EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2022
EMA/CHMP/225453/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inpremzia

International non-proprietary name: insulin human (rDNA)

Procedure No. EMEA/H/C/005331/0000

Note

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

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List of abbreviations

2-DG	2-Deoxyglucose
2-DG6P	2-DG-6-Phosphate
ACE	Angiotensin Converting Enzyme
ADA	anti-drug antibodies
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AKT	p-Protein Kinase B
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine Triphosphate
AUC	Area under the concentration-time curve
AUC_{GIR}	Area under the glucose infusion rate-time curve
AUC_{INS}	Area under the insulin concentration time curve
Bax	Bcl-2-like Protein 4
Bcl2	B-cell Lymphoma 2
BHI	Biosynthetic Human Insulin
BLQ	below the limit of quantitation
BMI	Body mass index
BUN	Blood urea nitrogen
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	Confidence interval
C_{max}	Maximum concentration
CMO	Chief Medical Officer
CRF	Case report form
CRO	Clinical Research Organisation
CSP	clinical study protocol
CTG	CellTiter-Glo
CV	Coefficient of variation
CYP	Cytochrome P450
DFT	Deviation from the target
dL	decaliter
DMF	Drug Master File
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic CRF
EEA	European Economic Area

ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
ENaC	Epithelial Sodium Channel
EPAR	European Public Assessment Report
EU	European Union
FACS	Fluorescence-Assisted Cell Sorting
FDA	United States Food and Drug Administration
FFA	Free Fatty Acid
FRAP	Fluorescence Recovery After Photobleaching
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GH	Growth Hormone
GIR	Glucose infusion rate
GLP	Good Laboratory Practice
GLUT4	Glucose Transporter Type 4
HbA_{1C}	Glycosylated hemoglobin
HbsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
hrs	Hours
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDDM	Insulin-Dependent Diabetes Mellitus
IEC	Institutional Ethics Committee
IFG	impaired fasting glucose
IGF-1	Insulin-like Growth Factor-1
IGT	impaired glucose tolerance
INN	International Non-proprietary Name
IR	Insulin Receptor
IRB	Institutional Review Board
IRS	Insulin Receptor Substrates
IU	International Units
IV	Intravenous
ka	Association Rate Constant
kd	Dissociation Rate Constant
KD	Equilibrium Dissociation Constant
K_{el}	Elimination Rate Constant

Kg	Kilogram
LH	Luteinizing Hormone
LS mean	Least squares mean
MAA	Marketing Authorisation Application
MAO	monoamine oxidase
MAOI	Monoamine Oxidase Inhibitors
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minutes
MPCC	Micro Patterned Co-cultures
ND	Not Determined
OECD	Organisation for Economic Co-operation and Development
PARP	Poly ADP Ribose Polymerase
PD	Pharmacodynamics
Ph.Eur.	European Pharmacopoeia
PHH	Primary Human Hepatocytes
PI	Principal Investigator
PI3K	Phosphatidylinositol-3'-kinase
PK	Pharmacokinetics
pM	picomolar
PPAR-γ	Peroxisome Proliferator-Activated Receptor
PPI	Purified Porcine Insulin
rDNA	Recombinant deoxyribonucleic acid
RHI	Regular human insulin
RMP	Reference Medicinal Product
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
SOA	Schedule of assessments
SPR	Surface Plasmon Resonance
SS	Steady state
$t_{½}$	apparent terminal insulin half-life
TAMC	Total Aerobic Bacterial Count
TEAE	Treatment-emergent adverse event
TG	Triglyceride

t_{GIRmax}	Time to maximum glucose infusion rate
T_{max}	Time to maximum serum insulin concentration (in concentration time curve)
TSH	Thyroid-stimulating hormone
TUNEL	Terminal Deoxynucleotidyl Transferase dUTP Nick End Labelling
TYMC	Total Yeast and Moulds Count
U	Unit
USP	Unites States Pharmacopeia
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Baxter Holding B.V. submitted on 5 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Inpremzia, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

'Treatment of patients with diabetes mellitus who require intravenous insulin administered by healthcare professionals for the maintenance of glucose homeostasis.'

1.2. Legal basis, 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 composed of administrative information, complete quality data, a clinical bioequivalent study with the reference medicinal product Actrapid and with appropriate own applicant's non-clinical and clinical data.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Actrapid, 100 IU/ml, Solution for injection in vial
- Marketing authorisation holder: Novo Nordisk
- Date of authorisation: 07-10-2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/230

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Actrapid, 100 IU/ml, Solution for injection in vial
- Marketing authorisation holder: Novo Nordisk
- Date of authorisation: 07-10-2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/230

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

- Product name, strength, pharmaceutical form: Actrapid, 100 IU/ml, Solution for injection in vial
- Marketing authorisation holder: Novo Nordisk
- Date of authorisation: 07-10-2002
- Marketing authorisation granted by:

- Union
- Union Marketing authorisation number(s): EU/1/02/230

- Bioavailability study number(s): Study CEL-HI-203

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The applicant sought scientific advice in 2017 (Procedure No.: EMEA/H/SA/3726/1/2017/III) concerning quality development, pre-clinical development and clinical development, including a clarification scientific advice in 2018.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Andrea Laslop Co-Rapporteur: Outi Mäki-Ikola

The application was received by the EMA on	5 March 2020
The procedure started on	26 March 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	10 June 2020
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 June 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	29 June 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 January 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	01 March 2021

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 March 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 March 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 January 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 February 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	18 February 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Inpremzia on	24 February 2022
The CHMP adopted a report on similarity of Inpremzia with Amglidia on (see Appendix on similarity)	24 February 2022

2. Scientific discussion

2.1. Problem statement

Inpremzia is a human insulin analogue produced by recombinant DNA technology. A pre-diluted insulin solution for IV infusion is not commercially available in the EU and insulin for infusions must be diluted on site in the hospital introducing multiple opportunities for dosing errors.

Inpremzia, formulated as ready-to-use insulin solution for IV application in the hospital or emergency department setting, was developed as a biological product similar to Actrapid (100U/ml, solution for injection, authorised in the EU since 2002) to address these insulin dosing-associated issues.

2.2. About the product

Inpremzia is a fast-acting human insulin analogue (ATC code: A10AB). The active substance in Inpremzia, produced in *Pichia pastoris* (also referred to as *Komagataella pastoris*) using recombinant DNA (rDNA) technology, is a polypeptide hormone structurally identical to natural human insulin. The molecule consists of 51 amino acids arranged in two chains (Chains A and B) that are linked by two inter- and one intra-disulphide bond.

Inpremzia has been developed as a biosimilar to the reference product Actrapid, which is indicated for treatment of diabetes mellitus. In contrast to Actrapid, which is approved for subcutaneous and intravenous application, but has to be diluted for intravenous application, Inpremzia is formulated as a pre-diluted infusion in bags containing 100 ml equivalent to 100 IU (equivalent to 3.5 mg) insulin.

The applicant initially applied for a restricted indication, "the treatment of patients with diabetes mellitus who require intravenous insulin administered by healthcare professionals for the maintenance of glucose homeostasis".

2.3. Type of Application and aspects on development

Inpremzia was developed as a biosimilar medicinal product to the European reference medicinal product (RMP), Actrapid solution for injection, which is marketed by Novo Nordisk with an initial EU date of first authoristion of 7 October 2002.

The clinical development of Inpremzia is based on two studies:

- Study CEL-HI-203, a comparative PK/PD, double-blind, randomised, two-treatment, two-period, 2-way crossover, hyperinsulinaemic euglycaemic clamp trial in healthy adult male subjects who received single IV infusions of the test (Inpremzia/Insulin Human Baxter/Celerity's Regular Human Insulin) and the EU-RMP Actrapid. 60 subjects were enrolled and 56 subjects completed the trial.
- Study CEL-HI-200, a comparative PK/PD, double-blind, randomised, 2-way crossover, active comparator, euglycaemic glucose clamp trial comparing Baxter's insulin product with the US reference listed drug Novolin R, conducted for US registration. Celerity's Regular Human Insulin (rDNA origin) 1 IU/mL product was approved in the US in June 2019 as MYXREDLIN. At EMA's request, a top-level summary (CSR) from the US study CEL-HI-200 was included in the dossier.

Study CEL-HI-203 is considered the pivotal study for this application due to comparison to the EU-reference product Actrapid. Study CEL-HI-200 is only considered for supportive purposes.

Scientific Advice

The applicant sought scientific advice in 2017 (Procedure No.: EMEA/H/SA/3726/1/2017/III) concerning quality development, pre-clinical development and clinical development, including a clarification scientific advice in 2018. Several points were noted during the procedure:

Different strength and method of administration than the RMP

The strength of the test product and the reference product Actrapid is different; Actrapid is formulated for injection with vials containing 100 U/mL whereas Inpremzia is formulated as an infusion bag containing 1 U/mL.

Despite the fact that the Guideline on similar biological medicinal products (CHMP/437/04 Rev 1) states that biosimilar and reference product must have the same posology and route of administration, the approach to develop a biosimilar product with reference to a non-authorised diluted preparation of Actrapid solution for injection was considered potentially acceptable by the CHMP, provided that the difference in strength will not affect the safety or the efficacy of the insulin and that all necessary measures are taken in order to minimize the risk for medication errors.

In contrast to the RMP Actrapid, which is usually administered subcutaneously, but can also be administered by intravenous (IV) infusion, Inpremzia will be administered exclusively by IV route. It was acknowledged that the subcutaneous route is not an option.

Choice of reference product for the initial and pivotal similarity assessment

The applicant proposed to use the US-comparator Novolin R for the initial similarity exercise, whereas the pivotal similarity exercise is based on EU reference product Actrapid only. This approach was agreed in principle.

Analytical biosimilarity exercise

The proposed analytical biosimilarity exercise was in principle agreed; however concerns were expressed concerning the initially proposed number of three Actrapid lots for similarity evaluation at the quality level. Following this advice, up to nine Actrapid lots were included in the pivotal similarity exercise. Furthermore, the strategy for setting similarity acceptance criteria was questioned in the Scientific Advice. In addition, it was highlighted that due to the different expression systems the focus should be laid on the impurity profile, in particular on differences in glycosylation variants. Additional comparison confirms the low and comparable levels of glycosylation variants in both products.

Further questions in the quality part addressed the proposed drug substance release specifications, the proposed reference standard strategy and the stability programme.

PK/PD measures insufficiently explained

Initially, the measurement periods of the PK endpoint C_{max} and PD endpoint GIR_{max} as well as the target blood glucose level in the clamp study were inadequately explained. In the clarification Scientific Advice, the applicant stated the target level and specified that the endpoint measurements are focussed on steady state conditions within the clamp procedure, which was considered appropriate.

No clinical immunogenicity data or testing planned

The product is intended only for short-term use, for hours or a few days. Hence, long-term safety studies on formation of anti-insulin antibodies (AIA) during the use of the product as for insulin formulations intended for chronic administration over years were not seen as crucial. The risk of uncontrolled surges of glucose due to pre-existing (neutralizing) AIA was considered a smaller problem for IV administration than for SC injection and moreover, assessment of clinically relevant

immunogenicity may be difficult to detect due to low frequency. Therefore, CHMP concluded that immunogenicity assessment has to rely strongly on the robustness of the biosimilarity exercise.

Overall, the recommendations of the Scientific Advice were in most parts followed and implemented.

2.4. Quality aspects

2.4.1. Introduction

Inpremzia is presented as a solution for infusion containing 1 IU/mL insulin human as active substance. Other ingredients are sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous and water for injections.

Inpremzia is a pre-mixed, sterile non-pyrogenic rapid acting regular insulin produced in *Pichia pastoris* using recombinant DNA (rDNA) technology. It is proposed as a biosimilar medicinal product to the EU authorised reference product Actrapid (EMEA/H/C/000424) and intended for intravenous administration for the treatment of diabetes mellitus.

The product is available in a laminate plastic bag, with a plastic infusion port. Infusion bags are packed in cardboard cartons. They are intended for single use only. A pack size of 12 infusion bags is proposed.

2.4.2. Active substance

2.4.2.1. General information

The Human Insulin Baxter/Inpremzia molecule consists of 51 amino acids arranged in two chains. The A chain contains 21 amino acids and B chain contains 30 amino acids. The A chain and B chain is further linked by two inter-chain disulphide bonds derived from cysteine residues (A7-B7 and A20-B19) and a single intra-chain disulphide bond exists within A chain (A6-A11). The primary activity of Inpremzia is the regulation of glucose metabolism. Insulin binds to insulin receptors present on a range of cells, which leads to decreased levels of blood glucose which is facilitated by cellular uptake of glucose and simultaneous inhibition of glucose output from the liver.

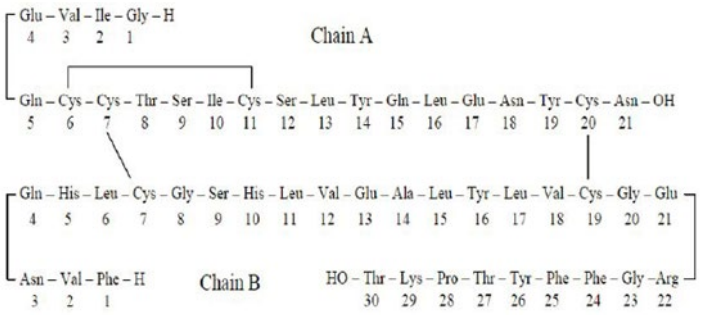
A Chain: GIVEQCCTSICSLYQLENYCN

B Chain: FVNQHLCGSHLVEALYLVCGERGFFYTPKT

The molecular formula of human insulin is $C_{257}H_{383}N_{65}O_{77}S_6$ and the relative molecular mass is 5828 Da.

The amino acid sequence of 3-letter code with indicated disulphide bond is as follows:

Figure 1: primary structure of human insulin



2.4.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The active substance is manufactured using *Pichia pastoris* methylotrophic yeast transformed with the expression plasmid harbouring the synthetic human insulin precursor gene.

The active substance upstream fermentation process consists of working cell bank (WCB) vial thaw, inoculum expansion in shake flasks, seed culture expansion in seed fermenter, a fed-batch production culture in a bioreactor, and harvest of cell culture supernatant from the bioreactor. During the batch phase, the fermentation uses glycerol as a carbon source to increase the cell mass. During the induction phase, methanol is used to induce the secretion of human insulin precursor into the medium.

The downstream process is separated into downstream processes I, II and III, each comprising of multiple steps. In the downstream process I (DSP-I), the human insulin precursor secreted out of the cells by fermentation is isolated via centrifugation, concentrated using cation exchange chromatography (CIEX), crystallised and centrifuged. In the DSP-II, the human insulin precursor is then subjected to a reaction, followed by crystallisation and. In the DSP-III, the product is purified by a series of chromatographic steps. The eluate from the last chromatography step is sterile filtered (0.2µ) and crystallised as human insulin. The crystal slurry is lyophilised and stored at -20±5ºC in amber coloured USP Type III glass containers. No reprocessing is intended.

In general, the manufacturing process is adequately defined and the purpose of each manufacturing step has been discussed. The manufacturing process, with process parameters and process controls and their ranges have been outlined in flow diagrams and additional information has been provided for each step.

