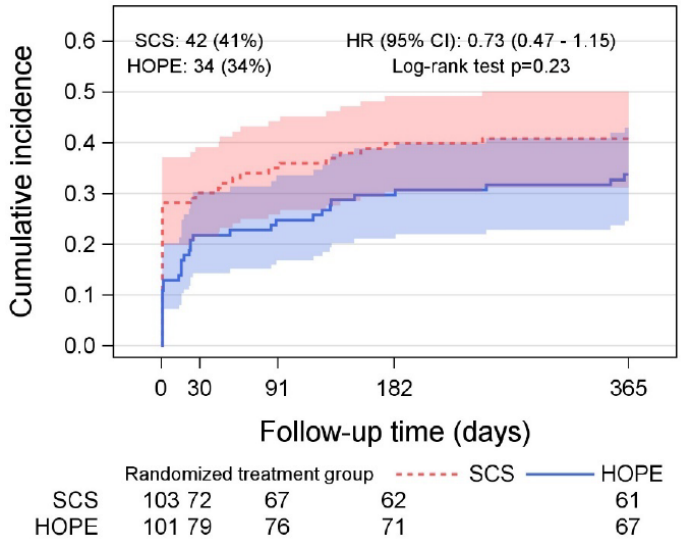

Figure 3. Cumulative incidence of key secondary endpoint events (12-month follow up)

The predefined sensitivity analysis adjusting for randomization strata for the composite secondary endpoint in HOPE compared to the SCS is provided in Table 9.

Table 9. Key secondary endpoint results (12-month follow up)

	HOPE N=101	SCS N=103	Treatment effect (95% CI)	p-value
Composite key secondary endpoint adjusted for randomization strata [4]	34 (33.7%)	42 (40.8%)	0.71 (0.45 - 1.11)	0.14
Unadjusted Composite endpoint [1]	34 (33.7%)	42 (40.8%)	0.73 (0.47 - 1.15)	0.23

[1] Descriptive data n (%), treatment effect expressed by HR (95% CI) from Cox regression (exact approximation of ties due to many ties), p-value from log-rank test.
[3] Descriptive data n (%), treatment effect expressed by RR (95% CI), p-value from Fisher's exact test.
[4] Descriptive data n (%), treatment effect expressed by HR (95% CI) from Cox regression (exact approximation of ties due to many ties), p-value from Cox regression.

The individual variables included in the key secondary endpoint were analysed separately (Table 10).

In the key secondary endpoint time-to-event analysis methodology, only the first occurring event for a subject was used. However, in the individual secondary endpoint analysis, all primary endpoint events were accounted for and included. A subject may had multiple endpoint events.

Table 10. Individual components of the key secondary endpoint (12-month follow up)

	HOPE N=101	SCS N=103	Treatment effect (95% CI)	p-value
Components of the key secondary endpoint				
PGD severe [1]	5 (5.0%)	21 (20.4%)	0.24 (0.10 - 0.62)	0.0013
PGD moderate [1]	5 (5.0%)	6 (5.8%)	0.85 (0.27 - 2.70)	1.00
PGD RV [1]	4 (4.0%)	9 (8.7%)	0.45 (0.14 - 1.42)	0.25
Cellular rejection [2]	14 (13.9%)	13 (12.6%)	1.10 (0.52 - 2.34)	0.80
Graft failure [2]	2 (2.0%)	1 (1.0%)	2.05 (0.19 - 22.57)	0.55
Coronary angiogram [2]	4 (4.0%)	2 (1.9%)	2.05 (0.38 - 11.19)	0.40
All-cause death [2]	8 (7.9%)	14 (13.6%)	0.57 (0.24 - 1.36)	0.20

PGD = primary graft dysfunction; PH = proportional hazard; ITT = intention-to-treat; MACTE = major adverse cardiac transplant events; MCS = mechanical circulatory support; HR = hazard ratio; OR = odds ratio; p25 = 25th percentile; p75 = 75th percentile; SD = standard deviation.
(1) Descriptive data n (%), treatment effect expressed by RR (95% CI), p-value from Fisher's exact test.
(2) Descriptive data n (%), treatment effect expressed by HR (95% CI) from Cox regression (exact approximation of ties due to many ties), p-value from log-rank test.

