26 February 2026
EMA/62379/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dazparda

International non-proprietary name: insulin aspart

Procedure No. EMEA/H/C/006187/0000

Note

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

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List of abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
ANOVA	Analysis of variance
$AUC_{GIR.0\text{-}24h}$	Area under the GIR curve from 0 to 12 hours
$AUC_{ins.0\text{-}24h}$	Area under the plasma insulin concentration curve from 0 to 12 hours
BMI	Body mass index
CI	Confidence Interval
$C_{ins.max}$	Maximum observed insulin concentration
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
E.coli	Escherichia coli
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GIR	Glucose infusion rate
GIR_{max}	Maximum observed glucose infusion rate
GL	Gan & Lee Pharmaceuticals
IMP	Investigational medicinal product
LS	Least Squares
MAA	Marketing Authorization Application
MedDRA	Medical dictionary for regulatory activities
PD	Pharmacodynamics
PK	Pharmacokinetics
PPS	Per Protocol Set
PT	Preferred term
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
T1DM	Type 1 diabetes mellitus

T2DM	Type 2 diabetes mellitus
$t_{50\%\text{-}ins(early)}$	time to half-maximum insulin aspart concentration before $C_{ins.max}$
$t_{50\%\text{-}ins(late)}$	time to half-maximum insulin aspart concentration after $C_{ins.max}$
$t_{ins.max}$	Time to maximum observed insulin concentration
$t_{max.GIR}$	Time to maximum glucose infusion rate
$t_{max.ins}$	Time to maximum observed plasma insulin concentration
US	United states
λz	Terminal elimination rate constant of insulin aspart

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gan & Lee Pharmaceuticals Europe GmbH submitted on 11 September 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Dazparda, 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:

> Dazparda is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

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.

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

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: NovoRapid Flexpen, 100 U/ml, Solution for injection in pre-filled pen
- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: 07-09-1999
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/99/119/011, EU/1/99/119/009

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

- Product name, strength, pharmaceutical form: NovoRapid Flexpen, 100 U/ml, Solution for injection in pre-filled pen
- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: 07-09-1999
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/99/119/011, EU/1/99/119/009

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: NovoRapid Flexpen, 100 U/ml, Solution for injection in pre-filled pen
- Marketing authorisation holder: Novo Nordisk A/S

- Date of authorisation: 07-09-1999
- Marketing authorisation granted by:
  - Union
  - (Union) Marketing authorisation number(s): EU/1/99/119/011, EU/1/99/119/009
- Bioavailability study number(s): GL-ASP-1008

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 did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: Kristina Nadrah

The application was received by the EMA on	11 September 2023
The procedure started on	28 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 December 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 December 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 December 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	09 October 2025
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy	

assessment of the product:	
– A GMP inspection at one manufacturing site in China between 13-15 March and 18-19 March 2024. The outcome of the inspection carried out was issued on.	28 May 2024
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	18 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	11 December 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 January 2026
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	8 February 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dazparda on	26 February 2026
The CHMP adopted a report on similarity of Bysumlog with Amglidia on (see Appendix on similarity)	26 February 2026

2. Scientific discussion

2.1. About the product

Dazparda (insulin aspart) was developed as a proposed biosimilar to NovoRapid (insulin aspart) for subcutaneous injection.

The active ingredient of Dazparda has the same amino acid sequence as the active ingredient of NovoRapid and is produced using the same recombinant deoxyribonucleic acid (DNA) technology as NovoRapid. Dazparda also has the same components and composition as NovoRapid.

The claimed therapeutic indication is the same as the therapeutic indication of NovoRapid:

> Treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

2.2. Type of Application and aspects on development

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) provided advice to the Applicant on two occasions:

- EMA Pre-MAA Meeting Preliminary Comments, 02 March 2023
- EMA Pre-MAA Meeting, 01 June 2023

Quality

The applicant was seeking advice on:

- Product Quality Data Reported in the MAA. The sponsor manufactured a number of lots of insulin aspart DS and DP for marketing and registration purposes.
- The proposed microbial control strategy for testing of in-process intermediates for insulin aspart DS.
- Lifetime study for resins used in DS manufacture.
- Comparative Analytical Assessment.

Most quality issues that the applicant was seeking advice for are a matter of this assessment report.

Non-clinical

The non-clinical development program for Dazparda focused on demonstrating similarity of Dazparda with a EU-licensed NovoRapid with regards to *in vitro* (insulin receptor and insulin growth factor-1 receptor binding and phosphorylation, metabolic activation, mitogenic potential and potency) and *in vivo* (toxicity and toxicokinetic profile) characteristics.

The non-clinical development program was conducted and assessed in accordance with EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and 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).

No national or EMA Scientific Advice (SA) was requested for the development of Dazparda. Pre-submission meetings with the EMA and Rapporteur/Co-rapporteur were held on the 2nd of March 2023 and 1st of June 2023, respectively. A question regarding the adequacy of the non-clinical package was raised at the Rapporteur/Co-rapporteur meeting and the response was that the package appeared sufficient to support biosimilarity assessment based on the pre-submitted material. Furthermore, it was emphasized that sufficient justification should have been provided to omit the environmental risk assessment (ERA).

Clinical

The Applicant did not receive CHMP scientific advice during this procedure. A pre-submission MAA meeting was held in 2023. The Applicant was informed that the acceptance of a waiver for the safety study would be a matter of assessment of the quality, non-clinical, and clinical data. The Applicant was further requested to submit the Integrated Summary of Immunogenicity. Lastly, due to the short duration of effect, the $AUC_{ins0\text{-}2h}$ interval was to be included in the submission package to support the primary outcome in demonstrating biosimilarity to NovoRapid.

2.3. Quality aspects

2.3.1. Introduction

The finished product (FP) is presented as solution for injection in pre-filled pen containing 100 units/ml of insulin aspart as active substance (AS).

Each pre-filled pen contains 3 ml equivalent to 300 units of insulin aspart.

Other ingredients are: glycerol, phenol, metacresol, zinc chloride, disodium hydrogen phosphate, sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), and water for injections.

The product is available in 3 ml solution in cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene.

Pack sizes of 1 and 5 pre-filled pens.

2.3.2. Active Substance

2.3.2.1. General Information

Insulin aspart (INN) is a two-chain peptide containing 51 amino acids; the A- and B-chain is composed of 21 and 30 amino acids, respectively. The primary structure is identical to that of human insulin except that it has an aspartic acid instead of proline at position 28 of the B-chain. Like human insulin, insulin aspart contains two interchain disulfide bonds and one intrachain disulfide bond. The molecular weight is 5826 Da.

2.3.2.2. Manufacture, process controls and characterisation

Insulin aspart active substance is manufactured by Gan & Lee Pharmaceuticals site in Beijing, China. Initially, a valid proof of EU-GMP compliance for this site was missing and a Major Objection was raised. During the procedure, a valid proof of EU-GMP compliance for the manufacturing site has been provided.

Insulin aspart AS is manufactured utilizing a recombinant *Escherichia coli* (*E. coli*) platform. A two-tiered cell bank system including Master Cell Bank (MCB) and Working Cell Bank (WCB) has been established.

Description of manufacturing process and process controls

The active substance manufacturing process has been adequately described. It consists of two stages: the upstream process (USP) and downstream process (DSP). The upstream process includes: inoculation with WCB and seed culture expansion steps; fed-batch production fermentation; cell harvest, cell washing concentrate preparation. A limit is defined for the number of cell generations at the end the batch.

The downstream process includes denaturation of the inclusion body and continues through refolding, enzyme digestion, ultrafiltration/diafiltration (UF/DF) and chromatography steps, crystallization and freeze drying.

The freeze-dried AS is filled into sterilized bottles.

An overview (flow chart) of the manufacturing process is provided, including process parameters and in-process controls (IPC) and their acceptable ranges, as well as process volumes and holding times. A detailed narrative description of each step is also provided listing also the criticality of the main process parameters and IPCs.

Media, buffers, and solutions used in the manufacturing process are listed, including composition, microbial control/sterilisation, and storage. Regarding microbial control of the process, culture purity is

controlled at each step during upstream and bioburden and endotoxin are tested at several steps in DSP, and bioburden reduction steps are included in DSP. Furthermore, prolonged in-process intermediate hold times are justified based on a microbial risk assessment.