Process parameters such as temperature, time, pH, DO_2, agitation speed, agitation frequency, flow rate, pressure, %UV, conductivity, and hold time are listed. In the initial application, criticality of process parameters in relation to the impact on the Critical Quality Attributes (CQAs) and associated controls were not defined. Moreover, the proposed operating ranges for process parameters and acceptance criteria for process controls were not supported by process characterisation data. Thus, an overarching **major objection** was raised during the procedure in view of the control strategy and process validation. To address this Major Objection a detailed process characterisation report was submitted. The main objectives of process characterisation were a) to identify key, critical and non-critical process parameters and b) to determine the proven acceptable ranges (PARs) (and in certain process steps the normal operating ranges (NORs)).

The dossier has been updated with an overview of process characterisation activity and a brief summary of the outcome of process characterisation including a reference to the detailed report. In this attached report for each single manufacturing stage a detailed description of the conducted characterisation is included. The first potential critical process parameters (CPPs) have been identified via risk assessment (i.e. FMEA). These process parameters were then studied at their higher and lower limits of study ranges using multivariate design of experiment (DOE). The experimental design includes control runs operated within the NOR. In addition, certain process parameters have been studied using an one-factor-at-a-time (OFAT) approach. Those process parameters, which were found to have significant impact on CQAs were classified as CPPs. The output of DOE and OFAT studies were within the specification limits or observed ranges of control, hence the studied ranges were considered as PAR.

The CPPs identified as part of the process characterisation exercise have been updated in Description of Manufacturing Process and Process Controls and Controls of Critical Steps and Intermediates. An update about consistent information of CPPs and PARs in the dossier were performed.

A sub-batch strategy is applied, a maximum number of four final batches generated from a fermentation batch is defined**.**

Control of materials

The raw materials and reagents used in the manufacture of Inpremzia active substance are commercially available. All raw materials used in the manufacturing of the active substance are derived from plant materials, mineral sources, and recombinant origin or as a result of chemical processing. No raw materials of animal-origin are included in the active substance manufacturing process or in the establishment of the cell banks. Lists of raw materials stating where they are used in the process and the attributes tested are provided. Materials are controlled either according to compendial specifications or parameter tests according to an in-house specification. Acceptance criteria for individual materials are provided.

The host cell, *Pichia pastoris*, and the development of the insulin precursor gene construct and vector system used for sub-cloning have been adequately described.

The clone construction is sufficiently described and the function of each genetic element is explained. Requirements of ICHQ5B/Q5D are fulfilled.

A two-tiered cell banking system is used. Appropriate information is provided on the establishment of cell banks. The MCB and WCB are stored in separate below -70°C freezers. Cell banks are sufficiently characterised. Method descriptions and validation status were provided for the methods used to characterize and test the cell banks. Genetic stability has been confirmed at the end of production. Adequate protocols for stability monitoring of the cell banks are provided.

Control of critical steps and intermediates

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

A summary table of the output parameters including their specifications are provided. However, the basis for, or justification of, the in-process specification ranges was not given. This was raised as part of the overarching **major objection** regarding the deficiencies in the control strategy and process validation. To address this part of the major objection a technical report titled "Justification of IPC/IPT

with criticality for Upstream, DSP-1 and DSP-2 stage of recombinant Human Insulin manufacturing process" has been provided in CTD. The in-process controls applied for control of the critical parameters during upstream and downstream process have been discussed. In-process controls have been further classified as critical and non-critical with a justification based on process understanding and its importance in the active substance manufacturing process. The rationale for designating a parameter as critical or non-critical is presented. With these additional details this **major objection** is considered solved.

A decision tree defining the actions taken in case the IPCs and in-process tests are observed to be outside the defined acceptable limits is provided.

The analysis methods for the in-process testing have been validated.

Stability and hold times of process intermediates have been derived based on physicochemical analysis from representative small-scale batches was provided. The data support the proposed hold times.

Process validation

The manufacturing process was originally validated in 2011 using manufacturing process I. Following the process validation, process changes were introduced to generate process II, process III, and finally the proposed commercial manufacturing process, process IV (see below). Processes II-IV have only been validated for those parts that were changed from the precluding process. For process II, only DSP-II and DSP-III stages were validated; for process III, only DSP-II stage was validated; and for the process IV, only DSP-III stage was validated. All process validations were performed with at least three consecutive commercial scale active substance batches.

The analytical methods used during the validations are stated to be validated and references to method validations are provided.

Overall, the results obtained during the process validations were homogenous. The process and quality parameters met the pre-determined acceptance criteria and the trends of the quality parameters were found to be comparable and consistent. However, as no information was provided on process development in support of the control strategy for routine manufacture and process validation, the process validation could not be accepted, and a **major objection** was raised in view of the control strategy and process validation. Taking into account that:

a) the manufacturing process was already validated in 2011 and subsequently, additional process validation activities were completed to address all specific process changes (up to process IV) in an iterative process in chronological order

b) a separately conducted statistical evaluation of process data including a comparison of input as well as output parameters using control charts and process-capability analysis, further demonstrates that process IV performs effectively and reproducibly to produce an active substance of the desired quality;

c) data compiled for the in-process parameters, critical quality attributes and stability from active substance batches manufactured in the years 2018 and 2019 (presented in the provided Annual Product Quality Review) further confirm that the process remains in a state of validation and is consistently and robustly able to generate active substance of the intended quality; and,

d) finally, the completed ongoing process validation (continued process verification) report was provided by the applicant. The available results are an additional indicator demonstrating that the overall process validated from 2011 through 2018 is still in a state of control;

the **Major Objection** can be considered solved.

The applicant has further clarified the splitting and pooling of DSP-I and DSP-II crystals during the manufacture, and explained the validation of the splitting and pooling procedures by highlighting the splitting and pooling procedures conducted during Process Validation of Process IV. The applicant's clarification is adequate and it is agreed that the splitting and pooling have been validated during the original Process IV validation. In addition, splitting and pooling procedures have been included in the ongoing Process IV validation protocol.

Holding times of the intermediates of validation batches have been justified based on risk assessment and physicochemical and microbial stability studies.

The results from the clearance of process- and product-related impurities studies confirm the reduction of several impurities, both product- and process-related, by end of the RPHPLC chromatographic steps and in the final active substance. Results from the bioburden evaluation at the DSP-III stage during process I and II validations indicate that bioburden is in control in the DSP-III stage.

A concurrent evaluation of the lifetime of the chromatography resins during routine production at commercial scale is proposed. Interim data are provided from the currently ongoing evaluation. In general, the approach is accepted as an adequate validation protocol with indicative criteria for the column performance and frequency of evaluation is provided**.**

Pre-filters and sterile filters used during active substance manufacturing have not been validated. However, as bacterial endotoxins and total aerobic microbial count are controlled on the final active substance specification and since filter validation has been performed for filters used in finished product manufacturing, it is acceptable to not validate filters used in active substance manufacturing.

Shipping validation has been conducted and the provided information is considered sufficient.

Manufacturing process development

Four manufacturing processes, process I-IV, were developed for manufacturing active substance at commercial scale. To support the comparability of the manufacturing processes, a comparability assessment was performed for each changed process in regards of the changed process steps. The assessment includes the comparison of in-process data, batch release data and stability data of three representative active substances batches from each process. Comparability on structural or functional level has been demonstrated between process III and IV batches. In addition, comparison of the batch release data and in-process data of the Process I and the subsequent Processes III and IV materials, support structural and functional comparability of the material from process I and the subsequent processes.

No side-by-side comparability studies are performed; rather, the in-process data and batch release and stability data for the comparability assessment are compiled from the process validation runs and stability studies. The provided data appear to support comparability between the active substance manufactured using the different processes.

Characterisation

Elucidation of Structure and Other Characteristics

Human insulin active substance structure has been sufficiently compared with compendial standards and the assigned protein structure is confirmed. Characterisation studies were performed for 3 representative batches, which, based on the batch number, are manufactured using manufacturing process III. The use of Process III material for elucidation of structure is accepted as comparability of Process III material with material from the intended commercial process (Process IV) has been demonstrated and process changes are minor.

Correct amino acid sequence, expected molecular mass for the intact protein as well as for the A and B chains, and accurate secondary and tertiary structure were confirmed by LC-MS, cIEF, peptide mapping, Western blotting, NMR, circular dichroism spectroscopy, FTIR and X-ray crystallography techniques (where applicable). The methods are shortly described and qualification status stated. The results were compared to theoretical values and the Internal Reference Standard (IRS) or the published structure. It is agreed that the used panel of analytical methods is appropriate for characterisation of a rather simple protein as human insulin.

Impurities

During Inpremzia active substance manufacturing, different side products and product-related impurities are generated. As product-related impurities and degradation products that are anticipated to impact product purity, Single Chain Precursor (SCP), A21 desamido human insulin, and insulin dimer and aggregates. Mass-based techniques were used for the identification and characterisation of the product-related impurities.

For monitoring the clearance of the product-related impurities during active substance manufacturing, HPLC based methods were used. Depletion study results from three active substance batches demonstrate that the manufacturing process is capable of consistently and substantially deplete and control the impurities at various process steps. The levels of deamidated, other related proteins and HMWP (high molecular weight products: dimers and aggregates) are also controlled at active substance release with acceptance limits in line with the EU monograph for Insulin Human.

Residual solvents (methanol, ethanol, acetonitrile, isopropyl alcohol, dimethyl formamide), residual trypsin, host cell protein (HCP), and host cell DNA (HCDNA) are considered as process-related impurities. The presented data demonstrate that the active substance manufacturing process clears process-related impurities to acceptable levels. In addition, the level of HCP, Total Aerobic Bacterial Count (TAMC) / Total Yeast and Moulds Count (TYMC), bacterial endotoxins and the solvents acetonitrile, methanol and isopropyl alcohol are controlled at active substance release. A risk assessment with regards to leachables for column materials used in the purification of the active substance was performed and is further discussed under *Manufacturing process development*.

To assess the risk of residual levels of process additives expected to be present in the final active substance, a risk assessment was conducted. The calculated EDI values are lower than the permitted daily exposure (PDE) values for the process additives. Therefore, it is acceptable not to control the additives at the active substance stage.

2.4.2.3. Specification

Specification for routine release of the active substance include test parameters required by the Ph. Eur. monograph for Human Insulin as well as additional tests for residual solvents and microbial enumeration are presented. The active substance specification includes tests for appearance, solubility, identification, HMWP, related proteins, assay, single chain precursor, zinc content, loss on drying, sulphated ash, bacterial endotoxins, host cell derived proteins, residual solvents, content of dimethyl formamide, microbial limits: TAMC/TYMC, and host cell DNA content.

Analytical methods

Analytical procedures for appearance, solubility, identification (RT comparison, peptide mapping), loss on drying, sulphated ash, related proteins (HPLC), HMWP (SEC), zinc content (AAS), assay (HPLC), and bacterial endotoxin are performed as per the procedures given in the Ph. Eur. Monograph for insulin, human. Residual solvents (GC), content of dimethyl formamide (GC), HCP (ELISA), SCP (HPLC), and microbiological enumeration assay are performed using in-house test methods. Validation summaries

for the compendial methods (assay, related proteins, HMWP, zinc content, and identification by peptide mapping) are presented in the dossier. For pharmacopoieial clotting assay for bacterial endotoxin determination, data on the determination of the required non-interfering dilution of the active substance are provided. Detailed method descriptions and full validation reports for the in-house analysis (residual solvents, dimethyl formamide, HCP, SCP, microbial enumeration) are included in the dossier.

Sufficient details on the analytical procedure and relevant validation parameters have been evaluated. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data was initially provided for 19 active substance batches of which five batches were manufactured using the proposed commercial manufacturing process IV. Additional batch data including information regarding the intended purpose of use has been provided for 12 active substance batches of which three were manufactured using process IV.

All presented batches meet the specifications enforced at the time of analysis as well as the current batch release specifications. The results demonstrate consistency between batches.

Reference materials

Insulin Human European Pharmacopoeia Chemical Reference Substance (EPCRS) is used for qualifying the current lot of Human Insulin Working Standard. Working Standard is selected from a routine production batch and used in routine analysis of human insulin active substance. As requested, the manufacturing process of the batch used for preparation of the Working Standard and its representativeness of clinical batch has been discussed, and the preparation process of the working standard has been described.

The Working Standard was qualified as per Ph. Eur. tests and acceptance criteria and characterised in regards of primary and secondary structure. Analytical methods used for the working standard qualification and characterisation are listed. Based on the provided qualification data, the prepared working standard is well within the Ph. Eur. or in-house specification and comparable to the theoretical values for mass of A and B chains and peptide fragment sizes. Once qualified, the working standard is considered valid for 12 months. Criteria for expiration and possible re-testing and re-qualification of the working reference standard is established.

The current lot of HMWP working standard used for routine analysis is qualified using the USP HMWP reference standard as no Ph. Eur. HMWP reference standard is available. Certificates of analysis are provided for the controls used in the applied analytical methods (HMWP, HCP, HCDNA, SCP, residual solvent, and impurity: Zinc oxide, endotoxin standards).

For the future, the applicant proposes the development of a two-tiered internal reference standard (primary and secondary IRS) system where the primary IRS is proposed to be qualified against the EPCRS, and the secondary IRS against the primary IRS.

Container closure

The lyophilised Inpremzia active substance is packed in depyrogenated amber coloured Type III glass bottles. The bottles are closed with inner polytetrafluoroethylene (PTFE, Teflon) faced foamed polyethylene liner cap and outer white polypropylene (PP) screw cap and Parafilm wrapping. The glass bottles and PP caps are tested as per in-house and compendial specifications.

Description of the sterilisation methods of the primary packaging materials that come into direct contact with the active substance as well as validation summaries of the sterilisation methods have been provided.

A risk assessment for leachables and extractables on the active substance primary packaging was performed. This is acceptable since the glass bottle is compendial class III glass material and the active substance is a freeze dried/lyophilised dry powder and no significant interference is expected upon storage at the intended storage condition at -20±5°C. The bottles are closed with polypropylene, polytetrafluoroethylene and polyethylene containing screw caps which are also not expected to present a risk with regards to leachables.

2.4.2.4. Stability

The applicant has provided stability data at long-term -20°C ± 5°C, at accelerated (5°C ± 3°C), and stressed (25ºC/60%RH and 40ºC/75%RH temperature stress, pH stress, oxidative stress, photo stability stress) conditions. The stability studies were designed following ICH Q5C guideline.

Under accelerated conditions (5°C ± 3ºC), the active substance met the proposed stability criteria for all of the test parameters monitored during the six months stability period.

Various size containers are used for the storage of the active substance. As requested, information on the container closure system, container sizes and filling volumes used for the stability studies have been provided together with critical evaluation of their representativeness.

The proposed shelf life of active substance when stored protected from light at -20°C ± 5°C is 48 months. This is based on real-time (60 months) stability studies. In summary, the proposed shelf-life can be agreed. The applicant commits to include at least one commercial batch (if manufactured) per year on stability study. A post-approval stability protocol is provided.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Inpremzia is a pre-mixed, sterile non-pyrogenic solution supplied in an infusion bag GALAXYTM (inner and outer film layer of linear low-density polyethylene LLDPE, a layer of biaxially oriented nylon, and a middle film layer of polyvinylidene chloride PVDC) of 100 mL and intended for intravenous administration. The finished product is composed of 1 IU/mL human insulin (rDNA origin). Sodium chloride is added as a tonicity agent and sodium dihydrogen phosphate monohydrate and disodium hydrogen phosphate anhydrous are added as buffers. The pH range of the dosage form is 6.5 – 7.2, with a target pH of 6.8 and it is iso-osmotic. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards with the exception of sodium dihydrogen phosphate monohydrate, which is not listed in the Ph. Eur. and complies to USP. There are no novel excipients used in the finished product formulation.