The number of days spent in intensive care were similar between the two groups with a mean of 8 days (Table 11). At 30-days post-transplant, 12 subjects from the NIHP arm were still being treated in the ICU compared to 10 subjects from the SCS group. No subjects remained in the ICU at 365 days post-transplant.

Table 11. Length of stay in ICU

	HOPE N=101	SCS N=103	Treatment effect (95% CI)	p-value
Length of stay at intensive care unit (days) [1]	8 (5-15)	8 (5-15)	1.07 (0.81 - 1.40)	0.65

p25 = 25th percentile; p75 = 75th percentile
[1] Descriptive data median (p25-p75) from cumulative incidence function handling death as competing risk, treatment effect expressed by HR (95% CI) from Cox regression (exact approximation of ties due to many ties), p-value from Cox regression.

The number of days spent in the hospital was similar between the two groups with a mean of 32 days in the NIHP group and 31 days in the SCS group (Table 12). At 365 days post-transplant, 1 subject in the SCS group was still being treated in the hospital.

Table 12. Length of Hospital stay

	HOPE N=101	SCS N=103	Treatment effect (95% CI)	p-value
Length of Hospital stay	32 (25-46)	31 (24-45)		0.37
Number of patients still at hospital at day 365	0	1		
Descriptive data median (p25-p75) from cumulative incidence function handling death as competing risk, treatment effect expressed by HR (95% CI) from Cox regression (exact approximation of ties due to many ties), p-value from Cox regression				

Australian and New Zealand Multicenter trial of Extended (6-8 hours) Non-Ischemic Heart Preservation of Donor Hearts for Transplantation (ANZ-NIHP)

The study was a non-randomized, single-arm, multi-centre trial of extended timeframe NIHP of donor hearts for transplantation. The aim of the trial was to investigate the effect of NIHP on donor hearts having an ischemic time of greater than 6 hours with respect to immediate and long-term post-transplant heart allograft function, the incidence of acute cardiac rejection and survival. In the initial phase of the trial, up to 10 donor hearts (i.e. 1-2 cases per site) were procured and transported with the NIHP method with <6 hours of anticipated ischemic time. The primary entry criterion into the trial for the remaining 26 donor hearts was a projected ischemic time of greater than 6 hours, a duration of ischemic time that would cause significant discomfiture in using cold static storage (CSS) because of the incidence of primary graft dysfunction which is significant and unpredictable in its occurrence.

Primary Endpoint

The primary endpoint was initially defined as either death, primary graft dysfunction (moderate or severe; according to Kobashigawa et al. 2014) or re-transplantation at 30 days.

The endpoint changed during the study to include only severe primary graft dysfunction. According with the Applicant, during the trial, it became apparent that the classification of PGD events according to the ISHLT guidance was potentially problematic particularly when using it as a tool to classify early donor heart performance. Specifically, vasoplegia is common after cardiac transplantation and the Applicant's experience demonstrates an incidence of 60-70%, particularly in heart recipients following transplant from a left ventricular assist device and after a longer cardiopulmonary bypass time. High doses of noradrenaline required to manage vasoplegia in these patients result in substantial inflation of the ISHLT inotrope score whilst not reflecting cardiac function. Therefore, the primary focus of the study was severe PGD and severe graft dysfunction (SGD) defined by need for post-transplant MCS.

Secondary Endpoints

The following exploratory measures were assessed at 30 days following heart transplantation:

- Graft function (secondary graft dysfunction (SGD)) including MCS
- ICU length of stay
- Re-transplantation
- Incidence of serious adverse events (SAEs)

SGD was defined as occurring at any time after transplantation where there was a clearly defined cause such as pulmonary hypertension, vasoplegia, or a technical problem.