Overall, the insulin aspart AS manufacturing process, process parameters, and process controls are considered adequately described.

Control of critical steps and intermediates

The overall control strategy for insulin aspart AS manufacturing consists of a set of controls derived from current product and process understanding, which assures process performance and product quality. Identification and justification of critical quality attributes (CQAs), critical process parameters (CPP) and IPCs, and justification of acceptable range of CPPs and the acceptance criteria of IPC are described. Quality control on other aspects includes control of raw material and control of AS.

CPPs and critical IPCs are listed, together with their acceptable ranges/limits and testing methods. Description and validation/qualification of the testing methods for critical IPCs is provided.

Action limits are internal (in-house) values used to assess the consistency of the process; whereas the acceptance criteria are numerical limits that should be met. The actions taken for IPCs in case of acceptance-criteria excursion and action-limit excursion are described in the dossier and is found adequate.

Microbial control of the process is performed by control of culture purity, bioburden, and endotoxin, and by bioburden reduction filtrations. Furthermore, prolonged in-process intermediate hold times are defined; these are justified based on a microbial risk assessment. Storage times of media and solutions are defined and justified based on a performed risk evaluation.

A major objection was raised for the cell bank and a control strategy is included and endorsed. The applicant's intention for development activities post-authorisation is highly endorsed, and the intended timeframe considered acceptable (REC). Overall, the control of critical steps is considered sufficiently described and adequate to control the process and ensure formation of active substance of adequate and consistent quality; there are no intermediates isolated within the manufacturing process of insulin aspart.

Process validation

Three consecutive AS PPQ batches were manufactured in accordance with pre-approved protocols and according to the commercial process, scale, and control procedures. The three downstream PPQ batches of AS were manufactured from three different upstream PPQ batches.

Sampling during the PPQ followed a pre-defined test strategy and samples were tested with the validated or qualified analytical methods. PPQ results are provided for all individual process steps and for process parameters as well as for process attributes/IPCs and for release testing. Overall, the process validation data are within the pre-defined ranges/acceptance criteria/specifications, including the critical parameters and attributes (CPPs, critical IPCs and CQAs). Some additional testing was performed for PPQ batches.

Resin and membrane lifetime studies

Resin lifetimes studies are ongoing for all chromatography material according to pre-approved protocols and acceptance criteria and pre-specified lifetime targets. The studies evaluate purity/impurity, step yield, DNA clearance, Host cell Protein (HCP) clearance, microbial control, mock run (protein carry over and HCP), and column efficiency as applicable for the relevant step. Sanitisation and storage solutions

is informed and considered justified. Resin lifetime studies are considered adequate to support the proposed lifetimes.

Membrane reuse verification at-scale for the reusable membranes used in manufacture of insulin aspart is ongoing according to pre-approved protocols and acceptance criteria and a pre-specified lifetime target for all membranes. The verification studies evaluate purity, step yield, protein content, membrane integrity, pressure, microbial control (bioburden, endotoxin), module replacement, as applicable for the relevant step. Sanitisation and storage solutions is informed and considered justified. Membrane lifetime studies are considered adequate to support the proposed lifetimes.

In-Process Intermediate Hold Time

Insulin aspart AS in-process intermediate hold times, have been defined based on risk-assessments and validated at small-scale and/or at-scale studies as applicable; the applied strategy can be supported. Definition of hold times were based on the small-scale or at-scale study results and manufacturing needs and were based on the more stringent requirement shown by the studies. A range of stability-indicating parameters were tested for each intermediate. The proposed in-process intermediate hold times are considered adequately supported.

Buffer Hold Time Validation

Multiple buffers are used in the AS manufacturing process. Buffer hold times have been defined based on a risk assessment, small-scale physicochemical study results, at-scale microbial study results, available hold time studies and manufacturing needs. The proposed buffer intermediate hold times are considered adequately supported.

Extractables and Leachables

Risk of contamination of product with extractables and leachables from relevant product-contact materials (resins, filters, container closure system) used in AS manufacturing has been evaluated. Based on this, it was concluded that the use of the materials will not impact the AS quality and patient safety. Evaluation of extractables and leachables is considered adequate and the conclusion can be supported.

Impurity Removal Validation

Removal of the impurities has been validated. Sampling points in the process are indicated for each impurity; sampling points and numbers depends on the impurity in question and are considered adequate. Limits for residual impurities are pre-defined in the impurity removal study protocol.

Process-related impurities include cell-substrate derived impurities, cell-medium derived impurities, residual solvents, process chemicals, elemental impurities. For all components, effective removal is demonstrated; furthermore, for all impurities, the results of validation batches are comparable between batches indicating consistent removal in the current process.

Product-related impurities include single-chain precursor, related proteins, high-molecular weight aggregates/protein (HMWP). For single-chain precursor and HMWP, effective removal is demonstrated; furthermore, the results of validation batches are comparable between batches indicating consistent removal in the current process.

A Major Objection (MO) was raised for the cell bank. The applicant performed a product quality impact assessment showing no impact on the product quality. The major objection was considered resolved during the procedure.

AS Shipping Validation

Not applicable as insulin aspart AS and FP are manufactured at the same site.

Control of materials

Raw materials

All materials for production are purchased from qualified suppliers. Compendial quality is stated as applicable and in-house specifications are in place for non-compendial materials. Quality agreements are in place for all suppliers. The criticality of the raw materials is evaluated; on-site audits of suppliers of critical materials are performed and audits of suppliers of noncritical materials are performed as written audits; both on-site and written audits are conducted every three years. Suppliers of complex raw materials are informed, and source is stated for animal-derived and biologically sourced materials.

Cell substrate

The DNA sequence of the gene of interest is provided and the function of the individual sequences is explained. The plasmid was introduced into the host strain by transformation.

The generation of primary seed lot for insulin aspart production is described. The generation and characterization of MCB and WCBs is described.

The analytical methods for cell bank testing, as well as the culture media used in generation of cell substrate and cell banks, are described.

A stability testing program is in place for the MCB and WCB. End of Production (EoP) cells were characterized, demonstrating that the strain is genetically stable at the end of fermentation even undergoing greater passage number than for EoP. A limit of *in vitro* cell age (LIVCA) study was performed demonstrating that the cell line is genetically stable and product quality is not affected.

Overall, the manufacture of cell banks is considered adequately described and the characterisation of the cells banks is considered adequate and in line with ICH Q5B and Q5C. The major objection raised was considered resolved during procedure.

A protocol for preparation of future working cell banks is included. According to this protocol, future WCBs will be prepared from the same MCB as the earlier and current WCB batches, and they will be manufactured and characterised according to the procedure described in the dossier. The information on generation of new WCBs is considered adequate for implementing new WCBs; the qualification protocol for new WCB includes whole genome sequencing and assessment of the encoded proteins.

Manufacturing process development

AS manufacturing was developed in different processes. The first process is used for material for toxicology studies, and clinical. Update to the commercial process, includes changes resulting in better control of the process.

The rationale for change and the effect on quality attributes were informed for each change. Overall, the manufacturing process changes from different processes can be considered non-significant with regard to process performance and AS quality.

Comparability assessment

Comparability acceptance criteria were calculated based on data from pre-change batches. The approach is considered acceptable.

Data were compared for the pre-change and post-change batches. Comparability is considered established between Processes.

Stability profiles were compared and it is considered demonstrated that the stability behaviour of pre- and post-change batches is comparable. A few exceptions were observed, however, the deviations are considered minor and have been adequately justified.

All data indicate that pre- and post-change batches of insulin aspart AS are comparable.

Development of manufacturing process

Identification of CQAs followed a risk-based approach based on impact and uncertainty. The assessment of impact focused on efficacy/biological activity, pharmacokinetics/pharmacodynamics (PK/PD), immunogenicity and safety. The approach is considered adequate.

Process Characterization: Based on the defined CQAs, the production process was assessed resulting in criticality classification of process parameters. The CPP ranges were developed. A summary of the results is provided for each individual process step. The classification of IPCs was justified based on the impact on CQA of active substance. Overall, the classification of criticality of process input and output parameters, and the designation of acceptable ranges/limits is considered adequate and supported by data. The proposed control strategy is considered adequate to ensure that the manufactured AS is of adequate and consistent quality.