Table 1: composition of finished product

Component	Quality Standard	Component Quantity
Insulin Human	Ph. Eur./USP	1 IU/mL
Sodium Chloride	Ph. Eur./USP	9.0 mg/mL
Monobasic Sodium Phosphate, Monohydrate	USP	0.290 mg/mL
Dibasic Sodium Phosphate, Anhydrous	Ph. Eur./USP	0.412 mg/mL
Water for Injection	Ph. Eur./USP	QS

Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopoeia; QS = Quantity Sufficient

Inpremzia has been developed as a biosimilar to the EU reference medicinal product (RMP), Actrapid (EMEA/H/C/000424), which contains Insulin Human as the active substance. Inpremzia and Actrapid have the same active substance, posology and route of administration for intravenous (IV) infusion treatment. Inpremzia is a pre-mixed insulin solution in an IV infusion bag containing 1 IU/mL human insulin. The proposed reference medicinal product Actrapid is a 100 IU/mL solution for injection in vials requiring dilution prior to IV administration.

During the formulation studies, it was recognised, that the solution pH is an important factor on satisfactory formulation stability and a pH of 6.8 was determined to be optimal for formulation stability. This pH also minimises assay loss as well as desamido impurity formation. pH is controlled through the addition of a phosphate buffer system to the formulation. Other critical quality attributes identified in the formulation studies were: Insulin Assay and Related Substances.

Formulation studies were conducted with the US RMP version of Actrapid (Novolin R) which consists of the same components and is presented in the same form as Actrapid. The and was used for the US NDA registration batches, stability testing, biosimilarity assessments and the US clinical study, which has been used for process validation, stability testing, biosimilarity testing and the EU clinical study. The process has been validated at the commercial scale.

For the comparability confirmation, comparative batch analysis data and stability data have been provided. Batch analysis data show comparative quality and the stability data up to 12 months is comparable between the batch sizes.

Manufacturing process development utilises the existing manufacturing experience, formulation development and process evaluation studies to identify the relevant manufacturing steps. Both batch sizes were used for the process development.

The critical aspects of the manufacturing process were identified as mixing process of the solution, aseptic filtration and filling, packing and cooling. CPPs are identified and process controls stated, but the control strategy needed further clarification. In the Day 120 responses the applicant informs that process parameters were assessed in the normal operation ranges, and each critical process parameter was assessed in permitted acceptable ranges, as appropriate. For permitted acceptable ranges, the worst-case end of the range was evaluated. The justification of the CPPs ranges were submitted for mixing and filtration steps.

Container closure

The primary packaging is a laminate plastic (polyethylene, nylon, polyvinylidene chloride) bag, with a plastic (polyolefin) infusion port. The material complies with Ph. Eur. and EC requirements. Generally, the principles outlined in the EMA Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03) regarding to the physiochemical and biological tests (e.g. extractables/leachables and interaction studies) have been followed. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

No manufacturing process development was necessary for the Seal/Fill/Seal process, as this process is already used to manufacture other similar premixed products

Container closure integrity has been evaluated using validated container closure integrity methods that demonstrate that the port/closure subassembly, port-to-bag seal, and main bag seals are all integral microbial barriers.

2.4.3.2. Manufacture of the product and process controls

Manufacturing of Inpremzia finished product takes place at the Baxter facility located in Round Lake, Illinois, USA. The finished product is imported to EU and released by Baxter S.A. and Baxter Distribution Center Europe S.A. in Belgium.

The manufacturing process is a fairly straightforward process including dissolving of the active substance and excipients during the mixing process, followed by filtration and filling into containers in a seal/fill/seal process. The quantity of Human Insulin Baxter required for each batch is calculated individually based on the Assay value from the Certificate of Analysis of the same lot of active substance used in the formulation.

Despite the simplicity of the finished product manufacturing process, there are several manufacturing steps that can potentially change the quality of the finished product significantly, especially points regarding to the sterilisation processes and microbial controls. The evolution of the control strategy and process controls are discussed in the dossier and the concerns that were raised have been adequately solved.

There are no provisions for reprocessing or reworking the finished product.

Initial and IPCs have been established sufficiently on critical steps of the manufacturing process. Critical steps identified by the applicant are Solution Mixing Process, Aseptic Filtration and Filling Process, Packing and Cooling Process. In this context a process evaluation report of the manufacturing process for one finished product batch was provided. This study evaluated the solution mixing parameters, tank homogeneity, and changes in chemical characteristics. Additionally, an evaluation of solution flush volume required for flushing the line/filter/filling system and an evaluation of the filling machine downtime were performed under this study. All achieved results are within the acceptance limits.

The process performance was qualified in accordance with a predefined process performance qualification (PPQ) protocol based on three consecutive full-scale batches manufactured from three different batches of active substance. PQQ reports are provided separately for all three manufacturing scale batches of. Equipment used was qualified according to internal Standard Operating Procedures.

The testing programme, the sampling plan and the number of samples taken were reasonable. All parameters tested met their acceptance criteria. Additionally, sterilising filter validation reports are provided and are adequately validated. Filter compatibility and bacterial retaining capacity in the presence of the finished product solution was verified. Finally, comprehensive extraction studies were conducted resulting in a list of potential leachables from all filter membranes used in the finished product production. The report on the biological tests performed to evaluate the toxicological risk of these extractables were presented.

Details are submitted regarding transport/shipment validation.

2.4.3.3. Product specification

The batch release and end of shelf life specifications for Inpremzia finished product cover the relevant quality attributes and the proposed specifications are same for release and shelf-life purposes.

Specification limits:
Overall, the specifications for the chosen quality attributes are acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 6

batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective permitted daily exposure (PDE). Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product.

Analytical methods

Analytical methods and the choice of the used standard
The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. Ph. Eur. methods are the primary analytical methods used.

One of the in-house methods, Reversed Phase UPLC, is an alternative to the method described in the Ph. Eur. monograph (UPLC instead of HPLC). This UPLC method was performed for the determination of related substances and quantitation of human Insulin. In addition, this method was used to identify Human Insulin (rDNA origin). The applicant described this method as an improvement to the Ph. Eur. described HPLC method.. The UPLC assay was full validated with the US reference standard and deviations during the validation were highlighted and reviewed accordingly.

Ultra-Performance Liquid Chromatography (SE-UPLC) is further performed to determine high molecular weight species (HMWP). High Molecular Weight Proteins (HMWP) are degradation products in Inpremzia, resulting from aggregation of insulin molecules. This assay is different to the Ph. Eur. Monograph, which is specified by SE-HPLC method. A full validation was provided and is acceptable.

As also advised in the SA given in 2018 (EMEA/H/SA/3726/1/2017/III), the use of the in-house methods in combination with the USP standard cannot be accepted, unless it has been demonstrated with full validation data, that the in-house methods perform better or at least equal to the methods described in the Ph. Eur. monograph.

Batch analysis

Batch analysis data (10 batches at commercial scale) of the finished product were provided. The results are within the specifications and confirm consistency of the manufacturing process. Batch analysis data is provided for US batches and for EU batches. The provided batch analysis data provided are within the specification limits. All test methods of the compendial product ingredients of Human Insulin Injection are executed by United States Pharmacopeia (USP). The applicant has provided a justification for this issue.

Reference materials

The reference standards 'Insulin Human USP RS and Insulin human EP CRS' were compared by Baxter. Working standards were made using both USP and EP reference standard materials. These working standards were prepared at a concentration of 1 U/mL (≈0.0347 mg/mL) per the finished product method.

Each standard met the finished product method system suitability agreement criterion.

Furthermore, a stock solution from the active substance at approximately 200 U/mL was prepared and dilutions of this stock solution were compared by testing with the UPLC-method with the equivalent dissolutions of the USP and Ph. Eur. Reference standards.

According to the applicant, the USP standard is used as a reference standard and has been determined to be comparable to the Ph. Eur. standard by using the finished product assay test for the comparison of the quality between the USP and Ph. Eur. reference standards. The applicant states, that the USP standard was chosen because the presentation of the standard would yield less error in the standard preparation. The company mentioned further, that a difference in the EP standard presentation can result in higher run to run variability. Literature citations were referred where in multiple investigations difference in the Ph. Eur. standard presentation has been observed and this standard preparation was determined to the likely cause for the observed failure of higher run to run variability. Cited literature on the difference in the EP human insulin standard presentation were provided. A justification to this discrepancy and for the potential impact was submitted.

2.4.3.4. Stability of the product

Stability studies have been conducted following the ICH requirements. Shelf-life of 24 months at refrigerated (5°C ± 3°C) conditions plus 30 days at room temperature (25°C) storage is proposed for Inpremzia.

To support this, real time data is available for commercial scale manufacturing batches () up to 12 months of long-term refrigerated storage (5°C), 12 months of refrigerated storage followed by 30 days of short-term storage (25°C), and 6 months of accelerated storage (25°C). Supportive stability study results are provided up to 24 months of long-term refrigerated storage (5°C), 12 months of refrigerated storage followed by 30 days of short-term storage (25°C), and 6 months of accelerated storage (25°C) for three batches at L scale.

For the applicant it was not able to present stability data with batches manufactured with active substance batches at the lower limits of the specification acceptance criteria because insulin active substance batches are not available with Desamido Insulins or Individual Related Substances approaching their limits. Therefore the applicant revised the limits of actual active substance lots and their subsequent finished product batches because this limits are representative for active substance and finished product lots. This approach is acceptable.

In photostability testing the product was demonstrated to be light sensitive and the individual cardboard carton secondary packaging is an effective barrier to light for the proposed finished product. The secondary packaging was proven to be sufficient in protecting the product from light. Light protection is not required during administration.

The applicant's intention to extrapolate the shelf-life from 12 months to 24 months with the supportive batches (US) is agreed. All available real time stability data available for batches of to support the proposed shelf-life are provided.

As described in the SmPC: Inpremzia may be stored at temperatures below 25 °C for a single period of up to 30 days, but not exceeding the original expiry date. The new expiry date must be written on the carton. If the expiry date has passed, discard immediately. Inpremzia must not be returned to refrigerated storage.

2.4.3.5. Adventitious agents

The expression system is a recombinant yeast. In principle, the section on adventitious agents safety evaluation has been appropriately addressed. No raw materials of animal origin are used in the manufacturing process of the active substance.

Microbial contamination testing as well as testing for bovine and porcine adventitious viral agents are conducted for the MCB and WCB. In-process controls at various steps of the manufacturing process are in place to check/eliminate potential microbial contamination. No viral clearance studies have been performed. Since *P. Pastoris* is an unsuitable host for infectious viral agents, this strategy is acceptable.

2.4.3.6. GMO

Not applicable.

2.4.3.7. Biosimilarity

The applicant has developed its Human Insulin Baxter/Inpremzia as a similar biological medicinal product to the reference medicinal product Actrapid containing recombinant human insulin as active ingredient. Of particular note, the proposed biosimilar insulin will be presented as pre-mixed, ready-to-use solution in an infusion bag containing 1 IU/mL human insulin whereas the proposed reference product is a 100 IU/mL solution for injection in vials. The reference product may be administered through two different routes: Subcutaneously by injection or, if necessary, as an intravenous solution. When administrated through IV infusion Actrapid has to be diluted to 1 IU/mL and mixed in the infusion fluids 0.9% sodium chloride, 5% dextrose or 10% dextrose with 40 mmol/l potassium chloride using polypropylene infusion bags according to the manufacturer's instructions.

According to the Guideline on similar biological medicinal products (CHMP/437/04 Rev 1), biosimilar and reference product must have same posology and route of administration. Deviations from the reference product such as strength, pharmaceutical form, formulation, excipients or presentation can be allowed with an appropriate justification. This approach was extensively discussed in the scientific advice (EMA/CHMP/SAWP/18162/2018 Procedure No.: EMEA/H/SA/3726/1/2017/III) and it was finally agreed that this approach can be considered suitable for the biosimilar pathway. Consequently, no principal concern on this outlined biosimilar approach has been raised. In addition, the applicant argued that access to a ready-to use solution without the need for any preparation steps prior to administration (e.g. dilution and mixing) would reduce the risk for potential risk dosing errors and an accident contamination of the infusion during preparation. However, despite the formulation and presentation differences, the scientific advice also emphasised the importance of demonstrating similarity at the level of the finished medicinal product.

To overcome this challenge the applicant presented a testing scheme, which was designed to allow an analytical comparison of all CQAs between Human Insulin Baxter (1 IU/ml) and Actrapid (100 IU/mL). Depending on the specific quality attribute either a direct comparison of (undiluted) Actrapid samples with finished product of Human Insulin Baxter and/or a comparison of Actrapid samples diluted in 0.9% normal saline or in finished product matrix with Human Insulin Baxter finished product was conducted. For a subset of quality attributes, also active substance of Human Insulin Baxter (either reconstituted in Actrapid matrix or reconstituted in Actrapid matrix and further diluted with finished product matrix/0.9% saline) was compared with Actrapid. In principle, this testing scheme is a way forward to address the complex situation with the differences in strength and presentation of reference product and the biosimilar development. This is also in line with the Guideline on similar biological

medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) (EMA/CHMP/BWP/247713/2012), which states that for some analytical techniques, a direct or side-by-side analysis of the biosimilar and reference medicinal product may not be feasible or give limited information. Thus, samples could be prepared from the finished product. Different preparation and dilution schemes for samples used in the analytical biosimilarity exercise have been used. A thorough discussion including appropriate rationale for the chosen preparation / dilution matrix of the samples has been provided. In addition, the potential impact of the different preparation and dilution matrices on critical quality attributes has been briefly addressed. Finally, it should be noted that the reference product when administered through the IV route can be diluted not only in 0.9% sodium chloride, but also in 5% dextrose and 10% dextrose with 40 mmol/L potassium chloride. Dilution in dextrose-based formulations was not evaluated as dextrose is a form of glucose and when injected IV provides carbohydrates to the body and can be used to treat low blood sugar (hypoglycaemia) - this is not part of the strategy for Inpremzia. The applicant`s arguments for not including alternative dilution matrices (5% dextrose, 10% dextrose with 40 mmol/l potassium chloride) in the testing scheme is reasonable.

Batches included

The number of batches analysed in each biosimilarity assessment study has been justified based on statistical considerations. It was concluded that a suitable number of batches to allow evaluation of similarity was evaluated. Biosimilar finished product batches include three commercial scale batches and four smaller scale batches. The representativeness of the batches could be confirmed. Nine Actrapid batches are tested in the biosimilarity assessment. According to the applicant, all available batches that could be sourced were used. The difference in the age distribution of these batches is 11 months. The Actrapid and Human Insulin Baxter batches which were used in the pivotal clinical trial were included in the quality biosimilarity exercise. The table presenting Inpremzia Batches Tested for Biosimilarity Assessment, have been updated with information on the active substance process used to manufacture each finished product batch as well as the age of each finished product batch at the time of biosimilarity testing.

Quality Target Product Profile

An initial biosimilarity quality assessment was performed against US-sourced comparator product batches (Novolin R) while the pivotal biosimilarity exercise was conducted against EU reference product.