Results

The study encompassed 36 transplantations. 7 of those had a projected ischaemic time of 6 hours (short preservation time cohort) and 29 had a projected time of 6-8 hours (long preservation time cohort).

There were no patient deaths within the first 30-days of follow-up (Table 13).

One patient in the long ischemic time cohort developed severe PGD-RV requiring a temporary right ventricular assist device.

Table 13. Primary endpoint

	ALL (N=36)	Long ischemic time (n=29)	Short ischemic time (n=7)
PGD - no. (%)	1 (2.8)	1 (3.4)	0
30 day mortality - no. (%)	0 (0)	0 (0)	0 (0)

Perfusion time, ischemic time and cardiopulmonary bypass time are indicated in Table 14. All hearts placed on the perfusion system were transplanted.

After 30-days of follow-up, 18 patients had been discharged from the hospital. A limitation of the provided 30-day analysis is that 18 patients were still in the hospital of which 3 patients were in the ICU.

Table 14. Operative Details

Operative Details	All (N=36)	Long Preservation Time (n=29)	Short Preservation Time (n=7)
Perfusion time - min	290.44±101.24	327.66±70.66	136.29±45.53
CPB time - min	165 (134.5, 234.5)	165 (134, 230.5)	227 (146, 257)
Total preservation time, min	382.14±83.50	413.59±53.01	251.56±54.63

2.4.2. Clinical safety of the ancillary medicinal substance incorporated in the medical device

Safety data from the NIHP2019 study (up to 12-months) is summarized below. Given the small size of the Australian and New Zealand multicenter trial and the single arm design, safety data from this trial is not further discussed in the report.

Adverse events

The proportion of subjects with a reported AE in NIHP was 100% (629 events) and in SCS 96.8% (704 events) (Table 15). The proportion of subjects with a reported SAE was 77.32% (238 events) in the NIHP compared to 79.2% (334 events) in SCS. In the NIHP group, 31 subjects (31.96%) had SAEs that were classified as a MACTE and in the SCS group, 61 subjects (48.8%) experienced a MACTE. MACTE was also a secondary endpoint at 30 days and was reported in 17.8% (n=18) and 32.0% (n=33) of subjects in the NIHP and SCS arm, respectively (RR 0.56 (0.34 -0.92) p=0.023).

Table 15. Summary of event reporting per group (Safety population)

Group	Events	Subjects		Events	Subjects
	NIHP, (N = 97)			SCS, (N = 125)	
Any event	629	97 (100%)		704	121 (96.8%)
Any non-serious AE	391	89 (91.75%)		370	105 (84%)
Any non-serious ADE	7	7 (7.22%)		1	1 (0.8%)
Any SAE	238	75 (77.32%)		334	99 (79.2%)
Any SADE	12	12 (12.37%)		33	33 (26.4%)
Any MACTE	32	31 (31.96%)		67	61 (48.8%)

Serious Adverse Events

Table 16 presents all serious adverse events (SAEs) reported during the 365 days of follow-up. The safety reporting was consistent with the findings in the primary and secondary endpoints, where more transplant dysfunction (PGD) and a slightly higher cardiac related mortality rate was seen in the SCS group.