Development of analytical methods

The HCP and residual DNA test used for testing insulin aspart have been changed. Where relevant, method bridging has been performed; bridging studies are considered adequate and demonstrate comparability of the methods.

Characterisation

Elucidation of structure and other characteristics

For characterization of structure and biological characteristics, several AS lots were tested, along with an internal reference standard (RS), and for comparison, a Ph. Eur. RS lot and a USP RS lot. Characterization results are consistent between AS lots and RSs. It can be noted that the same tests were also performed on FP lots as part of the biosimilarity exercise.

Primary structure was analyzed by MS (non-reduced, reduced), peptide mapping LC-MS, LC-MS/MS (full-length sequencing with 100% coverage), and Edman degradation. Isoelectric point was measured by icIEF. Secondary and higher-order structure was characterized by circular dichroism (CD) and intrinsic fluorescence spectrometry. This is quite limited, but as mentioned above, testing was also performed on FP in the biosimilarity exercise, and this included the additional tests of: Secondary structure by FTIR, tertiary structure by DLS and DSC, and quaternary structure by SEC-MALS. Disulphide linkage was analysed by Ellman's assay and LC-MS/MS peptide mapping. Overall, structure is deemed adequately characterized.

The biological characterization is considered adequate. Insulin aspart binds the receptors IR-A, IR-B and IGF-1R, causing autophosphorylation, which in turn affects metabolic and/or mitogenic activity. Binding to IR-A, IR-B and IGF-1R was examined by using SPR, with Ka, Kd and KD being determined. Phosphorylation of IR-A, IR-B and IGF-1R was assessed using cell-based assays. IR-B phosphorylation, also by an in-cell Western potency assay. Mitogenicity (IR- and IGF-1R-dependent), and metabolic activity (glucose uptake, glucagon synthesis, lipogenesis), were assessed by cell-based assays.

For characterization of product-related species, AS lots were used (same as for characterization of structure and biological characteristics), along with FP batches (clinical and commercial).

Multiple species were observed in RP-HPLC and/or CEX-HPLC chromatograms and identified by LC-MS/MS. They were then classified as product-related substances or product-related impurities, depending on whether they showed near-normal potency, or not.

The AS and FP degradation pathways are deemed adequately characterized. The AS was subjected to forced degradation by light stress, high temperature, and high humidity. The assessed conditions were high temperature, acidic pH, basic pH, oxidation, light, and mechanical stress. Multiple methods were used.

Process-related impurities

Process-related impurities include cell-substrate derived impurities, cell-medium derived impurities, residual solvents, process chemicals, elemental impurities. Adequate clearance of process-related impurities has been demonstrated.

2.3.2.3. Specification

The applicant has provided AS specifications that covers general tests, identity, content/activity, purity/impurity and microbial content.

The panels of tests are considered acceptable.

The acceptance criteria have been based on the Ph. Eur. <Insulin Aspart> or on USP monographs (for such attributes where no limits are defined in Ph. Eur. <Insulin Aspart>), and/or on other factors, including analysis of historical batch data, and safety considerations (the solvent limits were set based on ICH Q3C, and the residual DNA limit was set in accordance with WHO recommendation).

The acceptance criteria are considered adequately justified.

Analytical procedures

The analytical procedures are a combination of compendial and non-compendial methods.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. The validation data demonstrate that the methods are suitable for their intended use.

The panel of methods used to assure the quality of the active substance is in accordance with ICH Q6B. The compendial methods are performed in accordance with the methods described in Ph. Eur. For bacterial endotoxins, method suitability verification was performed for the active substance, demonstrating endotoxin recovery in the presence of the sample.

Suitability testing of the microbial limit method was performed with the active substance, showing recovery of the micro-organisms in the presence of the sample.

Some methods are carried out as described in the Ph. Eur. monograph Insulin aspart, . while some were fully validated in accordance with ICH Q2.

The analytical procedures used to test in-process intermediates at different steps of the process are adequately described and validated to a sufficient extend.

Batch analysis

Batch data are provided for the AS batch used for stability study for manufacturing FP for similarity study and toxicology study, and for the PPQ batches; certificates of analysis for PPQ batches are provided. All batch data comply with the release acceptance criteria and demonstrate that the commercial process is

capable of manufacturing an AS of consistent quality. Furthermore, batch data for batches used for setting proposed commercial AS specification were provided; all data comply with specification.

Reference standard

Several working reference standards (WRS) have been in use, which were sourced from AS batches representing different processes. The WRSs were qualified against Ph. Eur. insulin aspart reference standard, and stability is tested annually. Release and stability test results are shown, and were found acceptable.

The Applicant commits to establish an updated reference standard system for commercial phase after approval (REC).

The protocols for qualification of new WRSs is provided. The protocol for future WRS stability testing is also provided. The qualification and stability protocols were found overall acceptable.

Container closure

Insulin aspart AS container closure system consisting of bottles is described and drawings are provided, and the supplier is stated. Production certificates of compliance is provided, including confirmation and description of leak tests. In-house specifications are provided; specifications and analytical methods are established and performed in accordance with Ph. Eur. and USP as applicable. The containers used in the stability studies are representative of the commercial container closure system. Extractable and leachable studies have been performed; compatibility of the primary packaging materials with insulin aspart AS is considered demonstrated. The container closure system is considered sufficiently described and of adequate quality.

2.3.2.4. Stability

Long-term stability study

Long-term supportive stability data have been provided for the several at-scale batches; the data all comply with stability specifications and no trends are observed. Long-term stability data have been provided for the PPQ batches; the data all comply with stability specifications, and no trends are observed hitherto. The proposed shelf life and storage conditions are supported by data.

Accelerated stability studies

Accelerated stability studies were performed, including the PPQ batches. For some parameters, a gradual increase was observed as expected; however, after six months all attributes were within acceptance criteria, supporting the general stability of insulin aspart AS as well as comparability between different AS processes batches.

Photostability study

The photostability study demonstrates that the AS is sensitive to light. However, the results from the samples packaged with commercial package met the long-term stability lot release criteria, indicating that the commercial package can provide sufficient light protection for the AS storage. The relevant dossier sections specifies that the AS has to be protected from light.

Post-approval Stability Protocol and Stability Commitment

The applicant commits to continuing the stability studies as described in the dossier. Extension of the shelf life will be declared through a variation application.

Conclusion

Based on the demonstrated comparability of different AS process batches the proposed shelf-life of Insulin aspart AS t the recommended storage conditions can be accepted.

2.3.3. Finished Medicinal Product

2 . 3 . 3 . 1 . Description of the product and Pharmaceutical Development

Description of the product

The finished product is a sterile, clear and colourless solution supplied in a 3 mL Type 1 glass cartridge assembled into a pen device, presented as a disposable, variable-dose, multiple-dose prefilled pen. The product is intended for use with suitable pen needles, via subcutaneous injection.

The finished product contains 100 U/mL insulin aspart. The composition of the finished product was selected based on the published available information of the reference product NovoRapid. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

To ensure the extractable volume claimed on the label (3 mL), each cartridge is overfilled with defined volume of finished product. There is no overage in the formulation of the finished product.

Pharmaceutical development

All excipients in the formulation are the same chemical compounds as those used in NovoRapid. The intended commercial formulation is the same as that used throughout product development including clinical studies.

A formulation robustness study was performed to evaluate the impact on product quality of a variation from the target point in the concentration of each excipient. It is shown that the selected formulation is robust when the concentration of excipients varied from the target content.

The pH of finished product is consistent with that defined in the USP monograph <Insulin aspart injection> with an acceptance criterion of 7.0-7.8. This range was investigated in a pH robustness study to evaluate the effect of final pH on product quality, and data support the proposed pH range. In addition, a dedicated zinc robustness study was conducted to further investigate the impact of zinc content on product quality. Based on the study, stringent control has been implemented for commercial manufacture. Visible particles formation was investigated. The impact of the visible particles was evaluated on product quality and on the drug delivery system, concluding that the impact was negligible.