In the initial biosimilarity quality assessment US-sourced comparator product batches (Novolin R) were compared with active substance and finished product batches of the biosimilar. Based on the characterisation data of the US-sourced comparator product, an initial quality target product profile was established. The applicant cited guideline CHMP/437/04 Rev 1 which allows the combined use of non-EEA authorised comparator and EEA authorised reference product for the development of the quality target product profile of the biosimilar product. Although this strategy was in principle agreed in the above cited scientific advice, the value of this initial biosimilarity quality assessment is of only limited value as no EU reference product has been included.

The comparability between US-sourced Novolin R and EU-RMP Actrapid has not been addressed, which is, however, acceptable since the pivotal PK/PD clamp study (study 203) was conducted using Actrapid. The similarity data between Inpremzia and US sourced Novolin R has been provided as supportive information.

Comparability criteria

The biosimilarity exercise was designed to demonstrate the similarity of the Inpremzia and the reference medicinal product at the level of the finished medicinal product for all CQAs, despite the

formulation and presentation differences between Inpremzia (1 IU/mL) and EU-RMP (100 IU/mL). Relevant information on how the criticality of quality attributes have been assessed has been provided. A description of the used risk assessment tools for criticality assignment and how risk has been estimated considering the possible impact of each attribute on safety, efficacy, pharmacokinetics, and immunogenicity of the product is included.

Given the fact that no immunogenicity assessment was conducted as part of the clinical trials, a multidisciplinary major objection question was raised concerning criticality of quality attributes. It is considered of particular relevance to address the issue of similar immunogenicity potential at the quality level. As already pointed out in the scientific advice letter to the applicant, neither physico-chemical nor pharmacological data should give any indication of a relevant structural difference or a different impurity profile between the biosimilar and the reference product, which could give rise to a differential immune response. Hence, a thorough evaluation of the immunogenic potential of biosimilar candidate versus reference product with special focus on similarity evaluation of quality attributes critical for immunogenicity has been provided. A summary of the highest ranked CQAs, justification for the assignments, those most applicable to immunogenicity and conclusions are presented in Module 2, Section 2.5 Clinical Overview.

The selected CQAs for biosimilarity evaluation include those for primary structure, physicochemical attributes, content, impurities, higher order structure and functional activity.

Comparability criteria have been established, for many of the assays. These are based on monograph requirements and/or proposed specification acceptance criteria. The available data sets for the functional assays have been re-analysed using alternative similarity approaches where comparability ranges are based on characterisation results from the reference product. This re-evaluation of biosimilarity acceptance criteria has been provided as a separate technical report.

Method qualification

Appropriate standard and state-of-the-art methods have been used. Primary structure was assessed by N-terminal sequencing, amino acid analysis, and peptide mapping whereas the content and degradation products were compared by UPLC. Secondary and tertiary structure was evaluated by near and far UV CD spectroscopy, differential scanning calorimetry, 1-D and 2-D nuclear magnetic resonance, and analytical ultracentrifugation. The isoelectric point was determined by imaged capillary isoelectric focusing. The molecular mass was compared by reducing and non-reducing SDS-PAGE and mass spectrometry; aggregates were quantified by size exclusion chromatography. Furthermore, general and safety relevant quality attributes including visual inspection, osmolality, pH and sub-visible particles by micro flow imaging.

Functional characterisation and comparison was conducted by various binding and cell-based in-vitro assays: Insulin receptor A and B phosphorylation via the AlphaScreen Surefire technology, adipogenesis testing by quantifying the triglyceride in 3T3-L1 cells, inhibition of lipolysis via free fatty acid quantification, glucose uptake by a fluorometric assay, mitogenic potential of insulin on Saos-2 cells, insulin growth factor-1 receptor binding and insulin receptor binding (short and long form) via SPR.

Brief descriptions of analytical methods have been provided. Validation data is provided for the methods used also for finished product release. In addition, adequate qualification reports for functional tests used in the biosimilarity evaluation have been provided.

Critical evaluation of analytical biosimilarity

High similarity between Inpremzia and Actrapid has been demonstrated for the following quality attributes:

- Primary structure
  - identical amino acid sequence; identical amino acid composition; human origin; desamido insulins present in all sample types, although lower levels in biosimilar than in Actrapid
- Higher order structure
  - identical secondary and tertiary structures in near and far UV CD analysis
- Molecular mass/size
  - intact mass (MS)
  - aggregate levels
- Charge
  - comparative isoelectric points
- Assay
  - comparative content (% of label claim) in biosimilar and Actrpid
- Impurities
  - some differences in the formation of desamido insulins products and HMWPs were seen in comparative forced degradation and stability studies, these differences do not preclude similarity
  - presence of particles is similar

Regarding the presented results of the pivotal biosimilarity exercise the data indicate a similar quality profile of Actrapid and Human Insulin Baxter. During visual inspection testing performed on Actrapid and Human Insulin Baxter finished product samples as part of the similarity exercise, the presence of visible particles was reported in two finished product batches of Human Insulin Baxter. The applicant has isolated and identified these particles as process residuals, which are not formulation- or insulin-related. However, no further discussion on the presence of these particles was provided. Taking into account that this ready-to-use product is intended to be given through the IV route without any filtration step prior to the administration, a potential safety risk may arise from the presence of these particles. As this concern affects the safety profile of the product a **Major Objection** was raised. As requested, the applicant presented a detailed analysis of the observed particles from both affected containers and elucidated the chemical nature of these particles. The chemical nature of the particles together with further investigations indicate that these particles are not formulation depend, no additional safety impacts from the particle findings in the Process Evaluation lot are expected. As such, the **Major Objection** can be considered solved.

Another **Major Objection** addressing differences seen in *in vitro*-related functions, i.e. binding to key target receptors IR-A and IR-B isoforms and two out of three assays for metabolic activities (inhibition of lipolysis and induction of glucose uptake) as well as the considerable wider batch-to-batch variability of Inpremzia was raised at Day120. To address this deficiency the applicant was requested to provide more data to support the similarity claim. This data should include comparative side-by-side analysis of Inpremzia finished product with additional EU-RMP batches for target binding (IR-A and IR-B separately) and sufficiently sensitive and adequately qualified metabolic activity analyses.

The applicant has submitted as requested new comparative data from IR-A and IR-B binding, inhibition of lipolysis and glucose uptake and investigated the root cause for the wider batch-to-batch variability of Inpremzia.

Data was from 3 new Inpremzia and RMP batches, from assays qualified with Ph. Eur. chemical reference substance (EP CRS). RMP batches were selected based on the stock availability and Inpremzia batches were those that were in stability testing at the time of assays. 2 out of 3 Inpremzia batches were studied less than 3 months after the expiry date due to delays in performing the assays.

It was clarified that this did not have implications to the functional parameters (and batches were within shelf-life specification limits). The provided justification for the use of two expired RMP batches in the functional biosimilarity evaluation is considered acceptable and it is no expected that this short time expiry has any impact on the validity of the generated data.

The possible impact of reference standard used before in the comparative studies and matrix effects was assessed in root cause investigation. EP CRS (Batch 5 EDQM Cat. #I0310000) was used instead previous reference standard. Actrapid was dialysed to remove m-cresol, glycerol and zinc, acidified and diluted to better match Inpremzia formulation. Inpremzia was spiked with m-cresol and zinc chloride to better match Actrapid formulation, and all unmodified or matrix-modified Inpremzia and Actrapid was used in the assays.

The target binding (IR-A and IR-B separately) and qualified *in vitro* metabolic activity assays, including inhibition of lipolysis and glucose uptake, were then performed. Similar results were obtained as in previous studies for target binding of Inpremzia and Actrapid. The relative potency to inhibit lipolysis and the relative glucose uptake potency were both within acceptable ranges, and neither were significantly impacted by differences in the matrix between formulations.

In conclusion, the applicant has attempted to clarify the root cause of variability seen in the functional data between Inpremzia and Actrapid adequately. Matrix may have an effect on binding to insulin receptors with SPR in some extend, and the variability observed in previous analysis could be attributed to the use of previous reference standard. The differences observed between Inpremzia and Actrapid on IR binding were reduced with the matrix changes, but not in that extend that the Inpremzia would be ≥80% fitting within the variability range of Actrapid. Nevertheless, it is plausible that in in vivo, when matrix effects are even more diluted, the differences in binding activities could be further equalised. Furthermore, these differences in the target binding had no impact on the metabolic activity (inhibition of lipolysis) or glucose uptake activity. Consequently, despite the slight differences still seen in binding to IR, Inpremzia and Actrapid can be considered similar in functional attributes.

Comparative degradation and stability studies

Human Insulin Baxter finished product and Actrapid batches have been exposed to different stress factors (including light, acidic, basic, and oxidative stress). Although in some cases the levels of impurities were different for the different test articles depending on the type of stress, it can be concluded from this study that the degradation products pathways and the related compounds that were observed are the same for the finished product as compared to diluted and undiluted samples of the reference products.

In addition, a comparative long-term stability study with Actrapid samples was ongoing during the initial assessment period and an interim report was submitted. As requested, a final report with the complete data including comparison of the data was provided during the procedure. The available data when compared with the long-term stability data of Human Insulin Baxter finished product support as well the similarity claim.

The overall biosimialrity between impremzia and Actarapid is considered demonstrated.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The manufacturing process, elucidation of structure and specifications for Inpremzia active substance and finished product have been appropriately presented and a thorough discussion of potential impurities has been conducted. Comparability of the active substance batches manufactured using the proposed commercial process and the earlier process versions, as well as comparability between the development scale () and commercial scale () finished product batches have been demonstrated.

Additional information was provided during the procedure on the active substance manufacturing process development in support of the control strategy for routine active substance manufacture and process validation. Thus, the initial **major objection** regarding the control strategy and process validation for the manufacture of the active substance could be solved.

The applicant has addressed the similarity between Inpremzia and the reference product, EU-approved Actrapid, in a comprehensive comparability exercise. A **major objection** regarding the demonstration of biosimilarity and the high batch-to-batch variability of Inpremzia in the functional assays has been solved by submission of new data and a root cause analysis to address the observed variability of Inpremzia.

Finally, the presence of visible particles reported in finished product batches of Human Insulin Baxter during visual inspection could be justified to have no impact on the safety profile of the product. Consequently, also this **major objection** is considered solved.

To conclude, the major objections as well as the other concerns have been sufficiently addressed. Consequently, from a quality perspective the MAA for Inpremzia is approvable as a biosimilar to its reference product Actrapid.

At the time of CHMP opinion, there were a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to the biological activity of Desamido B. These points are put forward and agreed as recommendation for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Inpremzia is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation for future quality development

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

- The applicant is recommended to provide data concerning biological activity of Desamido B to justify the inclusion of Desamido B3 into the content of insulin assay.

2.5. Non-clinical aspects

2.5.1. Pharmacology

Pharmacodynamic *in vitro* studies have been conducted as part of the pivotal quality biosimilarity assessment to demonstrate that Inpremzia has similar functional attributes to Actrapid.

For the *in vitro* assessment of the pharmacodynamics of the proposed insulin biosimilar product, the following study packages were established: insulin receptor binding (IR-A and IR-B) profile, biological activity (adipogenesis, inhibition of lipolysis and glucose uptake) relative to the RMP, IGF-1 (Insulin-like growth factor 1) binding and mitogenic activity.

Comparative *in vivo* studies of pharmacodynamic effects would not be anticipated to be sensitive enough to detect differences not identified by in vitro assays, and are not required as part of the comparability exercise.

2.5.2. Pharmacokinetics

Inpremzia pharmacokinetic parameters are expected to be similar to those described for the reference product after intravenous administration. It is thus acceptable that no dedicated pharmacokinetic studies for ADME or drug interaction have been performed with Inpremzia. This is in accordance with currently effective guidance for similar biological medicinal products containing recombinant human insulin and insulin analogues.

2.5.3. Toxicology

No pivotal single or repeat dose toxicity studies with Inpremzia have been conducted. This is in agreement with the 'Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin analogues' (EMEA/CHMP/BMWP/32775/2005_Rev. 1, February 2015) and Scientific Advice received from the CHMP. Inpremzia is expected to have a similar toxicity profile to that of the reference medicinal product Actrapid. No dedicated toxicokinetic studies were conducted, which is acceptable for a biosimilar human insulin product. Supportive toxicokinetic data was acquired in the course of a two-week toxicity and toxicokinetic continuous intravenous infusion study in rats with a two-week recovery phase conducted to qualify degradants present in the final drug product.

Genotoxicity and carcinogenicity studies with Inpremzia have not been conducted. This is in accordance with the ICH S6 guideline on the development of biotechnology-derived pharmaceuticals (Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals, CPMP/ICH/302/95), the CHMP guideline on the development of biosimilar products (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues, EMEA/CHMP/BMWP/42832/2005), and the CHMP Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev. 1, February 2015).

No dedicated studies on reproduction toxicology were performed with Inpremzia. This is in line with the Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev. 1, February 2015). Reproductive and developmental toxicity profile for Inpremzia is expected to be similar to the reference product.

No stand-alone non-clinical studies to assess local tolerance have been conducted. However, data from supportive toxicity studies showed no relevant findings and results from clinical studies using the applicant's final product formulation suggest no local tolerance concerns.

No dedicated studies on the antigenic potential of Inpremzia were performed. This is in line with the Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev. 1, February 2015).

For the qualification of degradation products, a comparative toxicological study was performed. Inpremzia containing levels of either 2, 5 or 10% of respective degradants was continuously injected i.v. to rats of both sexes for 14-days with a two-week recovery period. Novolin R, the US equivalent to EU reference product Actrapid, was used as comparator. The desamido levels of Novolin R were measured in the formulated dosing samples. The use of US reference product appears acceptable to show similarity with regard to desamido degradants. No adverse effects were observed using either of the human insulin products. Individual insulin levels showed high variabilities, thus a conclusion on PK parameters in this study is uncertain.

2.5.4. Ecotoxicity/environmental risk assessment

Inpremzia, being developed as a biosimilar to Actrapid, is not expected to pose a risk to the environment and an environmental risk assessment is not required for this medicinal product. Recombinant human insulin is already used in existing marketed products and no significant increase in environmental exposure is anticipated. The applicant provided an appropriate justification for not conducting specific studies on Environmental Risk Assessment, as postulated in the CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00).

2.5.5. Discussion on non-clinical aspects

Insulin human (rDNA) is already used in existing marketed products and no significant increase in environmental exposure is anticipated.

Inpremzia was submitted as a biosimilar MAA in accordance with Article 10(4) of Directive 2001/83/EC. All non-clinical data provided by the applicant are in accordance with regulatory requirements, and relevant guidelines. The non-clinical programme was designed to support the similarity between Inpremzia and the RMP, and followed the risk-based approach with omission of *in vivo* studies.

The applicant requested Scientific Advice in November 2017 for their product Insulin human pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council [EMA/CHMP/SAWP/18162/2018 Procedure No.: EMEA/H/SA/3726/1/2017/III]. The advice received from the EMA on non-clinical topics has been followed by the applicant. Appropriate justifications for waiving non-clinical studies were provided and are in line with applicable CHMP guidelines.