Table 16. Serious Adverse events grouped by SOC (safety population)

SOC	PT	NIHP events	NIHP subjects	SCS events	SCS subjects
Blood and lymphatic system disorders		7	6 (6.2%)	3	3 (2.4%)
	Anaemia	2	1 (1%)	0	0
	Coagulopathy	2	2 (2.1%)	1	1 (0.8%)
Cardiac disorders		37	36 (37.1%)	61	56 (44.8%)
	Atrial fibrillation	4	3 (3.1%)	5	4 (3.2%)
	Cardiac arrest	3	3 (3.1%)	3	3 (2.4%)
	Cardiac failure	2	2 (2.1%)	2	2 (1.6%)
	Cardiac tamponade	7	7 (7.2%)	17	16 (12.8%)
	Pericardial effusion	10	10 (10.3%)	11	9 (7.2%)
	Right ventricular failure	1	1 (1%)	5	5 (4%)
	Atrial tachycardia	0	0	3	2 (1.6%)
Gastrointestinal disorders		11	11 (11.3%)	10	9 (7.2%)
General disorders and administration site conditions		2	2 (2.1%)	4	4 (3.2%)
	Multiple organ dysfunction syndrome	0	0	3	3 (2.4%)
Hepatobiliary disorders		5	5 (5.2%)	1	1 (0.8%)
	Acute hepatic failure	2	2 (2.1%)	1	1 (0.8%)
Immune system disorders		19	18 (18.6%)	28	22 (17.6%)
	Heart transplant rejection	12	11 (11.3%)	22	16 (12.8%)
	Transplant rejection	6	6 (6.2%)	6	6 (4.8%)
Infections and infestations		41	40 (41.2%)	59	58 (46.4%)
	COVID-19	1	1 (1%)	3	3 (2.4%)
	Cytomegalovirus infection	2	2 (2.1%)	2	2 (1.6%)
	Cytomegalovirus infection reactivation	3	3 (3.1%)	3	3 (2.4%)
	Mediastinitis	6	6 (6.2%)	8	8 (6.4%)
	Pneumonia	6	5 (5.2%)	6	6 (4.8%)
	Sepsis	3	3 (3.1%)	4	4 (3.2%)
	Septic shock	2	2 (2.1%)	5	5 (4%)
	Bronchopulmonary aspergillosis	0	0	3	3 (2.4%)
	Pneumonia bacterial	0	0	11	10 (8%)
Injury, poisoning and procedural complications		30	30 (30.9%)	55	54 (43.2%)
	Heart transplant failure	1	1 (1%)	2	2 (1.6%)
	Post procedural haemorrhage	4	4 (4.1%)	4	4 (3.2%)
	Transplant dysfunction	11	11 (11.3%)	36	36 (28.8%)
	Haemothorax	0	0	3	3 (2.4%)
Investigations		2	2 (1.7%)	1	1 (0.9%)
	Donor specific antibody present	2	2 (1.7%)	1	1 (0.9%)
Metabolism and nutrition disorders		9	8 (8.2%)	4	4 (3.2%)
Musculoskeletal and connective tissue disorders		0	0	1	1 (0.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		0	0	1	1 (0.8%)
Nervous system disorders		9	9 (9.3%)	17	17 (13.6%)
	Encephalopathy	1	1 (1%)	2	2 (1.6%)
	Cerebral haemorrhage	0	0	3	3 (2.4%)
	Ischaemic stroke	0	0	3	3 (2.4%)
Renal and urinary disorders		46	43 (44.3%)	54	54 (43.2%)
	Acute kidney injury	37	36 (37.1%)	47	47 (37.6%)
	Renal failure	8	6 (6.2%)	6	6 (4.8%)
Respiratory, thoracic and mediastinal disorders		9	9 (9.3%)	20	19 (15.2%)
	Acute respiratory failure	5	5 (5.2%)	10	10 (8%)
	Pleural effusion	2	2 (2.1%)	1	1 (0.8%)
Social circumstances		1	1 (1%)	0	0
Vascular disorders		10	9 (9.3%)	15	15 (12%)
	Chest wall haematoma	2	1 (1%)	1	1 (0.8%)
	Shock haemorrhagic	3	3 (3.1%)	1	1 (0.8%)
	Peripheral artery thrombosis	0	0	3	3 (2.4%)

*Events listed by System organ class (SOC) and Preferred Term (PT). Only PTs where a total of three (3) or more events have occurred are displayed separately.