In addition, a risk assessment was performed to address patient risk associated. The risk was considered negligible.

Manufacturing process development

Minor changes, including scale up and scale up-related adaptations, have been introduced to the manufacturing process of the FP between development, clinical and commercial processes. The changes were compared in comparability exercises.

With few differences observed, overall, the performed comparability study supports that finished product quality from development, clinical and commercial processes are comparable.

Comparability assessment was also performed between finished product filled in cartridges and filled in pens, for both clinical and commercial processes. The stability behaviour of the finished product filled either in pens or in cartridges was comparable, demonstrating that the pen assembly process did not negatively impact the quality of the finished product.

Overall, the comparability studies support that the changes introduced in the manufacturing process had no significant impact on product quality, and that comparability is demonstrated between processes.

Identification of CQAs

The quality target product profile (QTPP) of insulin aspart is based on the reference product NovoRapid. Assessment of the critical quality attributes (CQA) followed a risk-based approach evaluating impact and uncertainty. The assessment of impact focused on efficacy and biological activity, PK/PD, immunogenicity and safety. The approach used to identify CQAs and the proposed CQAs are found appropriate.

Container closure system

The primary packaging components were selected to be consistent with those used for the reference product, including a 3 mL Type I glass cartridge sealed at one end with a bromobutyl rubber plunger and at the other end with an aluminum cap with a bromobutyl rubber liner.

The suitability of the container closure system was demonstrated with respect to safety, protection, compatibility, and functionality. Extractable and leachable studies showed that the packaging material is considered safe. Photostability studies revealed that product quality may be impacted by light, but the pen and secondary packaging can protect the product from the influence of light. In addition, the container closure system maintains adequate protection against microbial contamination over the shelf life of the product. Stability studies conducted with filled cartridges and prefilled pens demonstrated physicochemical compatibility of the container closure system components with insulin aspart. Functionality of the prefilled pen was demonstrated by the primary stability studies, indicating that the primary packaging components do not impact drug delivery. In addition, the design of the prefilled pen was verified under different environmental conditions.

The Notified Body (NB) Opinion for medical device was missing, and a Major Objection was raised. During the procedure, the NB Opinion has been provided.

Shipping verification of insulin aspart injection pen was conducted, which covers testing of the shipping configuration throughout the range of physical hazards associated with transportation and handling by road, air and sea. Finished product quality and prefilled pen functional performance were not impacted by the simulated shipping conditions.

Container closure integrity is tested during the stability studies, which confirm the integrity and sterility of finished product over shelf life. In-use stability studies demonstrated the integrity of the product over the in-use period, which is also specified in the SmPC.

The finished product is formulated with metacresol and phenol preservatives as it is a multi-dose product. The functionality of metacresol and phenol as antimicrobial preservatives was adequately demonstratedin-use study. The antimicrobial effectiveness of metacresol and phenol was successfully tested in accordance with Ph. Eur. 5.1.3. Microbiological integrity was also verified after multiple doses administrated at in-use conditions in accordance with EMA/CHMP/QWP/BWP/259165/2019.

2.3.3.2. Manufacture of the product and process controls

Manufacture

EU QP release is conducted by IL-CSM Clinical Supplies Management GmbH, Baden-Wuerttemberg, Germany.

Initially, a valid proof of EU-GMP compliance for the AS/FP manufacturer and for the QC testing site was missing and Major Objections were raised. During the procedure, a valid proof of EU-GMP compliance for these sites has been provided.

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

A detailed description of the manufacturing process is provided. The manufacturing process is a standard process and consists of thawing of active substance, compounding and final formulation of finished product, sterile filtration, aseptic filling into sterilised cartridges, visual inspection of the cartridges followed by release testing of the filled cartridges. The cartridges are then assembled into pen injectors, labelled and packed. Process parameters and in-process controls, and their associated acceptable range, are indicated at the relevant steps. Hold times are indicated and validated

The product-contact components and equipment, and their sterilisation procedure, are sufficiently described. The nature, size and manufacturer of the sterile filter used for sterile filtration and bioburden reduction filter are provided.

Process controls

A risk assessment tool was used to classify PPs and IPCs. A justification for the classification of each process parameter is provided and found acceptable. Overall, the proposed CPPs and associated ranges are considered appropriate.

The analytical procedures used for the cIPCs are sufficiently described.

Overall, the control strategy is considered appropriate.

Process validation / verification

Process performance qualification (PPQ)

In the PPQ, consecutive batches of filled cartridges were manufactured using the commercial process.

From the PPQ batches of filled cartridges, corresponding batches of pre-filled pens were manufactured in either 1-pen package configuration (1 pen/carton) or 5-pen package configuration (5 pens/carton).

During PPQ, the results of PPs and IPCs, and the release results of cartridges and assembled prefilled pens met their acceptable ranges.

Validation of homogeneity of compounding was performed. The results met their acceptance criteria. It can be concluded that the compounding process has no impact on the homogeneity of the finished product prior to filling and the compounding process can be considered consistent. In addition, homogeneity of the filling process was demonstrated. All results met the acceptance criteria and no difference was observed between the cartridges samples, confirming homogeneity and consistency of the filling process.

Hold time validation

Product intermediate hold time validation runs were performed consecutive batches manufactured with the commercial process before PPQ. Relevant attributes were assessed at the end of each hold. All

results complied with the defined acceptance criteria. Based on these results and the fact that finished product contains metacresol and phenol as preservative, the risk of microbial growth during process hold times is considered very low. The proposed hold times are considered adequately validated and are found acceptable.

Sterilisation of equipment, aseptic process validation, sterilising filters

Autoclaves are used for sterilisation of product-contact materials used in the filling process. An annual requalification is conducted.

Media fills are performed in the same way as the manufacture of finished product batches.

Sterile filtration is performed using membrane filters. The retention capacity of the filter membrane was validated by a bacterial retention study which demonstrated that the membrane can effectively remove viable micro-organisms from the process.

Shipping qualification

Shipping qualification was designed to demonstrate temperature control during the transportation. The packaging and loading pattern as well as the containers used for the qualification study simulated the real shipping conditions. Acceptable temperature control was demonstrated. Shipping qualification is considered adequately validated.

Overall, it can be concluded that the PPQ campaign and the additional validation studies demonstrate that the commercial manufacturing process performs as designed and provides a product that consistently meets its predefined quality attributes at the commercial manufacturing site.

2.3.3.3. Product specification

The applicant has provided FP specifications that covers general tests, identity, content/activity, purity/impurity and microbial content. The release specification of finished product filled in cartridge includes the general tests appearance, pH, extractable volume, cartridge appearance and break-loose/gliding force, test for identification, purity tests for related proteins and HMWP, test for assay, tests for excipients, tests for visible and subvisible particles as well as tests for safety.

The proposed acceptance criteria were established. Overall, the parameters included in the specification and corresponding acceptance criteria are found acceptable to control the quality of insulin aspart finished product at release and during shelf life.

Analytical procedures

The analytical procedures are a combination of compendial and non-compendial methods. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

The panel of methods used to assure the quality of the finished product is in accordance with ICH Q6B. and are considered suitable for their intended use.

The compendial methods are generally performed in accordance with the methods described in Ph. Eur..

Batch analysis

Different processes (development, clinical, commercial) were used for manufacture of finished product material.

Batch analyses data are provided for batches produced in development and by the clinical and commercial processes. All batch data comply with the specifications valid at the time of testing. The batch data confirm batch-to-batch consistency and process comparability.

Characterisation of impurities

Product-related impurities encompass related proteins and HMWP.

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. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product (for filled cartridges and prefilled pens) has been performed (as requested) 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. Therefore, no additional control measures are deemed necessary.

Container closure

The primary packaging consists of a cartridge, a rubber plunger and an aluminium seal cap with rubber liner. The finished product is only in contact with the primary packaging material. All components are of compendial quality standard and sterilised before the aseptic filling step.

The secondary packaging consists of the cartridge holder, the dosing mechanism and a pen cap. Functionality of the pen injector is controlled at release and during shelf life.

The container closure system is found appropriate for delivery of finished product.

2.3.3.4. Stability of the product

The proposed shelf life of insulin aspart FP is 30 months when stored unopened at 5 °C ± 3 °C.