2.5.6. Conclusion on the non-clinical aspects

All issues raised during the assessment have been adequately clarified, and the CHMP concluded that functional similarity has been sufficiently demonstrated from a non-clinical viewpoint.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

The clinical development programme is based on two completed phase I, euglycaemic clamp studies in healthy volunteers. Study CEL-HI-203 is considered the pivotal study for this procedure due to use of the EU-authorised reference product Actrapid as comparator. Study CEL-HI-200, in which the US-authorised reference product Novolin R was applied, will be considered as supportive (see section 'supportive study' below). Both studies were designed to primarily demonstrate PK/PD similarity between the test and reference product. No other studies, such as efficacy- or safety/immunogenicity studies, have been performed.

CEL-HI-203 (pivotal): Phase I PK/PD equivalence, euglycaemic clamp study, Chula Vista, CA, USA	Study design	Double-blind, randomised, two-treatment, two-period, 2-way crossover, hyperinsulinaemic euglycaemic clamp trial
	Source of reference product	EU-authorised comparator product Actrapid
	Sample size and study population	60 subjects were enrolled and 56 subjects completed the trial, all healthy adult male subjects received a total dose of 0.36 units/kg of each product
CEL-HI-200 (supportive): Phase I PK/PD equivalence, euglycaemic clamp study, Chula Vista, CA, USA	Study design	Double-blind, randomised, two-treatment, two-period, 2-way crossover, hyperinsulinaemic euglycaemic glucose clamp
	Source of reference product	US-authorised comparator product Novolin® R
	Sample size and study population	54 healthy volunteer subjects completed the trial, all healthy adult male subjects received a total dose of 0.36 units/kg of each product

2.6.2. Clinical pharmacology

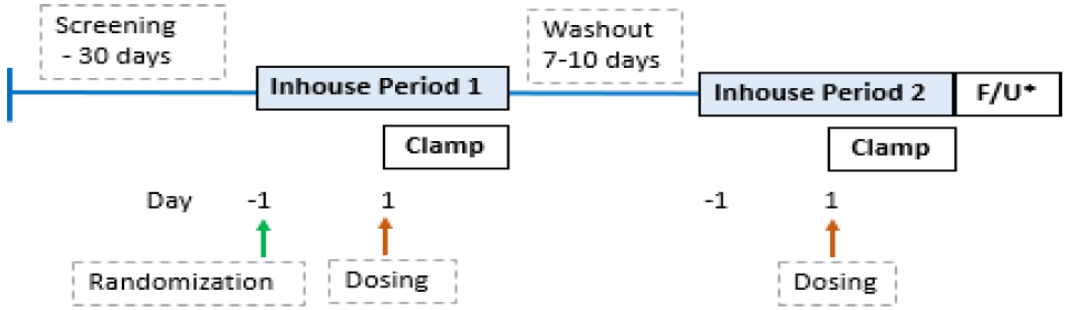
Pivotal Study CEL-HI-203

Study design

Study CEL-HI-203 was a phase I, double-blind, randomised, two-treatment, two-period, two-way crossover, euglycaemic glucose clamp trial conducted in healthy adult male subjects.

Biosimilarity to the comparator Actrapid was assessed in a 6-hour infusion and 8-hour blood sampling clamp procedure. 60 subjects enrolled of which 54 provided evaluable PK data. The subjects received a total dose of 0.36 U/kg of each study drugs with a washout period of 7-10 day between the two clamps.

Figure 9-1 Study Design Schematic for CEL-HI-203



*F/U = Follow-up Visit to be performed at the conclusion of In-house Period 2

Table 9-3 Clamp Sampling Schedule

Approx. hour[1]	Nominal timing	Activity	Blood Sampling[2] for		
			Blood Glucose (via YSI)	Celerity's insulin or Actrapid	C-peptide
06:00 am	–2 to –1 h	Connection to automated blood glucose analyzer.	Sampling pre-dose at least every 30 min		
07:00	–60 min				
	-30 min		X	X	X
	-20 min		X	X	X
	-10 min		X	X	X
08:00	0 min[4]	Start of study drug administration[3]. Start of clamp period.	Sampling pre-dose and thereafter at least every 30 min	X	X
	5 min			X	X
	10 min			X	X
	15 min			X	X
	20 min			X	X
	30 min			X	X
	40 min			X	X
	50 min			X	X
09:00	60 min (1h)			X	X
	75 min			X	X
	90 min			X	X
	105 min			X	X
10:00	120 min (2h)			X	X
	150 min			X	X
11:00	180 min (3h)			X	X
	210 min			X	X
12:00	240 min (4 h)			X	X
	270 min			X	X
13:00	300 min (5 h)			X	X
	315 min			X	X
	330 min			X	X
	345 min			X	X
14:00	360 min (6 h)	End of IV insulin infusion		X	X
	365 min			X	X
	370 min			X	X
	375 min			X	X
	380 min			X	X

Approx. hour[1]	Nominal timing	Activity	Blood Sampling[2] for		
			Blood Glucose (via YSI)	Celerity's insulin or Actrapid	C-peptide
	390 min			X	X
	405 min			X	X
15:00	420 min (7 h)			X	X
	450 min			X	X
16:00	480 min (8 h)	End of clamp Disconnect from Biostator		X	X

[1] Actual starting time is approximate but nominal timing was followed in any case.
[2] Collection of blood samples for pharmacokinetic assessment at the correct time point relative to dosing was of primary importance. The actual sampling time point should not have deviated more than ± 2 minutes from the nominal time.
[3] Intravenous infusion of Celerity's regular Human Insulin (rDNA origin) for infusion or Actrapid for 6 hours, according to randomization.
[4] Samples scheduled at time 0 were taken within 5 minutes before start of study drug infusion.

Study population

The study population consisted of healthy men. The mean (± SD) age of the subjects was 33.4 (± 7.78) years. The subjects were mostly Caucasians (66.7%, 40/60), 26.7% (16/60) were Hispanics or Latinos. The mean (± SD) BMI of the subjects was 24.14 (± 2.243) kg/m^2.

Subject disposition

Safety data set

The Safety data set included all subjects who received at least one dose of each treatment. Of the 93 subjects who were screened, 60/93 (64.5%) were enrolled in the study. Of the 60 subjects enrolled in the study, 56/60 (93.3%) completed the study:

- Two subjects voluntarily withdrew consent: Subject 136 (Sequence AB) and Subject 116 (Sequence BA) were withdrawn.
- One subject was withdrawn because of an AE: Subject 178 (Sequence AB) experienced an acute change in medical condition during the first clamp (vomiting, hypokalaemia, atrial fibrillation, and headache) and was withdrawn due to the AEs vomiting, hypokalaemia, and headache.
- One subject was withdrawn from the study at the discretion of the Investigator: Subject 115 (Sequence BA) had multiple haemolysed samples and missed PK time points due to difficult sampling during Period 1.

Table 10-1 Subjects Disposition: Safety Set (N=60)

Subject Disposition, n (%)	Treatment Sequence[1]		
	AB (N=30)	BA (N=30)	All Subjects (N=60)
Completed the Study	28 (93.3)	28 (93.3)	56 (93.3)
Withdrew	2 (6.7)	2 (6.7)	4 (6.7)
Ongoing or Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Completed Clamp for Treatment Period 1	30 (100)	30 (100)	60 (100)
Completed Clamp for Treatment Period 2	28 (93.3)	28 (93.3)	56 (93.3)
Reason for Withdrawal			
Voluntary Withdrawal of Consent	1 (3.3)	1 (3.3)	2 (3.3)
Adverse Event	1 (3.3)	0 (0.0)	1 (1.7)
Discretion of Investigator	0 (0.0)	1 (3.3)	1 (1.7)

Source data: Table 14.1.1.1

Pharmacokinetic/Pharmacodynamic data set

The PK/PD Set included all subjects with evaluable PK/PD data appropriate for the evaluation of interest (with no major protocol deviations thought to significantly affect the PK/PD of the drug or who did not meet the clamp quality criteria) from all subjects who received Inpremzia or Actrapid. The PK and PD Sets each included 54 of initially 60 enrolled subjects; six subjects were removed from the PK and PD Sets prior to unblinding:

- One subject's clamp data for both periods were excluded from the final analysis because the original source printout from the Biostator was misplaced for Treatment Period 1.
- One subject's clamp quality of Treatment Period 2 did not meet the pre-defined clamp data quality parameters as stated in the protocol and hence, the clamp data for both periods for this subject were excluded from the final analysis.
- One subject was withdrawn from the study at the discretion of the Investigator due to multiple haemolysed samples and missed PK time points due to difficult sampling in Period 1.
- Two subjects withdrew consent and were withdrawn from the study.
- One subject was withdrawn from the study due to the TEAEs of vomiting, hypokalaemia, and headache.

Euglycaemic clamp procedure

There is general agreement that the euglycaemic hyperinsulinaemic clamp technique is the best available method for the measurement of insulin action. In such clamp experiments, the plasma insulin concentration is raised (e.g. by subcutaneous injection of insulin) and the blood-glucose level maintained ('clamped') at a pre-defined level by means of a variable infusion of glucose.

In the study, the test and reference product were administered by continuous intravenous infusion for a 6-hours period to mimic the intended use, i.e. for the treatment of patients with diabetes mellitus who require intravenous insulin for the maintenance of glucose homeostasis.

Blood sampling was performed throughout these 6 hours and additional 2 hours for a total of 8 hours. According to the study protocol, the 6-hour duration of the infusion was chosen to ensure that steady state conditions are reached during the last 60 minutes (minutes 300- 360).

Actual clamp quality data (e.g. accuracy) were not provided.

Handling of test and reference product

The study drugs were prepared by unblinded pharmacy staff that were not participating in study drug administration or interacting with trial subjects in any other way.

2.6.2.1. Pharmacokinetics

Pharmacokinetic Methods

Bioanalytical methods – PK assays

Serum insulin and C-peptide concentration measurements were performed by Celerion, Zurich, Switzerland. The same PK assays have been used in both, the pivotal and the supportive clinical studies. An ELISA assay was performed using a commercially available kit (Mercodia Insulin ELISA Kit) to quantify human insulin in human serum whereas the Human C-peptide immunoassay is a sandwich ELISA assay. The method as well the validation of the methods have been provided. For method validation summaries as well as the detailed reports are included in the dossier. Both ELISA methods used for the determination of human C-peptide and human insulin in serum met all validation requirements. It was concluded that the ELISA methods showed an acceptable performance and are suitable for their use.

Primary PK endpoints

- Area under the insulin concentration-time curve (AUC_{INS}) at steady state PK, measured from 300-360 minutes ($AUC_{INS\text{-}SS\ 300\text{-}360\ min}$).
- Maximum concentration (C_{max}), measured at steady state from 300-360 minutes ($C_{max\ INSSS\ 300\text{-}360\ min}$).

Other PK endpoints

- Time to reach C_{max} (T_{max}).
- Apparent terminal half-life ($T_{1/2}$).
- K_{el}
- Total AUC_{INS} and incremental (i.e., time increments) AUC_{INS} (e.g., $AUC_{INS\ 0\text{-}6hrs}$, $AUC_{INS\ 0\text{-}8hrs}$, $AUC_{INS\ 6\text{-}8hrs}$).
- Geometric mean (± SE) serum insulin concentration (pM) by treatment

Pharmacokinetic results

Primary PK measures

For the primary PK endpoints $AUC_{INS\text{-}SS\ 300\text{-}360min}$ and $C_{max\ INS\text{-}SS\ 300\text{-}360\ min}$, the 90% confidence intervals of the GM ratios were within the pre-specified limits of 80% and 125% [1.0023, 1.0650 and 1.018, 1.079, respectively]. For both measures, unity is not included, while the upper limits of the CI remain well below the 125% equivalence limit.

Table 11-1 Comparison of $AUC_{INS\ 300\text{-}360\ min}$ and $C_{max\ INS\text{-}SS\ 300\text{-}360\ min}$ Between Celerity's Regular Human Insulin (rDNA origin) for infusion and Actrapid: PK set (N=54)

Parameter	Statistics[2]	Treatment[1]			
		A (N=54)	B (N=54)	Geometric LS Mean Ratio (SE)	Geometric 90% CI Ratio
$AUC_{INS\text{-}SS\ 300\text{-}360\ min}$ (min*pmol/L)	Geometric LS Mean (SE)	21002.740 (602.5707)	20328.069 (583.2144)	1.033 (0.0187)	1.0023, 1.0650
$C_{max\ INS\ 300\text{-}360\ min}$ (pmol/L)	Geometric LS Mean (SE)	390.16 (11.164)	372.35 (10.654)	1.05 (0.018)	1.018, 1.079

Source data: Table 14.2.2.2
Note: Parametric analysis was conducted using a mixed effects model with treatment, period, and sequence as fixed effects, and subject-within-sequence as a random effect.
[1] Treatment: A = Infusion of Celerity's regular Human Insulin (rDNA origin) for infusion; B = Infusion of Actrapid.
[2] Geometric Mean = exp(Mean(log(X))). SE of Geometric Mean = Geometric Mean * SE of Mean(log(X)).

Additional PK measures

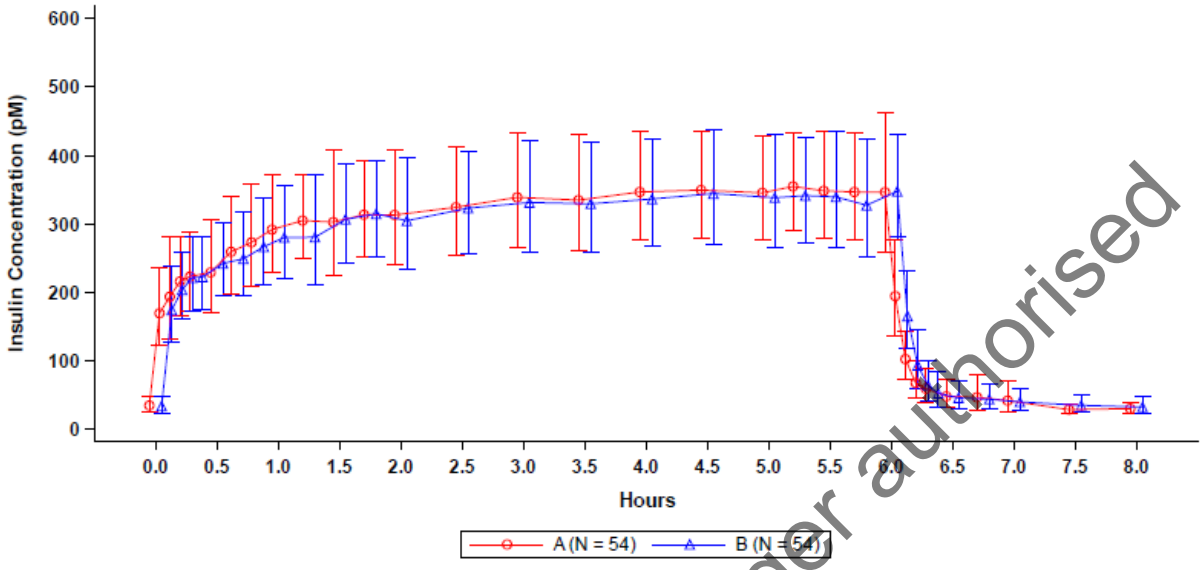
For the additional AUC_{INS} endpoints ($AUC_{INS\ 0\text{-}6hrs}$, $AUC_{INS\ 0\text{-}8hrs}$, and $AUC_{INS\ 6\text{-}8hrs}$) the 90% confidence intervals of the GM ratios were also within the pre-specified limits of 80% and 125% [1.0002, 1.0499; 1.0026, 1.0505 and 0.9827, 1.1093, respectively]. T_{max}, K_{el}, and $T_{1/2}$ values were almost identical or closely similar. Moreover, the geometric mean of the serum insulin concentration over time was similar between the treatments.