Serious Adverse Device Related Events (SADEs) from Transplant Through 30 Days

In total, 40 of the SAEs reported during the initial post-transplant period and listed above were events where the relationship to the devices was considered possible, probably or causal. There were 9 events reported in the NIHP group. Eight out of the 9 events were judged as having a possible relationship to the use of the devices and 1 event was considered to have a causal relationship. This report concerned

an aorta perforation that was thought to have been caused by the attachment of the aorta to the cannula. The event was extensively reviewed and discussed, and it was clarified that the distal part of the aorta where the cable tie is used should have been removed prior to initiating the transplant surgery. The site was retrained to avoid further incidents. In the SCS group, there were a total of 31 SADEs reported, a majority of which were transplant dysfunctions or right ventricular failure.

Major Adverse Cardiac Transplant Event

A comparison of the number of MACTEs that have occurred in both groups can be found in Table 17.

MACTEs were defined as:

- Primary graft dysfunction (moderate or severe primary graft dysfunction of the left ventricle or primary graft dysfunction of the right ventricle (according to Kobashigawa et al., 2014))
- Cardiac allograft failure with need for mechanical circulatory support
- Cardiac allograft rejection (acute cellular rejection ⩾2R (according to Stewart et al., 2005))
- Acute onset of persisting ventricular arrythmia or cardiac arrest
- Multi-organ failure secondary to cardiac allograft failure

There was a significant difference in the number of subjects experiencing a MACTE event between the two groups (N=18 in NIHP and N=41 in SCS). The difference was driven by the large number of recipients with PGD (moderate, severe or RV) events in the SCS group (n=38) as compared to the NIHP group (n=8). Note that the incidence of MACTE was also analysed as a secondary endpoint on the mITT population, where similar results were obtained.

Table 17. Major Adverse Cardiac Transplant Events

	NIHP (N = 97)	SCS (N=125)	p-value
Major Adverse Cardiac Transplant Event D30	18 / 97 (19%)	41 / 125 (33%)	0.017
PGD (moderate/severe left ventricle PGD or presence of right ventricle PGD)	8 / 21 (38%)	38 / 50* (76%)	
Cardiac Allograft Failure/Re-Transplant (with need for mechanical circulatory support)	2 / 21 (9.5%)	3 / 50 (6.0%)	
Cardiac Allograft Rejection (acute cellular rejection > 2R)	5 / 21 (24%)	5 / 50 (10%)	
Acute Onset of Persisting Ventricular Arrhythmia or Cardiac Arrest	5 / 21 (24%)	1 / 50 (2.0%)	
Multi-Organ Failure Secondary to Cardiac Allograft Failure	1 / 21 (4.8%)	3 / 50 (6.0%)	

*Two (2) events in the SCS group fulfill two (2) different MACTE criteria but have been reported in the same SAE form. Hence, only 48 separate events are presented in the corresponding listing in Appendix G.

Survival

There were 23 deaths reported during the first year of follow-up in the safety population. 7 of these occurred in the NIHP group (2 cardiac related) and 16 occurred in the SCS group (8 cardiac related) (Table 18). None of the deaths were considered to have any relation to the devices used.

Table 18. Mortality – Safety population

Rejection grade	NIHP, N = 97	SCS, N = 125
All cause death	7 (7.2%)	16 (12.8%)*
Cardiac related	2 (2.1%)	8 (6.4%)

2.4.3. Clinical benefit/risk profile of the ancillary medicinal substance incorporated in the medical device

The XVIVO Heart Assist Transport System is a system for preservation of donor hearts during transportation using hypothermic non-ischaemic perfusion. In addition to the mechanical perfusion and transportation parts, the system consists of two different solutions, the XVIVO Heart Solution and XVIVO Heart Solution Supplement.