The proposed in-use stability is 4 weeks at a temperature below 30 °C, protected from light.

Long-term stability study

Stability data from different process batches are provided. The stability behaviour of PPQ batches is the same as for the clinical and commercial process batches; that is HMWPs and related proteins slightly increased, whereas assay slightly decreased correspondingly; for the other parameters no trends are observed. All data were well within stability specification.

Accelerated stability study, 25 °C ± 2 °C

The same stability trends were observed for all batches at accelerated conditions: HMWPs and related proteins increased, and assay decreased correspondingly, as expected.

In-use stability study, 30 °C ± 2 °C

The proposed in-use period is 4 weeks when stored below 30°C. A 28 days in-use stability study was performed. The results showed that related proteins and HMWPs increased with time within 28 days, however, the test results were well within the acceptable range.

Time-out-of-refrigeration (TOR) and in-use stability

In addition to the in-use stability studies, the studies were also performed on PPQ batches of disposable pens placed under long-time stability. The studies of long-term storage after out-of-refrigeration has been completed; the results showed that the product meets acceptable criteria during simulated patient use after out of refrigeration conditions.

Stress studies

Forced degradation studies (high temperature stress, acid stress, basic stress, oxidative stress, light exposure, and mechanical stress) were performed on PPQ batches (cartridges and prefilled pens). Overall, similar trends are observed. The data indicate that high temperature stress, oxidative stress, extreme pH can impact on the quality of insulin aspart injection.

Post-approval Stability Protocol and Stability Commitment

The applicant commits to continue the stability studies as described. Extending the shelf life will be submitted through a variation application.

Conclusion

The proposed shelf-life of insulin aspart FP of 30 months at 5 °C ± 3 °C, and the proposed in-use period of 4 weeks below 30°C are considered supported by data and can be accepted.

2.3.3.5. Biosimilarity

Design of the biosimilarity exercise

Analytical similarity of this FP to the reference medicinal product (RMP), EU NovoRapid (flexpen prefilled syringe), was assessed in a comprehensive biosimilarity exercise performed in line with the relevant EU guideline on quality aspects of the development of similar biological medicinal products (EMA/CHMP/BWP/247713/2012).

Quality attributes (QAs) included in the biosimilarity exercise cover: Protein content (assay and total protein), excipient content (zinc, phenol, metacresol), primary structure, pI, secondary and higher-order structure, disulfide linkage, product-related substances and impurities (as assessed by multiple methods, including RP-HPLC, CEX-HPLC, HI-HPLC, LC-MS peptide mapping, SE-HPLC), and biological characteristics, i.e. target binding, phosphorylation, mitogenicity, and metabolic activity (glucose uptake, glycogen synthesis, lipogenesis). The selected panel of QAs is deemed appropriate.

The methods used for assessing the QAs were generally either fully validated or qualified.

For all quantitative QAs, quality ranges (QRs) were calculated based on data for EU RMP lots.

The selection of test lots and RMP lots to include in the biosimilarity exercise is considered acceptable. A freeze/thaw study was performed and showed no impact on QAs of the product.

Qualification results of RS lots demonstrate that the RSs are sufficiently comparable.

Testing results

A summary of the results for the comparative analytical assessment is presented below. For the majority of the QAs, 100% of GL aspart lots were within the QR. These outliers were discussed individually.It can also be noted that some impurities showed lower levels for test lots than RMP lots. The differences in impurity levels are not considered concerning.

Table 1 - Comparative analytical assessment results. CAA – Results Overview.

Quality Attributes			**Test Method**	**Whether Highly Similar [1]**
Primary structure and disulfide linkage	Intact molecular weight (MW) and reduced MW		LC-MS	Yes
	Peptide mapping and full-length sequencing		LC-MS/MS	Yes
	Disulfide linkage		Partial reduction and LC-MS/MS	Yes
			NMR	Yes
	Isoelectric point (pI)		iCIEF	Yes
Secondary and higher order structure	Far-UV CD		CD	Yes
	Near-UV CD			
	Fluorescence		Fluorescence spectrometry	
	α-helix		FTIR	Yes
	β-sheets			
	β-turns			
	Random coil			
	Oligomer		N-SEC-MALS	Yes*
			AUC	Yes
	Thermal stability		DSC-Tm1	Yes
			DSC-Tm2	Yes*
	Hydrodynamic diameter		DLS	Yes
Product related variants	Deamidation	A21Asp+B3isoAsp+B3Asp	RP-HPLC	Yes
	Isomeride	B28isoAsp		Yes
	Total of other impurities			Yes
	Aggregates	HMWP	SE-HPLC	Yes
	Truncation	N-terminal Truncation (DesPheB1 -N-oxalyl-ValB2)	CEX-HPLC	Yes
		N-terminal Truncation (Des FVN&Q-pyro)	LC-MS	Yes
		C-terminal Truncation (DesKT)	CEX-HPLC	Yes
	Free thiols		Ellman's assay	Yes
	C-terminal extension		LC-MS	Yes
	Dehydration		CEX-HPLC	Yes
	Carbamylation	A-chain- Carbamylation	CEX-HPLC	Yes
		B-chain- Carbamylation		
	Sum of acidic peaks and sum of basic peaks		CEX-HPLC	Yes
	Sum of hydrophobic peaks and sum of hydrophilic peaks		HI-HPLC	Yes
Content	Assay		RP-HPLC	Yes
	Total protein content			Yes

[1] "Yes" indicates that the results support demonstration of highly similar between GL Aspart Injection and EU NovoRapid.
"Yes*" indicates that the results did not meet the similarity acceptance criteria, however, the differences observed do not preclude a demonstration of high similarity between GL Aspart Injection and EU NovoRapid, justification is provided in specific section.

Excipient	Zn content		AAS	Yes
	pH		pH meter	Yes
	Phenol content		RP-HPLC	Yes*
	Metacresol content			Yes
Target binding	IR-A binding	Ka	Surface plasma resonance (SPR)	Yes
		Kd		Yes
		KD		Yes
	IR-B binding	Ka		Yes*
		Kd		Yes
		KD		Yes
	IGF-1R binding	Ka		Yes
		Kd		Yes
		KD		Yes
Receptor phosphorylation	IR-A phosphorylation		Cell based assay	Yes
	IR-B phosphorylation			Yes
	IGF-1R phosphorylation			Yes
Mitogenic activity	IGF-1R-dependent mitogenicity		Cell based assay	Yes
	IR-dependent mitogenicity			Yes
Metabolic activity	Glucose uptake		Cell based assay	Yes
	Glycogen synthesis			Yes
	Lipogenesis			Yes
In vitro potency			Cell based assay. (In-cell western)	Yes

For some outliers, the Applicant performed a root cause analysis, showing that the differences are not relevant to safety or efficacy, but only to stability during storage. It is agreed that the differences are mainly risk factors in relation to stability prior administration. As follows below, degradation pathways and impacts on biological QAs were deemed overall similar between test and RMP lots in head-to-head comparative accelerated stability and forced degradation studies. The differences in oligomer contents are therefore considered to not significantly impact stability, and thus to be acceptable.

The thermal stability curves were obtained. The DLS, FTIR, CD, and fluorescence spectra were found to be similar, showing that there are no large differences in structure. In general, differences in Tm can affect protein function and/or stability. In the case of GL Aspart, there appears to be no significant impact on function, as there are no clear differences in some bioassays between clinical, commercial, and RMP lots. Concerning stability, degradation profiles were deemed sufficiently similar between the clinical and commercial lots in comparative accelerated stability studies, and between the commercial and RMP lots in head-to-head accelerated stability and forced degradation studies (see below). Therefore, it is considered that the rather small differences can be accepted.

For other outliers, a justification is provided and it is therefore agreed that the minor differences do not preclude a conclusion of biosimilarity.

Comparative stability studies

Comparative stability studies were carried out to assess similarity in GL aspart and RMP degradation profiles, testing for a wide range of QAs. The studies were performed under accelerated and forced degradation conditions, where the latter included: High temperature, low pH, high pH, oxidation, light exposure, and mechanical agitation. As noted above, a freeze/thaw study was also carried out.

Under the accelerated condition, trends were overall similar between test and RMP lots.