Table 11-3 Comparisons of T_{max}, K_{el}, and $T_{1/2}$ Between Celerity's Regular Human Insulin (rDNA origin) for infusion and Actrapid: PK Set (N=54)

Parameter (Unit)	Statistics[2]	Treatment[1]	
		A (N=54)	B (N=54)
T_{max} (min)	Median	330.0	330.0
K_{el} (/min)	Geometric Mean (SE)	0.025 (0.0016)	0.024 (0.0018)
$T_{1/2}$ (min)	Geometric Mean (SE)	26.872 (1.5370)	27.510 (1.9489)

Source data: Table 14.2.4.1
[1] Treatment: A = Infusion of Celerity's regular Human Insulin (rDNA origin) for infusion; B = Infusion of Actrapid.
[2] Geometric Mean = exp(Mean(log(X))). SE of Geometric Mean = Geometric Mean * SE of Mean(log(X)).

Figure 11-1 Geometric Mean (SE) of Serum Insulin Concentration (pM) Over Time by Treatment[1]: PK Set (N=54)



Source data: Figure 14.2.1.2
Treatment: A = Infusion of Celerity's regular Human Insulin (rDNA origin) for infusion; B = Infusion of Actrapid.
The exp(Mean(log(X)) +/- SD(log(X))) was displayed as the upper and lower bound.

Table 11-4 Comparison of Incremental AUC_{INS} Between Celerity's Regular Human Insulin (rDNA origin) for infusion and Actrapid: PK Set (N=54)

Parameter	Statistics[2]	Treatment[1]		Geometric LS Mean Ratio (SE)	Geometric 90% CI Ratio
		A (N=54)	B (N=54)		
$AUC_{INS\ 0\text{-}6hrs}$ (min*pmol/L)	Geometric LS Mean (SE)	114490.714 (3195.6862)	111726.893 (3118.5419)	1.025 (0.0148)	1.0002, 1.0499
$AUC_{INS\ 0\text{-}8hrs}$ (min*pmol/L)	Geometric LS Mean (SE)	120523.591 (3401.4412)	117434.707 (3314.2661)	1.026 (0.0143)	1.0026, 1.0505
$AUC_{INS\ 6\text{-}8hrs}$ (min*pmol/L)	Geometric LS Mean (SE)	5694.471 (314.9011)	5454.083 (301.6077)	1.044 (0.0378)	0.9827, 1.1093

Source data: Table 14.2.3.2
Note: Parametric analysis was conducted using a mixed effects model with treatment, period, and sequence as fixed effects, and subject-within-sequence as a random effect.
[1] Treatment: A = Infusion of Celerity's regular Human Insulin (rDNA origin) for infusion; B = Infusion of Actrapid.
[2] Geometric Mean = exp(Mean(log(X))). SE of Geometric Mean = Geometric Mean * SE of Mean(log(X)).

Sensitivity analyses

The applicant performed sensitivity analyses for the primary PK endpoints $AUC_{INS\text{-}SS\ 300\text{-}360\ min}$ and $C_{max\ INS\text{-}SS\ 300\text{-}360\ min}$ [Geometric 90% CI ratio 1.0033, 1.0657 and 1.018, 1.079, respectively] and other PK endpoints (incremental PK AUC_{INS} endpoints ($AUC_{INS\ 0\text{-}6hrs}$, $AUC_{INS\ 0\text{-}8hrs}$, and $AUC_{INS\ 6\text{-}8hrs}$)) that included subjects with evaluable data for only one period.

Exploratory analyses

The applicant further performed exploratory analyses in which the primary PK endpoints $AUC_{INS\text{-}SS\ 300\text{-}}$

$_{360\ min}$ and $C_{max\ INS\text{-}SS\ 300\text{-}360\ min}$ [Geometric 90% CI ratio 1.0108, 1.0734 and 1.0287, 1.0873, respectively] and the other PK endpoints T_{max}, K_{el}, and $T_{1/2}$, $AUC_{INS\ 0\text{-}6hrs}$, $AUC_{INS\ 0\text{-}8hrs}$, and $AUC_{INS\ 6\text{-}8hrs}$, were derived using correction for C-peptide. C-peptide is part of proinsulin where it connects the A-chain to the B-chain. During production of insulin, C-peptide is cleaved off and is secreted into the blood stream; C-peptide measurement allows detection of potential changes in endogenous insulin secretion. In this study, the C-peptide concentration was used as a biomarker to check if the measured insulin concentration was derived from both, endogenous or exogenous sources of insulin, which is in line with the GL (EMEA/CHMP/BMWP/32775/2005_Rev. 1).

Except for the additional/other PK endpoint $AUC_{INS\ 6\text{-}8hrs}$, where the 90% CI ratio was 1.0782 to 1.2530 and thus slightly outside of the pre-specified range, the data of the C-peptide corrected primary and other endpoints were within the pre-specified range of 80-125%. However, the study was not powered to show similarity in this exploratory measure.

2.6.2.2. Pharmacodynamics

Pharmacodynamic Methods

Primary PD endpoints

- Area under the glucose infusion rate (AUC_{GIR})-time curve at steady state from 300-360 minutes ($AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$).
- Maximum glucose infusion rate, GIR_{max}, measured at steady state from 300-360 minutes ($GIR_{max\ SS\ 300\text{-}360\ min}$).

Other PD endpoints:

- Total AUC_{GIR} and incremental (i.e., time increments) AUC_{GIR} (e.g., $AUC_{GIR\ 0\text{-}6\ hrs}$, $AUC_{GIR\ 0\text{-}5\ hrs}$, $AUC_{GIR\ 0\text{-}8\ hrs}$, $AUC_{GIR\ 6\text{-}8\ hrs}$).
- Time to maximum glucose infusion rate (T_{GIRmax}).
- Time to onset of action (onset of action being defined as start of IV glucose infusion during the clamp).
- Geometric Mean (SE) of glucose infusion rate (GIR) (mg/min)

Pharmacodynamic results

Primary PD measures

For the primary PD endpoints $AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$ and $GIR_{max\text{-}SS\ 300\text{-}360\ min}$, the 95% confidence intervals of the GM ratios were within the pre-specified limits of 80% and 125% [0.9660, 1.0745 and 0.9723, 1.0780, respectively].

Table 11-2 Comparison of $AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$ and $GIR_{max\text{-}SS\ 300\text{-}360\ min}$ Between Celerity's Regular Human Insulin (rDNA origin) for infusion and Actrapid: PD Set (N=54)

Parameter	Statistics	Treatment[1]			
		A (N=54)	B (N=54)	LS Mean Ratio (SE)	95% CI Ratio
$AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$ (mg)	LS Mean (SE)	47670.154 (1735.6102)	46722.722 (1735.6102)	1.020 (0.0277)	0.9660, 1.0745
$GIR_{max\text{-}SS\ 300\text{-}360\ min}$ (mg/min)	LS Mean (SE)	971.111 (30.2171)	947.284 (30.2171)	1.025 (0.0269)	0.9723, 1.0780

Source data: Table 14.2.6.2
Note: Parametric analysis was conducted using a mixed effects model with treatment, period, and sequence as fixed effects, and subject-within-sequence as a random effect.
[1] Treatment: A = Infusion of Celerity's regular Human Insulin (rDNA origin) for infusion; B = Infusion of Actrapid.

Additional PD measures

Additional PD endpoints were analysed: $AUC_{GIR\ 0\text{-}6\ hrs}$, $AUC_{GIR\ 0\text{-}5\ hrs}$, $AUC_{GIR\ 0\text{-}8\ hrs}$, $AUC_{GIR\ 6\text{-}8\ hrs}$, T_{GIRmax}, Time to onset of action (onset of action was defined as start of IV glucose infusion during the clamp) and geometric mean of glucose infusion rate (GIR) (mg/min).

For $AUC_{GIR\ 0\text{-}6\ hrs}$, $AUC_{GIR\ 0\text{-}5\ hrs}$, $AUC_{GIR\ 0\text{-}8\ hrs}$, $AUC_{GIR\ 6\text{-}8\ hrs}$, the 95% confidence intervals were within the pre-specified limits of 80% and 125%: [0.9574, 1.0739]; [0.9624, 1.0710]; [0.9560, 1.0635] and [0.8921, 1.0827], respectively.

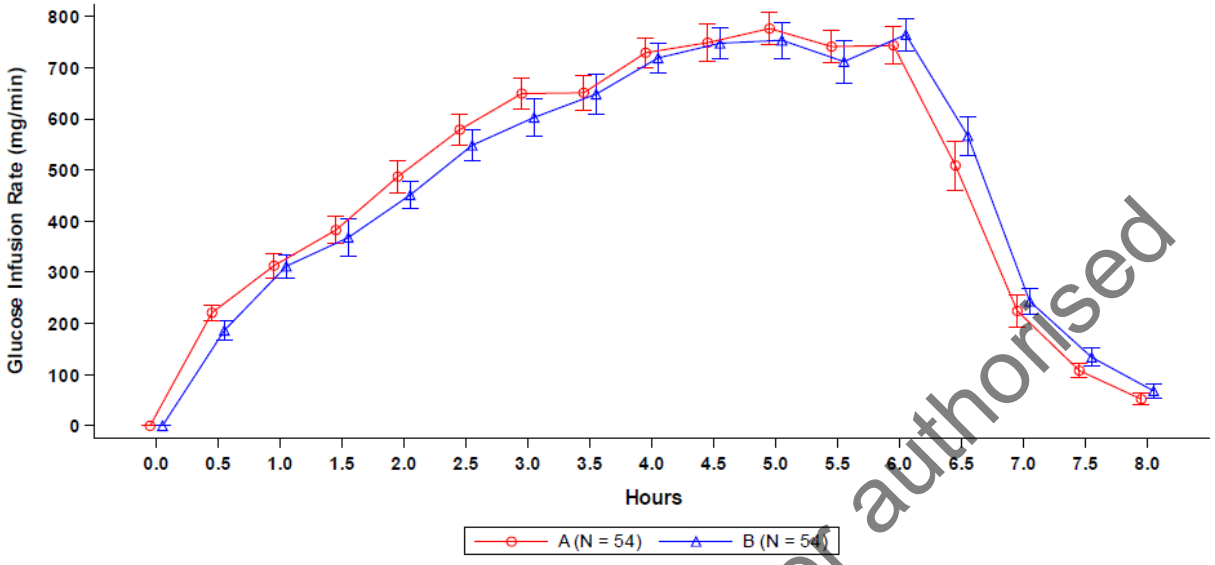
T_{GIRmax}, time to onset of action and geometric mean of GIR exhibited similar values.

Table 11-5 Comparison of $T_{GIR\ max\text{-}SS\ 300\text{-}360\ min}$ and Time to Onset of Action Between Celerity's Regular Human Insulin (rDNA origin) for infusion and Actrapid: PD Set (N=54)

Parameter (Unit)	Statistics	Treatment[1]	
		A (N=54)	B (N=54)
PD Set			
$T_{GIR\ max\text{-}SS\ 300\text{-}360\ min}$ (min)	Median	324.0	331.0
Time to Onset of Action (min)	Median	18.5	20.0

Source data: Table 14.2.8.1
[1] Treatment: A = Infusion of Celerity's regular Human Insulin (rDNA origin) for infusion; B = Infusion of Actrapid.

Figure 11-2 Geometric Mean (SE) of Glucose Infusion Rate (mg/min): PD Set (54)



Source data: Figure 14.2.5.2
Treatment: A = Infusion of Celerity's regular Human Insulin (rDNA origin) for infusion; B = Infusion of Actrapid.
The exp(Mean(log(X))) +/- SE of Geometric Mean was displayed as the upper and lower bound, where the SE of Geometric Mean = Geometric Mean * SE of Mean(log(X)).

Table 11-6 Comparison of Incremental AUC_{GIR} Between Celerity's Regular Human Insulin (rDNA origin) for infusion and Actrapid: PD Set (N=54)

Parameter	Statistics[2]	Treatment[1] A (N=54)	Treatment[1] B (N=54)	LS Mean Ratio (SE)	95% CI Ratio
$AUC_{GIR\ 0\text{-}5hrs}$ (mg)	LS Mean (SE)	164065.748 (6968.6841)	161542.376 (6968.6841)	1.016 (0.0297)	0.9574, 1.0739
$AUC_{GIR\ 0\text{-}6hrs}$ (mg)	LS Mean (SE)	211735.901 (8565.1028)	208265.099 (8565.1028)	1.017 (0.0277)	0.9624, 1.0710
$AUC_{GIR\ 0\text{-}8hrs}$ (mg)	LS Mean (SE)	253784.169 (10316.7310)	251333.266 (10316.7310)	1.010 (0.0274)	0.9560, 1.0635
$AUC_{GIR\ 6\text{-}8hrs}$ (mg)	Geometric LS Mean (SE)	39066.952 (2249.5109)	39749.815 (2288.8308)	0.983 (0.0474)	0.8921, 1.0827

Source data: Table 14.2.7.2
Note: Parametric analysis was conducted using a mixed effects model with treatment, period, and sequence as fixed effects, and subject- within-sequence as a random effect.
[1] Treatment: A = Infusion of Celerity's regular Human Insulin (rDNA origin) for infusion; B = Infusion of Actrapid.
[2] Geometric Mean = exp(Mean(log(X))). SE of Geometric Mean = Geometric Mean * SE of Mean(log(X)).

Sensitivity analyses

The applicant performed sensitivity analyses for the primary PD endpoints $AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$ and $GIR_{max\text{-}SS\ 300\text{-}360\ min}$ [95% CI ratio 0.9627, 1.0698 and 0.9697, 1.0739, respectively] and the other PD endpoints ($TGIR_{max\text{-}SS\ 300\text{-}360\ min}$ and time to onset of action, incremental PD AUC_{GIR} parameters (AUC_{GIR}

$_{0\text{-}5hrs}$, $AUC_{GIR\ 0\text{-}6hrs}$, $AUC_{GIR\ 0\text{-}8hrs}$, and $AUC_{GIR\ 6\text{-}8hrs}$)) that included subjects with evaluable data for only one period.

Supportive PK/PD studies

Study CEL-HI-200 was a phase I, double-blind, randomised, 2-way crossover, active comparator, euglycaemic glucose clamp trial to demonstrate PK and PD bioequivalence between Baxter's insulin product (Celerity's Premixed Regular Human Insulin) and the US reference listed drug Novolin R in healthy subjects between 22 May 2017 and 21 October 2017. Inpremzia 1 IU/mL product was approved in the US in June 2019 as MYXREDLIN (insulin human in sodium chloride injection). Of the 58 enrolled healthy volunteer subjects, 54 subjects (93.1%) completed the study.

In Study CEL-HI-203, $C_{max\ INSSS\ 300\text{-}360\ min}$ and $GIR_{max\ SS\ 300\text{-}360\ min}$ were evaluated as primary endpoints whereas in Study CEL-HI-200, C_{max} and GIR_{max} were evaluated as additional endpoints. The other PK/PD endpoints pre-specified in the protocol were the same for both studies.