The XVIVO Heart Solution, which is the scope of the present consultation procedure, is a perfusion solution consisting of electrolytes, nutrients, human serum albumin (7.69%) and other additives. The ancillary role of human serum albumin is assessed in the present procedure. The final HSA concentration in the XVIVO Heart solution is 75 g/L after buffering and supplementation. In plasma, the albumin concentration is approximately 45 g/L and other plasma proteins also contribute to the final oncotic pressure in plasma. The Applicant clarified that the HSA concentration in the product was chosen to provide a physiological oncotic pressure solely by HSA and without other contributing proteins. The Applicant has chosen an HSA concentration that yields an oncotic pressure in the upper physiological range to ensure sufficient compensation to the lack of other plasma proteins in order to prevent formation of oedema during the hypothermic perfusion.

With the present submission, the Applicant submitted the study report for two clinical trials.

Non-ischemic preservation of the donor heart in heart transplantation (NIHP2019) was a single blinded, randomized controlled, multi-center clinical trial. Adult candidates for heart transplantation were randomized in a 1:1 ratio to the non-ischemic heart preservation group using the XVIVO Preservation System (NIHP, treatment arm) and the ischemic cold static storage group (SCS, control arm) that underwent preservation according to standard practices. In total 229 patients were enrolled across 15 investigational sites in 8 European countries. The patients were planned to be followed for 12 months post-transplantation.

The study failed to show superiority of NIHP compared to SCS in the primary analysis (log-rank p-value = 0.059). An additional concern is that a large number of randomized patients have been excluded from the primary analysis and that more patients were excluded in the NIHP arm than the SCS arm which may lead to bias favouring the NIHP arm. The incidence of primary outcome events was 19 (18.8%) in the NIHP group and 31 (30.1%) in the SCS group, corresponding to a hazard ratio of 0.56, (95% CI, 0.32 to 0.99).

Most of the primary endpoint events were PGD, which occurred in 11 (10,9%) subjects in the NIHP group and in 29 (28,2%) subjects in the SCS group. The key secondary endpoint at 365 days (encompassing similar components as the primary endpoint) showed a numerically lower incidence in the NIHP group (33.7%) compared to the SCS group (40.8%) but the difference was not significant (HR 0.73 [95% CI 0.47 - 1.15] log-rank p-value= 0.23). The total donor heart preservation time was slightly longer in the NIHP compared to the SCS group (240 vs. 215 minutes; $p<0.003$) which was according to the applicant in part related to the additional surgical preparation.

Given that the study failed to meet the primary objective and that no testing hierarchy appears to have been used for the secondary endpoints, the data is viewed as descriptive. The incidence of major adverse cardiac transplant events was lower in the NIHP group compared to SCS group (7.9% [8 cases] vs. 26.2% [27 cases]) with a RR of 0.56 [95% CI 0.34; 0.92).

The Australian and New Zealand Multicenter trial of Extended (6-8 hours) Non-Ischemic Heart Preservation (NIHP) of Donor Hearts for Transplantation (ANZ-NIHP) was a non-randomized, single-arm, multi-centre trial of extended timeframe NIHP of donor hearts for transplantation. The aim of the trial was to investigate the effect of NIHP on donor hearts with a projected ischemic time of greater than 6 hours. The trial did not involve randomization of donor hearts to either CSS or NIHP because, with an ischemic time of more than 6 hours with the known increasing risk of PGD, randomization to CSS was considered unethical. The study encompassed 36 transplantations; 7 of those had a projected ischaemic time of 6 hours (short preservation time cohort) and 29 had a projected time of 6-8 hours (long preservation time cohort). The mean total preservation time in the long cohort was 413 minutes and in the short cohort 251 minutes. The longest preservation time in the study was 8 hours and 47 minutes.

The primary endpoint was initially defined as either death, primary graft dysfunction (moderate or severe; according to Kobashigawa et al., 2014) or re-transplantation at 30 days. The endpoint was changed during the study to only include severe primary graft dysfunction. Patients were planned to be followed for 12 months. In the current procedure, a 30-day analysis of the primary endpoint was provided. There were no patient deaths within the 30-days follow up period. One patient in the long ischaemic time cohort developed severe RVD requiring a temporary right ventricular assist device. The 12-month data is not yet available and limited conclusions can be drawn from the presented 30-day analysis.