For most forced degradation conditions, one or more QA showed differences in their rates of change. However, the differences were inconsistently observed among the different conditions and generally quite small. Therefore, they are not considered concerning. With respect to light stress, a difference was observed. However, considering the outcome of the other forced degradation studies, and that the product is to be protected from light, this is not deemed to preclude a conclusion of biosimilarity.

Overall, the comparative stability studies are considered supportive of a conclusion of biosimilarity.

2.3.3.6. Adventitious agents

Viral safety

The AS is produced by fermentation with *E. coli*; thus, the risk of contamination of the product with mammalian viruses can be considered negligible.

A major objection was raised for the cell bank. Further development studies, process characterization studies, and development of additional analytical methods for characterization and routine control, have been performed by the Applicant and the major objection was resolved.

A recommendation, on the strategy and timeframe for a post authorisation manufacturing change, is endorsed (REC).

TSE safety

For the animal derived material used in manufacturing, a CoA is provided, confirming that risk of TSE transmission can considered negligible.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Dazparda is a biosimilar to NovoRapid. Manufacture, development, characterisation and control of AS and FP are adequately described. The proposed AS and FP manufacturing processes are considered justified and the control strategy is considered sufficient to assure consistent and adequate quality of the product.

The major objections initially identified, concerning GMP inspections of manufacturing and testing sites and the missing notified body opinion, were adequately addressed during the assessment by providing adequate documentation.

The insulin aspart AS manufacturing process, process parameters, and process controls are considered adequately described.

A comprehensive control strategy to ensure sufficient quality of AS has been presented. The control of critical steps is considered sufficiently described and adequate to control the process and ensure the manufacture of an AS of adequate and consistent quality; there are no intermediates isolated within the manufacturing process of insulin aspart. The manufacturing process has been appropriately validated, including in-process intermediate hold times, impurity removal, extractables and leachables, and resin and membrane lifetime studies. Comparability of the proposed commercial manufacturing process with the earlier process has been adequately demonstrated. Batch data provided demonstrate that the commercial process is capable of manufacturing an active substance of consistent quality.

Raw materials and establishment of MCB and WCB have been appropriately described. A major objection was raised for the cell bank. Following comprehensive evaluation and amendment of the

control strategy, the major objection was resolved. A recommendation, on the strategy and timeframe for a post authorisation manufacturing change, is endorsed (REC).

The structure and biological characteristics of insulin aspart are adequately characterised, including product-related species. Regarding process-related impurities, these have been identified and adequate clearance has been demonstrated.

The panel of methods used to assure the quality of the AS is in accordance with ICH Q6B and the panels of tests are considered overall acceptable. The acceptance criteria have been based on the Ph. Eur. Insulin Aspart or on USP monographs and/or on other factors, including analysis of historical batch data, and safety considerations. The specification is considered adequately justified. The analytical procedures used for release testing are described in sufficient details and are considered suitable for their intended use. The analytical procedures used to test in-process intermediates are adequately described and validated to a sufficient extend. Working reference standards (WRS) were established through development. The reference standards are qualified against Ph. Eur. insulin aspart reference standard. The Applicant commits to establish a reference standard system for commercial phase after approval (REC).

The AS container closure system is considered sufficiently described and of adequate quality. The provided stability data support the proposed AS shelf-life.

The finished product manufacturing process is standard and consists of thawing of active substance, compounding and final formulation of finished product, sterile filtration, aseptic filling into sterilised cartridges, visual inspection of the cartridges followed by release testing of the filled cartridges. The cartridges are then assembled into pen injectors, labelled and packed. The control strategy of the manufacturing process has been outlined and is found appropriate. Process validation has been completed and demonstrates that the process is well controlled.

The finished product is presented in a 3 mL Type I glass cartridge that is assembled into a pen device. A Notified Body Opinion for the pen injector was provided during the procedure.

The formulation is based on the reference medicinal product, and its composition is suitable to maintain the quality of the finished product, which is supported by stability studies.

Visible particles were observed. It was demonstrated that these particles have negligible impact on product quality and on drug delivery system. The proposed specifications for filled cartridges and prefilled pens are in general found acceptable and in line with ICH Q6B.

A shelf life of 30 months at 5°C ± 3°C when stored unopened and the shelf-life during use (4 weeks at a temperature below 30°C, protected from light), are acceptable.

Biosimilarity

A comprehensive biosimilarity exercise has been performed, testing Dazparda against the reference product, EU NovoRapid. The results of the individual tests generally support a conclusion of biosimilarity.

2.3.5. Conclusions on chemical, pharmaceutical and biological aspects

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

2.3.6. Recommendations 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:

1. The Applicant has proposed a strategy and timeframe for the proposed manufacturing change. The Applicant should file for the respective variation in the future. In case of unforeseen events or issues needing further discussion, the Applicant should actively communicate accordingly and seek advice at EMA.
2. The Applicant commits to establish an updated reference standard system. The Applicant commits to update the dossier, via a variation application, with the necessary information once in place.

2.4. Non-clinical aspects

2.4.1. Introduction

Dazparda is a proposed biosimilar to the EU-licensed NovoRapid (NovoRapid Flexpen-Insulin Aspart-EU), a rapid-acting human insulin analogue for improvement of glycaemic control in adults and paediatric patients (children ≥ 1 year of age) with diabetes mellitus. Dazparda is structurally similar to NovoRapid. They share the same components and composition of active and inactive ingredients (e.g. similar amino acid sequence and excipients) in equivalent amounts and follows the same route of administration.

The non-clinical development program for Dazparda focused on demonstrating similarity of Dazparda to EU-licensed NovoRapid with regards to *in vitro* (insulin receptor and insulin growth factor-1 receptor binding and phosphorylation, metabolic activation, mitogenic potential and potency) and *in vivo* (toxicity and toxicokinetic profile) characteristics.

The non-clinical development program was conducted and assessed in accordance with requirements in the EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and 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).

As Dazparda relates to a marketing authorisation application for a biosimilar medicine there are no GLP requirements with regard to the non-clinical studies. Furthermore, only the conduct of pharmacodynamic *in vitro* studies is required for marketing authorisation of biosimilar insulin analogues. Nevertheless, a GLP compliant 28-day repeat-dose toxicity study in rats including validated bioanalytical methods was conducted.

All the pharmacodynamic *in vitro* studies were conducted at the Gan & Lee Pharmaceuticals facility in China. The GLP compliant *in vivo* 28-day repeat-dose toxicity study in rats was conducted at Sinclair Research Center, LLC, Auxvasse, USA. Method validation reports for the *in vitro* pharmacology studies were submitted and assessed as part of the quality dossier and no concerns were identified.

2.4.2. Pharmacology

The *in vitro* pharmacology studies conducted as a part of the non-clinical development program for Dazparda focused on demonstrating similarity to the EU-licensed NovoRapid (and the US-approved NovoLog) with regards to:

- Receptor binding affinity (IR-A, IR-B, and IGF-1R).
- Functional activity (receptor phosphorylation of IR-A, IR-B, and IGF-1R).
- Metabolic activity (glucose uptake, glycogen synthesis and lipogenesis).
- Mitogenicity (IR and IGF-1R).
- Potency (IR-B).

2.4.2.1. Primary pharmacodynamic studies

Receptor binding affinity

IR-A, IR-B and IGF-1R binding affinity was determined by Surface plasma resonance (SPR). Results were reported as tabulated summary data of IR-A, IR-B and IGF-1R binding presented as relative Ka/Kd/KD values and scatter plots, both generated on the basis of sensorgrams. Only selected representative sensorgrams were presented by the Applicant and these were submitted in black and white.

High similarity was seen for IR-A and IGF-1R binding affinity, as all data points (100%) for the tested Dazparda lots fell within the quality range (QR) of the EU-reference product NovoRapid (and US-NovoLog). This is also clearly visualized from the scatter plot presentations, where all Dazparda data points for relative Ka, Kd and KD were seen within the dotted lines representing the QR of NovoRapid and NovoLog, respectively.