The 90% CI ratio of the primary PK measure $AUC_{INS\text{-}SS\ 300\ -\ 360\ min}$ [0.96, 1.03] and the 95% CI ratio of the primary PD measure $AUC_{GIR\text{-}SS\ 300\ -\ 360\ min}$ [0.95, 1.05] are within the respective pre-specified limits thus, seem to support the notion of similar pharmacokinetics and pharmacodynamics between Baxter Insulin (Celerity's Premixed Regular Human Insulin) and Novolin R. Regarding the additional PK/PD data, the results indicate a higher variability between the two applied treatments compared to their counterparts analysed in the pivotal study.

Parameter	Statistic	Celerity's Insulin[1] (N=56)	Novolin R (N=56)	Ratio (SE)[3]	90% CI for Ratio[3]
$AUC_{INS\text{-}ss\ 300\text{-}360\ min}$ (pM*min)	Geometric LS Mean (SE)[2]	19097.3 (514.34)	19266.5 (518.44)	1.0 (0.02)	0.96, 1.03
$AUC_{INS\text{-}ss\ 300\text{-}360\ min}$ (pM*min) (C-peptide corrected)	Geometric LS Mean (SE)[2]	18423.4 (493.99)	18585.5 (497.92)	1.0 (0.02)	0.96, 1.02

Source Data: Table 14.2.2.2 and 14.2.2.2.s
1 – Celerity's Premixed Regular Human Insulin (rDNA origin) Injection
2 – Geometric Mean = exp(Mean(log(X))). SE of Geometric Mean = Geometric Mean * SE of Mean(log(X)).
3 – Compared to Novolin R

Table 11-2 Comparing $AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$ between Celerity's Premixed Regular Human Insulin (rDNA origin) Injection and Novolin R for the PD Population in CEL-HI-200

Parameter	Statistic	Celerity's Insulin[1] (N=56)	Novolin R (N=56)	Ratio (SE)[3]	90% CI for Ratio[3]	95% CI for Ratio[3]
$AUC_{GIR\text{-}ss\ 300\text{-}360\ min}$ (mg)	Geometric LS Mean (SE)[2]	46461.9 (1424.53)	46543.0 (1425.55)	1.0 (0.03)	0.96, 1.04	0.95, 1.05

Source Data: Table 14.2.6.2
1 – Celerity's Premixed Regular Human Insulin (rDNA origin) Injection
2 – Geometric Mean = exp(Mean(log(X))). SE of Geometric Mean = Geometric Mean * SE of Mean(log(X)).
3 – Compared to Novolin R

In Study CEL-HI-200, C-peptide correction had a considerably higher effect on PK values than in Study CEL-HI-203, particularly regarding the additional PK parameter $T_{1/2}$: Study CEL-HI-203: $T_{1/2}$ (min)

Geometric Mean: A (Baxter): 26.872, B (Actrapid): 27.510 and Corrected $T_{1/2}$ (min) Geometric Mean A (Baxter): 19.995, B (Actrapid):19.914 vs Study CEL-HI-200: $T_{1/2}$ Mean A (Baxter): 68.211, B (Novolin R): 59.412 and Corrected $T_{1/2}$ Mean: A (Baxter): 23.3850, B (Novolin R): 25.5350.

However, the primary PK parameters (and PD parameters) of the supportive study were within pre-specified limits and hence, do not give rise to concerns pertaining the finding of similar pharmacokinetic and pharmacodynamic between Inpremzia and Actrapid.

2.6.3. Discussion on clinical pharmacology

Biosimilarity of the PK and PD to the EU- and US RMP was investigated in two studies, of which one (Study CEL-HI-203) is considered pivotal for this MAA due to the use of the EU-authorised reference product (Actrapid) as control treatment; study CEL-HI-200, in which the US-authorised reference product (Novolin R) was applied, is considered as supportive.

Due to its pivotal character, the pharmacology discussion focusses on results of study CEL-HI-203: a phase I, double-blind, randomised, two-treatment, two-period, 2-way crossover, hyperinsulinaemic euglycaemic clamp study. The study was conducted in healthy adult male volunteers; no studies in the target population were conducted, which is in line with the EMA Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev. 1).

Overall, the study was of acceptable design and was well conducted.

According to guidance (EMEA/CHMP/BMWP/32775/2005_Rev. 1), 8 to 10 hours are typical clamp durations for rapid-acting insulins such as the test and reference product. In addition, the GL states that the duration of the clamp studies needs to take into account the known duration of action of the investigated insulin preparation and its dose-dependency. Hence, overall, a 6-hour duration is considered acceptable due to almost immediate availability by IV administration.

The applicant stated that generally, overall mean clamp CV and DFT for the clamps should have been less than 10% and only one subject was excluded from PK/PD data set based on failure to meet pre-defined clamp data quality. Additionally, the applicant provided data on clamp quality during the procedure. Based on this data, the definition of clinically implausible blood glucose is acceptable and the total number of clinically implausible blood glucose values was less than 40, which is negligible given that glucose level was determined once per minute over 9 hours in each clamp. In conclusion, the data demonstrate that overall and clamp-level quality goals were achieved.

The chosen PK and PD parameters are in line with guidance and the recommendations of the CHMP Scientific Advice were implemented. It should be noted that primary PK/PD measures were chosen to measure PK and PD at steady state (SS); this was also accepted in the CHMP Scientific Advice. Statistical and bioanalytical methods applied for the evaluation of equivalence were adequate. During the procedure, the applicant provided analyses regarding potential sequence or period effects for PK and PD endpoints. Based on these data, no statistically significant treatment sequence or period effects in PK or PD primary and additional endpoints were observed.

Concerning the primary PK endpoints $AUC_{INS\text{-}SS\ 300\text{-}360min}$ and $C_{max\ INS\text{-}SS\ 300\text{-}360\ min}$, the 90% confidence intervals of GM ratios were within the pre-specified limits of 80% and 125%, in detail 1.0023, 1.0650 and 1.018, 1.079, respectively. For both measures, unity is not included, however the range of the 90% CI of the GM ratios is tight for both measures and even the upper limits of the CI with 1.065 ($AUC_{INS\text{-}SS\ 300\text{-}360min}$) and 1.079 ($C_{max\ INS\text{-}SS\ 300\text{-}360}$) $_{min}$ remain relatively close to "unity". Hence, no potential for dissimilarity is derived from the observation. Also, the 90% confidence intervals of GM ratios of the incremental AUC_{INS} endpoints ($AUC_{INS\ 0\text{-}6hrs}$, $AUC_{INS\ 0\text{-}8hrs}$, and $AUC_{INS\ 6\text{-}8hrs}$) were within the

pre-specified limits of 80% and 125% [1.0002, 1.0499; 1.0026, 1.0505 and 0.9827, 1.1093, respectively]. Noteworthy, the values of additional PK endpoints T_{max}, K_{el}, and $T_{1/2}$ were almost identical or closely similar and the geometric mean of the serum insulin concentration over time was similar between the treatments. Additionally performed sensitivity analyses, which included subjects with evaluable data for only one period, and exploratory measures, which allow for correction of endogenous insulin by measuring C-peptide, supported overall the findings of the primary analyses.

Regarding the primary PD endpoints $AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$ and $GIR_{max\text{-}SS\ 300\text{-}360\ min}$, the 95% confidence intervals of GM ratios of were 0.9660, 1.0745 and 0.9723, 1.0780, respectively, and thus within the pre-specified limits of 80% and 125%. Also the 95% confidence intervals of GM ratios of the additional PD endpoints ($AUC_{GIR\ 0\text{-}6\ hrs}$, $AUC_{GIR\ 0\text{-}5\ hrs}$, $AUC_{GIR\ 0\text{-}8\ hrs}$, $AUC_{GIR\ 6\text{-}8\ hrs}$) showed similarity and fell within the pre-specified limits of 80% and 125% [0.9574, 1.0739; 0.9624, 1.0710; 0.9560, 1.0635 and 0.8921, 1.0827, respectively]. T_{GIRmax}, Time to onset of action and geometric mean of GIR exhibited similar values between the two treatments. Sensitivity analyses that included subjects with evaluable data for only one period supported overall the findings of the primary analyses.

Additionally, results observed in Study CEL-HI-200, which was in many aspects similarly planned and conducted as the pivotal CEL-HI-203, were suggestive of similarity to US RMP (Novolin R) and support results observed vs. the EU RMP Actrapid.

2.6.4. Conclusions on clinical pharmacology

The data provided provide solid evidence of similarity in PK and PD between Inpremzia and the EU RMP Actrapid.

2.6.5. Clinical efficacy

No efficacy studies have been performed with Inpremzia, which is acceptable. The Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev. 1) does not request specific efficacy studies, since endpoints (usually HbA1c) used in such studies are not considered sensitive enough to detect potentially clinically relevant differences between two insulins.

2.6.6. Conclusions on the clinical efficacy

Not applicable.

2.6.7. Clinical safety

Clinical safety data were provided from two clinical studies (Study CEL-HI-203 & Study CEL-HI-200), both comparative PK/PD trials, in which healthy adult male subjects received single IV infusions of the test and reference product.

Study CEL-HI-203 is considered the pivotal study for this procedure due to application of an EU-authorised reference product (Actrapid). Study CEL-HI-200, which applied an US-authorised reference product (Novolin R), will thus be considered as supportive. The discussion on the safety of this trial focusses mainly on the biosimilar arm regarding external validity of results observed in the pivotal trial.

Patient exposure

In the pivotal trial CEL_HI-203, subjects received a total dose of 0.36 units/kg (infusion rate of 1.0 mU/kg/min) of Actrapid or Inpremzia for infusion over the 6-hour infusion. This dose was chosen for this trial in order to provide a robust metabolic response after intravenous insulin administration to healthy subjects. According to guidance (EMEA/CHMP/BMWP/32775/2005_Rev. 1), frequently used insulin doses in clamp studies are 0.2 to 0.3 U/kg bodyweight for rapid-/short-acting insulins and 0.3 to 0.4 U/ kg bodyweight for intermediate-acting insulins. The GL states that doses in the upper range usually produce a more reliable PD response, thereby reducing PD variability; hence, the dose choice is acceptable.

Table 10-7 Study Drug Administration: Safety Set (N=60)

Visit Study Drug Administration, n (%)	Treatment Sequence[1]		
	AB (N=30)	BA (N=30)	All Subjects (N=60)
Period 1 Day 1			
Study Drug Administered	30 (100)	30 (100)	60 (100)
Period 2 Day 1			
Study Drug Administered	28 (93.3)	28 (93.3)	56 (93.3)

Source data: Table 14.1.7.1
[1] Treatment: A = Infusion of Celerity's regular Human Insulin (rDNA origin) for infusion; B = Infusion of Actrapid.

Adverse events

The most frequent TEAEs reported in Study CEL-HI-203 were headache (n=7) and vomiting (n=3). Considerable differences in TEAEs between Inpremzia and Actrapid that would raise concerns could not be identified; it should be noted, however, that the sample size is not considered sufficient to obtain a definite conclusion.

Table 12-1 Summary of Treatment-Emergent Adverse Events: Safety Set (N=60)

Category, n (%) Events	Treatment[1]		
	A (N=58)	B (N=58)	All Subjects (N=60)
All Treatment-Emergent Adverse Events	7 (12.1) 12	7 (12.1) 10	13 (21.7) 22
All Serious Treatment-Emergent Adverse Events	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
All Treatment-Emergent Adverse Events Related to Treatment	1 (1.7) 1	1 (1.7) 1	1 (1.7) 2
All Treatment-Emergent Adverse Events Leading to Withdrawal	1 (1.7) 3	0 (0.0) 0	1 (1.7) 3
All Treatment-Emergent Adverse Events Leading to Death	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

Source data: Table 14.3.1.1
Notes: Treatment-emergent adverse events were defined as those with onset at or after initiation of study medication.
Summaries by individual treatment were based on the treatment at or immediately prior to the onset of the adverse event.
Subjects experiencing multiple episodes of a given adverse event were counted once in each relevant category.
[1] Treatment: A = Infusion of Celerity's regular Human Insulin (rDNA origin) for infusion; B = Infusion of Actrapid.

As this procedure involves a product intended for short-term use, long-term safety data, which would be required for chronic use, are not considered essential, provided that as stated in the GL (EMEA/CHMP/BMWP/32775/2005_Rev. 1), biosimilarity between the biosimilar and the reference insulin can be convincingly concluded from the physicochemical and functional characterisation and comparison using sensitive, orthogonal and state-of-the-art analytical methods, and from the comparison of the pharmacokinetic and pharmacodynamic profiles and additionally, the impurity profile and the nature of excipients of the biosimilar do not give rise to concerns. These data provide sufficient reassurance that adverse drug reactions, which are related to exaggerated pharmacological effects (e.g. hypoglycaemia) can be expected at similar frequencies.

Serious adverse events and deaths

There were no SAEs and deaths reported in Study CEL-HI-203 or Study CEL-HI-200.

Laboratory findings

The presented laboratory findings from Study CEL-HI-203 do not give reasons for any concerns. It should be noted that the overall exposure was low and time-limited, which reduces a definite conclusion regarding safety. However, based on the intended application for short-term usage applied by healthcare professionals, this does not raise concerns.

Safety in special populations

N/A

Immunological events

The applicant did not provide results of a separate immunogenicity study nor immunogenicity data from the pivotal Study CEL-HI-203 or supportive Study CEL-HI-200.

The applicant explains the omission of a separate immunogenicity study as follows:

In accordance with the CHMP Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev. 1), a separate safety study including an immunogenicity study has not been performed, because:

- Biosimilarity between the biosimilar and the reference insulin can be convincingly concluded for the physiochemical and functional characterisation and comparison using sensitive, orthogonal and state of the art analytical methods, and from the comparison of the PK and PD profiles;
- The impurity profile and the nature of excipients of the biosimilar do not give rise to concerns.

Also in line with the CHMP Scientific Advice in 2017 (Procedure No.: EMEA/H/SA/3726/1/2017/III), it is noted that the product is only intended for short-term use and thus, long safety studies on evolution of anti-insulin antibodies (AIA) are not as crucial as for insulin formulations intended for chronic administration over years.

Omission of clinical immunogenicity data in pivotal study

The risk of hyperglycaemia (due to ADA mediated lack of efficacy) or hypersensitivity of IV formulated insulin for short-term application by healthcare professionals is considered low because the formation of antibodies targeting a protein with presumably identical structure to human body-produced insulin requires a certain level of exposure (in time and amount). However, even minor changes in structure or modification compared to the RMP may elicit an immune response not elicited by use of the RMP. Hence, regarding the decision on similarity, the robustness of the biosimilarity exercise (especially on quality level) is crucial.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to AES

One Subject was withdrawn due to an AE. This subject experienced an acute change in medical condition (vomiting, hypokalaemia, headache and atrial fibrillation) during the first clamp receiving Inpremzia and was withdrawn due to these AEs. This event does not raise important concerns for the following reasons: It was a single event and overall, the AEs vomiting and headache were almost evenly distributed between the test and reference drug. It is plausible that the brief and spontaneously self-resolving episode of atrial fibrillation is related to vomiting and hypokalemia. Hypokalemia itself (which was reported only once and in this single subject) could have been plausibly caused by vomiting.

Post-marketing experience

The US version of the product, MYXREDLIN (insulin human in 0.9% sodium chloride injection) for IV use, was approved in June 2019 and safety monitoring is ongoing. In the time period between US product launch and 31 December 2019, the Company has received one spontaneous report. No new confirmed safety signals have been identified and the positive benefit-risk balance of the product remains unchanged.
No means of comparability to the US version have been provided.