The NIHP2019 study is considered relevant for the assessment of safety given the controlled design. The proportion of subjects with a reported AE in the NIHP group was 100% (629 events) and in the SCS group was 96.8% (704 events). The proportion of subjects with a reported SAE was 77.32% (238 events) in the NIHP compared to 79.2% (334 events) in SCS. Among the PTs, frequencies were similar in the two treatment arms but it is noted that transplant dysfunction was more frequent in the SCS group than in the NIHP group (28.8% vs. 11.3%).

During the first year of follow-up, there were 23 deaths, with a higher number in the SCS group (12.8% [16 cases]) compared to the NIHP group (7.2% [7 cases]). Among these, the number of cardiac-related deaths was higher in the SCS compared to the NIHP group (6.4% [8 cases] vs. 2.1% [2 cases]).

The reported device deficiencies were mainly related to other components of the system than the perfusion solution. Two reports concerned the perfusion solution but was related to the instructions of use and handling of the device.

No donor hearts were lost during the perfusion procedure. Two hearts were not transplanted due to suspected malignancies in the donors and one heart was not transplanted since recipient died when preparing for the transplant.

The long-standing clinical experience with albumin solutions and with medicinal products containing albumin as a constituent should be taken into account. Provided that the albumin is produced according to current regulatory standards, the risk for transmission of infective agents via albumin appears negligible.

2.4.4. Discussion and conclusion on the clinical evaluation

The current assessment concerns the ancillary role of HSA in the XVIVO heart solution which is added to provide oncotic pressure. The submitted clinical studies provide general information on the performance of the device but not on the specific influence of human serum albumin. The applicant has chosen an HSA concentration (75g/L) that yields an oncotic pressure in the upper physiological range,

to ensure sufficient compensation for the lack of other plasma proteins preventing formation of oedema during the hypothermic perfusion. The overall rational for inclusion is thus clear. The main RCT failed to show superiority of the XVIVO heart assist transport system versus the standard of care SCS when used for transplantations with the median preservation time used in the study (240 min vs. 215 min in the NIHP and the SCS group, respectively). However, the safety data of up to 1 year do not indicate any new risks compared to standard of care. The second small single arm study employed longer perfusion times in order to use organs that would not otherwise be available due to long transport times which may be relevant in support for the proposed claim "the heart may be stored in the XVIVO Heart Assist Transport System at least 8 hours." This is however considered out of scope of the current assessment of HSA while the device in its entirety is evaluated by the notified body.

2.5. Overall conclusions

With respect to quality and safety, the available documentation of the ancillary human blood derivative is considered sufficient to comply with the requirements of the Medical Device Regulation 2017/745, MDCG guidance 2020-12 and previous MEDDEV 2.1/3 rev 3. The application is recommended for approval from a quality point of view.

From a clinical point of view, the usefulness of Human Serum Albumin in XVIVO heart Solution is considered demonstrated given the clear rationale for inclusion. The provided safety data from the RCT have not indicated any new risks. Provided that the HSA is produced according to current regulatory standards, the risk for transmission of infective agents appears negligible. The instructions for use states that the heart may be stored in the XVIVO transport system for at least 8 hours. When assessing the device in its entirety, it is recommended that the notified body considers whether this statement is supported by clinical data (please see recommended measures to the notified body).

The B/R for the use of Human Serum Albumin in the product is considered positive.

2.6. Recommendation

Based on the review of data submitted, the CHMP considered by consensus that the quality and safety of Human albumin solution used as ancillary medicinal substance in the XVIVO Heart Solution are acceptable (including a favourable benefit risk profile) therefore granted a positive opinion in the consultation procedure.