For IR-B binding affinity, one of tested Dazparda lots had a higher value of relative Ka than the upper limit of the QR of EU-approved NovoRapid. It was concluded that this might be attributable to method variability, but no proper discussion was provided by the Applicant. However, no deviations were seen for the same lot in the downstream processes of receptor phosphorylation and metabolic activity. Hence, it is agreed with the Applicant that the observed deviation appears to be method related and unlikely to impact the safety or efficacy of the proposed biosimilar product. Comparability for IR-B binding between Dazparda and EU-NovoRapid is therefore accepted.

Overall, SPR is considered an acceptable method for determining IR-A, IR-B and IGF-1R binding affinity. The choice of concentrations tested appears adequate, as the resulting curves are evenly spaced out over the sensorgrams. Dazparda was tested against the EU-approved reference product NovoRapid, as required in guideline, in addition to the US-approved NovoLog. The number of batches tested with relevance for this EMA application is considered sufficient.A list of the lots included in the study was presented in the study report.

The QR for the reference products (EU-NovoRapid/US-NovoLog) was defined for all three receptor binding assays. Hence, the QR is considered acceptable for similarity conclusion, and this applies for all the conducted *in vitro* studies.

Of note, only selected sensorgrams were included in the non-clinical part of the dossier and curve fittings for all lots could therefore not be visually inspected. This provided a limitation, however, based on the method qualification results and the data presented, the assessor has no reason to believe that the presented sensorgrams are not representative.

Receptor phosphorylation

Receptor phosphorylation activity was determined in Chinese Hamster Ovary-K1 cells overexpressing IR-A, IR-B or IGF-1R after stimulation with diluted concentrations of insulin aspart in the form of Dazparda, the reference products EU-NovoRapid/US-NovoLog and EP/USP RS.

High similarity was seen for IR-A, IR-B and IGF-1R phosphorylation capability between Dazparda and EU NovoRapid with 100% of the data points within the QR interval.

Representative IR-A, IR-B and IGF-1R concentration-response curves were presented. Overall, the position of the data points generated a relatively well-fitted sigmoid curve, as expected. Additionally, the sigmoid shape of the curves also reflected the sufficiency of the selected concentrations.

Metabolic activity (glucose uptake, glycogen synthesis and lipogenesis).

In accordance with the guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1), three different assays of metabolic activity were performed comparing glucose uptake, glycogen synthesis and lipogenesis between Dazparda and EU NovoRapid. Results were reported as relative potency % calculated based on dose-response curves.

Pre-adipocytes (3T3-L1 MBX) from an embryonic cell line of murine origin, were differentiated from fibroblasts into mature adipocytes and incubated with Dazparda, EU NovoRapid, US NovoLog and insulin aspart EP/USP RS in various concentrations.

Glucose uptake was measure by the Glucose Uptake-Glo Assay Kit, which utilizes a series of enzyme-coupled reactions to measure 2-deoxyglucose 6-phosphate (2DG6P) formed by from 2-deoxyglucose (2DG) in the same manner as glucose is transported and formed. In contrast to glucose, 2DG6P cannot be further modified and hence accumulates in the cells. The cells are then lysed and luciferin reacted thorough enzyme-coupled reactions to produce a luminescent signal proportional to the concentration of 2DG6P. Glycogen formation was detected using the Glycogen-Glo Assay Kit, where the glycogen concentration in the sample is proportional to the luminescent signal conducted by series of enzyme-coupled reactions. The same principle was applied for demonstrating lipogenesis in the Triglyceride-Glo Assay Kit, where triglycerides are converted to glycerol and the amount of glycerol is detected by a luminescent signal conducted thorough enzyme-coupled reactions.

Overall, the three methods are considered acceptable for evaluation of glucose uptake, glycogen synthesis and lipogenesis, respectively. The tested concentrations appear sufficient and created a sigmoid sharped dose-response curve, as expected, and comparable dose-response profiles were seen within the same assay. The number of samples testedis considered sufficient for both Dazparda and the reference product EU NovoRapid

For glucose uptake, glycogen formation and lipogenesis, all of the data points (100%) for Dazparda fell within the QR, demonstrating high similarity between Dazparda and the reference products NovoRapid (and NovoLog) with respect to stimulation of metabolic activity. This was also visualized from the scatter plots. Compared to glucose uptake and lipogenesis values, more scattering of the data points was seen for glycogen relative potency % values. However, all values were still within the QR of EU NovoRapid.

The reported relative potency percentages (%) were calculated based on curve fitting. When visually inspected, the selected representative dose-response curves appeared well-fitted. However, it should be mentioned, that it is considered a limitation that not all curves were presented for visual inspection of the fit.

Mitogenic activity

IGF-1R-dependent mitogenic activity was assessed in a human sarcoma osteogenic-2 cell (Saos-2 cell) line displaying high ratio of IGF-1R to IR. Hence, cell growth is mostly initiated through IGF-1R signalling pathway. The Cell Titer-Glo luminescent cell viability assay was used for quantification by measuring the amount of adenosine triphosphate (ATP) proportional to the number of viable cells. Overall, this is considered an acceptable method.

IR-dependent mitogenic activity was assessed in a rat H4IIE hepatoma cell line deficient in IGF-1R expression and dependent on insulin for cell proliferation. Viable H4IIE cells were detected using the cell counting kit-8 (CCK8) measuring a yellow product (formazan) produced in amounts representative of the number of viable cells. This is also considered an acceptable method, however, it should be emphasized that only the overall IR-dependent mitogenicity was reported, as the method does not differ between IR-A and IR-B activation.

The number of samples tested are considered sufficient for both Dazparda and the EU reference product NovoRapid . Selected representative dose-response curves were presented and when visually inspected the curves appeared well-fitted and showed a sigmoid pattern with relative similar dose-response profiles between Dazparda and NovoRapid. However, as previously mentioned it is considered a limitation that not all curves were presented for visual inspection of the fit.

Results were reported as relative potency % for IGF-1R- and IR-dependent mitogenic activity. All of the data points (100%) for Dazparda for IGF-1R and IR-dependent mitogenicity fell within the QR of EU reference product NovoRapid, demonstrating similarity between the two products It was noted that for IGF-1R mitogenicity, one data point fell outside the QR of the US-approved NovoLog. However, as it was the only data point deviating from a more grouped set of data points centered around the mean and the point was still within the QR of the EU reference product NovoRapid, this is not considered of relevance for the biosimilarity conclusion.

The QR was defined and was sufficiently justified in section 2.1 in Analytical Biosimilarity Report of Insulin Aspart Injection.

Potency

In vitro potency of Dazparda lots and NovoRapid lots were tested using In-Cell Western assay, which was developed and targeted to assess IR-B phosphorylation through CHO-K1 cells overexpressing IR-B. The method qualification met all acceptance criteria. Setting the QR is accepted based on the justification given in section 2.1 in Analytical Biosimilarity Report of Insulin Aspart Injection.

All points for Dazparda with respect to *in vitro* potency fell within the QR of NovoRapid. Hence, the *in vitro* potency was considered similar between Dazparda and NovoRapid.

2.4.2.2. Secondary pharmacodynamic studies

No studies conducted. The absence of secondary pharmacodynamics studies is acceptable according to the guidance.

2.4.2.3. Safety pharmacology programme

Assuming Dazparda is highly similar to NovoLog and NovoRapid, the safety pharmacology of Dazparda is also expected to be similar. According to 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) safety pharmacology studies are not required.

2.4.2.4. Pharmacodynamic drug interactions

No studies conducted. The absence of pharmacodynamic drug interaction studies is acceptable according to guidance (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).

2.4.3. Pharmacokinetics

Distribution, metabolism, excretion, pharmacokinetic drug interaction and other pharmacokinetic studies are not required in support of similar biological applications. Absorption and exposure of Dazparda compared to US-approved NovoLog and EU-licensed NovoRapid were evaluated during the repeat-dose toxicity study in rats (study No S14051) to provide preliminary toxicokinetic information.

Bioanalytical methods (study Nos XBL 16096 and XBL 16121) were validated to support the bioanalyses of insulin aspart and anti-insulin aspart antibodies in the 4-week repeat-dose toxicology study in rats. In addition, method validation reports for the conducted *in vitro* pharmacology studies were submitted and assessed as part of the quality dossier and no concerns were identified.