2.6.8. Discussion on clinical safety

The applicant provided safety data from two clinical studies that enrolled healthy volunteer subjects, which is in line with the Guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1) and thus acceptable.

In the pivotal CEL-HI-203 study, no meaningful differences in AEs between Inpremzia and Actrapid were reported. Of the 60 subjects enrolled in the study, 56 (93.3%) completed the study; two subjects voluntarily withdrew consent; one subject was withdrawn because of the AEs vomiting, hypokalaemia, atrial fibrillation and headache after receiving test product, and one subject was withdrawn due to multiple haemolysed samples and missed PK time points due to difficult sampling during Period 1 (received reference product). However, the overall sample size, despite being adequate for the biosimilar procedure, is not suitable to provide a definite conclusion on safety. Of note, as this procedure involves a product intended for short-term use, long-term safety data, which would be required for chronic use, are not considered essential, provided that as stated in the Guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1), the biosimilarity exercise sufficiently reassures adverse drug reactions at similar frequencies. Moreover, the data from the supportive CEL-HI-200 study did not raise additional concerns.

The most critical part in this MAA is the absence of clinical immunogenicity data. The Guideline accepts the waiving of a *separate* immunogenicity study if the results of the biosimilar exercise and the impurity profile provide sufficient reassurance that adverse drug reactions are expected with similar frequencies between test and reference product, but does not discuss the absence of *any* immunological data. Two factors (also addressed in the CHMP Scientific Advice (Procedure No.: EMEA/H/SA/3726/1/2017/III)) somewhat attenuate the need of comparative immunogenicity data: Firstly, the biosimilar candidate is only intended for short-term use and thus, studies evaluating long-term formation of anti-insulin antibodies (AIA) are of minor importance here compared with insulins intended for chronic administration over years. Secondly, acute hypersensitivity reactions caused by insulin administration occur very rarely and the risk of hyperglycaemia due to pre-existing (neutralizing) AIA is smaller for IV administered insulins than for SC formulations. However, even minor structural differences on the molecular level (including post-translational modifications) between the test and reference product may entail an immune response considerably different from the RMP. Consequently, concerning similarity on the safety level, the robustness of the biosimilarity exercise on the quality level is considered crucial. In this regard, the CHMP concluded that the provided cumulative information is considered sufficient to compensate for the missing clinical immunogenicity assessment.

2.6.9. Conclusions on the clinical safety

Overall acceptable, no critical safety concerns were identified.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	None

Summary of safety concerns	
Important potential risks	None
Missing information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

None.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

This MAA is submitted according to Article 10(4) of Directive 2001/83/EC; biosimilar application. Inpremzia, formulated in pre-diluted infusion bags (1 U/ml, for IV application), was developed as a biosimilar of Actrapid (100 IU/ml, solution for injection).

Compared with the reference product Actrapid, the applicant initially sought only a restricted indication. While Actrapid is indicated "*for treatment of diabetes mellitus*", the proposed indication of Inpremzia was initially "*for the treatment of patients with diabetes mellitus who require intravenous insulin administered by healthcare professionals for the maintenance of glucose homeostasis*." This was not considered acceptable and upon request by the CHMP, the applicant agreed to amend the indication accordingly to "…is indicated for the treatment of diabetes mellitus" in line with EU requirements.

In contrast to the RMP Actrapid, which is approved for subcutaneous and intravenous application, but has to be diluted before IV application, Inpremzia is formulated as a pre-mixed infusion in bags containing 100 ml equivalent to 100 IU human insulin.

Quality aspects

The applicant has developed Inpremzia as a similar biological medicinal product to the reference medicinal product Actrapid, containing recombinant human insulin as active ingredient. A comprehensive similarity exercise following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012), has been performed. Of particular note, the proposed biosimilar insulin will be presented as a pre-mixed, ready-to-use solution in an infusion bag containing 1 IU/mL human insulin, whereas the reference product is a 100 IU/mL solution for injection in vials. The assessment of biosimilarity is affected by the differences in the formulation and the presentation between Inpremzia (1 IU/mL) and the RMP Actrapid (100 IU/mL).

State of the art analytical test methods have been used to characterise the RMP and Inpremzia. The biosimilarity assessment includes structural and functional characterisation studies comparing primary and higher order structures, molecular mass, charge, content and impurities (such as HMWP), receptor binding and functional attributes.

An initial biosimilarity quality assessment has been performed against US-sourced comparator product batches (Novolin R), while the pivotal biosimilarity exercise has been conducted against the EU reference product Actrapid. The number of batches analysed in each biosimilarity assessment study has been justified based on statistical considerations. According to the applicant, all available batches that could be sourced were used. The difference in the age distribution of these batches is 11 months. Sufficient information on the DS process used to manufacture each DP batch as well as the age of each DP batch at the time of biosimilarity testing has been provided.

The comparability between US-sourced Novolin R and the EU-RMP Actrapid has not been addressed, which is acceptable since the pivotal PK/PD clamp study (study 203) was conducted using the EU-RMP Actrapid. The similarity data between Inpremzia and US sourced Novolin R has been provided as supportive information.

Biological comparative studies included analysis of insulin receptors IR-A and IR-B and their phosphorylation, IGF-1R and following metabolic activity analyses; induction of apidogenesis and glucose uptake and inhibition of lipolysis. Furthermore, IGF-R1-related induction of mitogenesis was assessed.

Non-clinical aspects

The non-clinical programme was designed to support similarity between Inpremzia and the RMP Actrapid, and followed the risk-based approach with omission of *in vivo* studies.

The applicant followed CHMP Scientific Advice (EMEA/H/SA/3726/1/2017/III) on non-clinical topics and appropriate justifications for waiving non-clinical studies were provided, in line with applicable CHMP guidelines.

Clinical aspects

The clinical development of Inpremzia/Insulin Human Baxter is based on two clinical comparative PK/PD studies, of which only Study CEL-HI-203 is considered pivotal due to use of the EU-reference product Actrapid as comparator. The second study, Study CEL-HI-200, is only considered as supportive.

Study CEL-HI-203, a comparative PK/PD, double-blind, randomised, two-treatment, two-period, 2-way crossover, hyperinsulinaemic euglycaemic clamp trial in healthy adult male subjects, was conducted in accordance with the EMA Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev. 1). Furthermore, the applicant sought EMA scientific advice in 2017 (Procedure No.: EMEA/H/SA/3726/1/2017/III) concerning quality development, pre-clinical development and clinical development (including a clarification). In general, the recommendations of the CHMP Scientific Advice were followed.

3.2. Results supporting biosimilarity

Quality aspects

High similarity between Inpremzia and Actrapid has been demonstrated for the following quality attributes:

- Primary structure:
  - identical amino acid sequence; identical amino acid composition; human origin present in all sample types, although lower levels in Inpremzia than in Actrapid.
- Higher order structure
  - identical secondary and tertiary structures in near and far UV CD analysis
- Molecular mass/size
  - similar intact mass (MS)
  - aggregate levels
- Charge
  - comparative isoelectric points
- Assay
  - comparative content (% of label claim) in Inpremzia and Actrapid
- Impurities
  - formation of degradation products and HMWP in forced degradation and comparative stability studies had some differences that do not preclude similarity
  - similar size and count for sub-visible particles
- Similar IR-A and IR-B autophosphorylation activity, binding to IGF-R1, induction of adipogenesis and mitogenic activities.
- Finally, data from 3 new Inpremzia and RMP batches, from assays qualified with Ph. Eur. chemical reference substance (EP CRS) provided for the IR-A and IR-B binding, inhibition of lipolysis and glucose uptake together with the investigation of the root-cause for the wide batch-to-batch variability further support the conclusion of biosimilarity.

Non-clinical aspects

The non-clinical programme was designed to support similarity between Inpremzia and the reference medicinal product Actrapid, and followed a risk-based approach with omission of *in vivo* studies. Pharmacodynamic *in vitro* studies were conducted as part of the pivotal quality and functional biosimilarity documentation. Non-clinical biosimilarity is supported since additional data from the *in vitro* functional assays, reviewed in the Quality part of the AR, demonstrate similarity at functional level.

Clinical aspects

- The pivotal study was planned and conducted according to current guidance and the recommendations of the CHMP scientific advice were implemented.
- The 90% CIs of GM ratios of the primary PK parameter $AUC_{INS\text{-}SS\ 300\text{-}360min}$ and $C_{max\ INS\text{-}SS\ 300\text{-}360\ min}$ were within the pre-specified limits of 80% and 125%, in detail 1.0023, 1.0650 and 1.018, 1.079, respectively. Similarly, the 95% CIs of GM ratios of primary PD endpoints $AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$ and $GIR_{max\text{-}SS\ 300\text{-}360\ min}$ were within the pre-specified limits of 80% and 125%: 0.9660, 1.0745 and 0.9723, 1.0780, respectively. Additional PK and PD parameters were also within the pre-specified limits of 80-125%. These results indicate similar pharmacokinetics and pharmacodynamics between the test product Inpremzia and the reference product Actrapid. Sensitivity analyses and exploratory measures support this notion.
- Results observed in the supportive study, which was in many aspects similarly planned and conducted as the pivotal study, were suggestive of similarity to US RMP (Novolin R) and support results observed vs. the EU RMP.
- No relevant differences in AEs between Inpremzia and Actrapid were reported.

3.3. Uncertainties and limitations about biosimilarity

Quality aspects

The observed differences in *in vitro*-related functions, i.e. binding to key target receptors IR-A and IR-B isoforms and two out of three assays for metabolic activities (inhibition of lipolysis and induction of glucose uptake) as well as the considerable wider batch-to-batch variability of Inpremzia, were raised during the procedure. Upon request, the applicant submitted new comparative data from IR-A and IR-B binding, inhibition of lipolysis and glucose uptake and investigated the root cause for the wider batch-to-batch variability of Inpremzia. Data was provided from 3 new Inpremzia and RMP batches, from assays qualified with Ph. Eur. chemical reference substance (EP CRS). Matrix may have an effect on binding to insulin receptors with SPR to some extent, and the variability observed in previous analysis could be attributed to the use of previous reference standard. The differences observed between Inpremzia and Actrapid on IR binding were reduced with the matrix changes, but not to the extent that Inpremzia would be ≥80% fitting within the variability range of Actrapid. Nevertheless, it is plausible that *in vivo*, when matrix effects are even more diluted, the differences in binding activities could be further equalised. Furthermore, these differences in the target binding had no impact on the metabolic activity (inhibition of lipolysis) or glucose uptake activity. Consequently, despite the slight differences seen in binding to IR, Inpremzia and Actrapid can be considered similar in functional attributes.

Clinical aspects

<u>Pharmacology</u>

Initial issues pertaining to sequence or period effects, conduct of the study and clamp quality were resolved during the procedure.

Safety

No clinical immunogenicity data was provided and initially, the absence of any immunological data in the clinical studies was not adequately justified. The robustness of comparative quality data is crucial to decide on the necessity for clinical immunogenicity data, and the applicant sufficiently addressed this issue during the procedure by providing a thorough analysis on quality level.

Moreover Inpremzia is the first IV insulin presentation that is not to be diluted before use. The applicant has provided detailed information regarding the risk minimisation measures implemented to reduce the risk of accidental dilution (ready to use bag with adequate bag labelling, lack of injection port and carton labelling). Medication errors will be monitored by routine pharmacovigilance, which is acceptable.

3.4. Discussion on biosimilarity

Quality aspects

A solid pivotal biosimilarity evaluation of Inpremzia against a sufficient number of Actrapid batches has been conducted. The data on quality attributes show a high level of similarity. Certain uncertainties and limitations raised during the assessment period have been addressed; in particular, the issue addressing similarity in functional assays. In summary, the quality data is sufficient to conclude that Inpremzia is biosimilar to Actrapid.

Non-clinical aspects

Non-clinical biosimilarity can be supported since the additionally provided *in vitro* functional data, reviewed in the Quality part of the AR, show a similar functionality.

Clinical aspects

The applicant investigated similarity between Inpremzia and Actrapid (EU-RMP) in a single pivotal euglycaemic clamp trial; a similarly designed trial vs Novolin R (US-RMP) was conducted for the US FDA approval and is regarded as supportive for this MAA.

The pivotal study, which was primarily designed to demonstrate similarity on PK/PD level, was conducted in healthy subjects and in accordance with CHMP guidelines and CHMP Scientific Advice. The 90% confidence intervals of the GM ratios of the primary PK endpoints $AUC_{INS\text{-}SS\ 300\text{-}360min}$ and $C_{max\ INS\text{-}SS\ 300\text{-}360\ min}$ and the 95% confidence intervals of the GM ratios of the primary PD endpoints $AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$ and $GIR_{max\text{-}SS\ 300\text{-}360\ min}$ of the biosimilar candidate and the RMP were within the pre-specified limits of 80% and 125%, indicating similarity of PK and PD.

In line with the product specific guideline for biosimilar insulins, waiving an immunogenicity study might be justified in certain cases based on a robust demonstration of similarity in all important physicochemical and functional attributes using appropriately validated and sensitive state-of-the-art methods, when similarity in PK and PD has been established, and if the impurity profile and excipients of the biosimilar do not give rise to concerns. In this case, any conclusion whether the immunological profile of Inpremzia and Actrapid are comparable can only be drawn from quality- and functional data. However, two aspects tightly linked to the intended short-term IV application attenuate the criticality of this issue to some extent. Antibody formation to a usually immunologically unobtrusive protein with (presumably) identical structure to endogenous human insulin requires a certain exposure. Due to the

envisaged short-term use, it is plausible that exposure to Inpremzia will not cause relevant ADA formation, causing an altered clinical profile compared with Actrapid. In addition, hypersensitivity reactions associated to insulins occur very rarely and the risk of hyperglycaemia due to pre-existing (neutralizing) AIA is smaller for IV administered insulins than for SC formulations. That being noted, however, even minor structural differences on the molecular level (e.g. post-translational modifications) between Inpremzia and Actrapid may entail an immune response different from the RMP. In any case, the applicant has sufficiently addressed this issue during the procedure by providing a thorough analysis on the quality level. Consequently, the totality of evidence is strongly supportive of similarity and the issue of potential immunogenicity has been sufficiently addressed.

3.5. Extrapolation of safety and efficacy

Not applicable.

3.6. Additional considerations

The applicant initially applied only for a restricted indication compared with the broad indication of the reference product Actrapid "*for the treatment of diabetes mellitus*". This was a consequence of the decision to only develop the intravenous route of administration for Inpremzia, while the RMP Actrapid also has a SC dosage form. The motivation for developing a ready-to-use insulin solution for injection is avoidance of a dilution step, which may lead to medication error, especially in stressful situations.

On the other hand, a potential risk of medication error could result from availability of the new formulation (e.g. resulting in under-dosing of insulin) since the concentration of Actrapid (which needs to be diluted before IV application), is much higher (100 IU/mL), while Inpremzia solution has an insulin concentration of 1 IU/mL. This has been appropriately addressed by the applicant during the procedure and sufficient risk minimisation measures implemented.

Upon request by the CHMP during the procedure, the applicant agreed to amend the indication to "…is indicated for the treatment of diabetes mellitus" in line with the EU RMP Actrapid.

3.7. Conclusions on biosimilarity and benefit risk balance

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

The benefit/risk balance is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Inpremzia is not similar to Amglidia within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

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

Treatment of diabetes mellitus

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.