2.4.3.1. Methods of analysis

A liquid chromatography-tandem mass spectrometry method was developed and adequately validated for the quantitation of insulin aspart in rat plasma (study No XBL 16096).

An electrochemiluminescence immunoassay method was also developed and sufficiently validated for the quantitation of anti-insulin aspart antibodies in rat serum. (study No XBL 16121).

2.4.3.2. Absorption

Absorption and exposure of Dazparda compared to NovoLog and NovoRapid at doses of 0, 10 or 50 U/kg were evaluated following s.c. administration in Sprague-Dawley rats for 28 consecutive days. The toxicokinetic results of insulin aspart concentrations showed dose-proportional increase in mean C_{max} and AUC_{last} on Day 1 and 28. The plasma C_{max} at 50 U/kg was 2710, 2980, 2230 ng/mL after a single dose and 3040, 2630 and 3160 ng/mL after 28 daily repeated doses of Dazparda, NovoLog and NovoRapid, respectively. Hence, with repeated dosing up to Day 28, the exposure (C_{max} and AUC_{last}) of Dazparda, NovoLog and NovoRapid slightly increased compared with Day 1, suggesting small accumulation after multiple dosing. The insulin T_{max} was generally reached at 30 minutes, and $t_{1/2}$ was approximately between 15 to 40 minutes. There were no sex differences in the systemic exposures for the three insulin aspart injections. It is concluded that the 10 and 50 U/kg dose systemic exposures (C_{max} and AUC_{last}) of insulin were comparable between Dazparda, NovoLog and NovoRapid, which is supported.

Since a comparable number of main and recovery animals developed serum anti-drug antibodies (ADA) after treatment with Dazparda, NovoLog or NovoRapid, ADA occurrence was not expected to impact toxicokinetics when comparing NovoLog and NovoRapid with Dazparda-treated groups.

2.4.4. Toxicology

According to ICH guideline S6(R1), Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and 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) no *in vivo* single-dose, repeat-dose, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance and other toxicity studies are required. Nevertheless, the Applicant submitted a 4-week repeat-dose study in rats comparing Dazparda to US-approved NovoLog and EU-licensed NovoRapid.

2.4.4.1. Repeat dose toxicity

In a 28-day repeat-dose GLP study with a 14-day recovery period Dazparda, NovoLog or NovoRapid was given to rats (main: 10/sex/group; toxicokinetics: 6/sex/group; recovery: 6/sex/group) by daily s.c. injection at dose levels of 10 and 50 U/kg/day.

One mortality was noted: One female rat in the 50 U/kg/day NovoRapid group was found dead on dosing Day 14, approximately two hours post-dose. The cause of death was likely associated with hypoglycaemia.

Overall, Dazparda, NovoLog or NovoRapid-related increased body weight gain and food consumption were noted, likely compensatory to reduced glucose levels. No remarkable changes on clinical observations, ophthalmology, clinical pathology or anatomic pathology parameters were seen in the main or recovery animals when comparing Dazparda, NovoLog and NovoRapid groups.

The NOAEL was 50 U/kg/day in animals administered with Dazparda, NovoLog or NovoRapid. In general, findings were comparable whether animals were given Dazparda, NovoLog or NovoRapid and were consistent with the pharmacological action of both products. All findings were of small magnitude and had no toxicological relevance (study No S14051).

2.4.5. Ecotoxicity/environmental risk assessment

In line with guidance (EMEA/CHMP/SWP/4447/00 corr. 2), the Applicant provided an acceptable justification for not conducting a full Environmental Risk Assessment. Since Dazparda is a protein, it is expected to be fully metabolised into smaller peptides and amino acids via catabolic pathways in the body with negligible excretion of intact, biologically active protein.

Dazparda is therefore considered to be of no particular hazard to the environment and no special precautions in terms of use and disposal are needed.

2.4.6. Discussion on non-clinical aspects

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

The non-clinical program by Gan & Lee Pharmaceuticals aimed at proving similarity between Dazparda and the EU-approved NovoRapid. The conducted studies were in accordance with the requirements presented in the CHMP insulin biosimilar guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1) showing evidence of comparative receptor binding affinity for IR-A, IR-B and IGF-1R, receptor activation by autophosphorylation of IR-A, IR-B and IGF-1R and metabolic effects with respect to glucose uptake, lipogenesis and glycogen formation. Additionally, mitogenic activity and potency studies were also conducted. As requested by the guideline, these tests were performed *in vitro* since a higher accuracy can be achieved compared to *in vivo*. Nevertheless, an *in vivo* study (study no S14051) was also

presented characterizing the toxicokinetic and toxicity profile following repeated administration of Dazparda and NovoRapid (and NovoLog) for up to 4 weeks in the rat.

All *in vitro* pharmacology studies were conducted at the Gan & Lee Pharmaceuticals analytical platform lab, which is located in No.8, Nanfeng West First Road, Huoxian, Tongzhou District, Beijing, China. All Dazparda lots used in the conducted *in vitro* studies were representative of commercial lots intended for marketing, expect for several lots representing clinical lots. The representativeness of the clinical lots to the commercial lots was justified in the Quality part of the dossier.

Pharmacology

Receptor binding affinity was assessed based on surface plasma resonance (SPR) technology using the Biacore system. Overall, the results suggested similarity for IR-A, IR-B and IGF-1R binding affinity when comparing Dazparda to the EU-approved reference product NovoRapid. For IR-B binding affinity, one of tested Dazparda lots had a higher relative Ka value than the upper limit of the QR of EU NovoRapid. It was properly justified. Hence, the observed outlier did not compromise comparability for IR-B binding between Dazparda and EU-NovoRapid.
On request, the Applicant re-presented data of Receptor Binding Assay using surface plasma resonance (SPR) technology to allow an adequate head-to-head comparison between EU NovoRapid/US NovoLog and Dazparda batches. Ka (1/Ms), Kd (1/s) as well as calculated KD (M) values and corresponding RSD (%) were presented. The data demonstrated the similarity in receptor binding between investigated batches of EU NovoRapid/US NovoLog and Dazparda with expected higher affinity for IR-A and IR-B over IGF-1R. For some batches higher RSD values were detected, particularly for binding to low affinity IGF-1R, which is attributed to method variability. Since summary of data in submitted qualification report show the precision and accuracy of the method to be able to detect small differences, it can be concluded that EU NovoRapid/US Novolog and Dazparda are similar with respect to receptor binding properties.

Receptor phosphorylation activity was determined in Chinese Hamster Ovary-K1 cells overexpressing IR-A, IR-B or IGF-1R after stimulation with diluted concentrations of insulin aspart. Based on the presented results, high similarity was seen for IR-A, IR-B and IGF-1R phosphorylation capability between Dazparda and NovoRapid with 100% of the data points within the QR interval. Representative IR-A, IR-B and IGF-1R phosphorylation concentration-response curves were presented.

Pre-adipocytes (3T3-L1 MBX) from an embryonic cell line of murine origin, were differentiated from fibroblasts into mature adipocytes and incubated with Dazparda, EU NovoRapid, US NovoLog and insulin aspart EP/USP RS in various concentrations. The Applicant justified the use of primary mouse adipocytes as robust insulin-sensitive cells by summarizing their long use in literature for that purpose, the high similarity with primary human cells with respect to adipogenic and glucose pathways, and the relatively high culturing cost as well as the potential individual variations of primary human preadipocytes. The position that mouse adipocytes are a suitable model for studying insulin responses is supported. Insulin aspart-stimulated glucose uptake, glycogen formation, and lipogenesis was determined using Glucose Uptake-Glo Assay Kit, Glycogen-Glo Assay Kit and Triglyceride-Glo Assay Kit, respectively. For glucose uptake, glycogen formation and lipogenesis, all of the data points (100%) for Dazparda fell within the QR, demonstrating high similarity between Dazparda and the reference products NovoRapid (and NovoLog) with respect to stimulation of metabolic activity.

IGF-1R- and IR-dependent mitogenic activity was determined in a human osteosarcoma Saos-2 cell line and in a rat H4IIE hepatoma cell line by Cell Titer-Glo luminescent cell viability assay and Cell Counting kit-8 (CCK8), respectively. Similarity with respect to mitogenic activity was demonstrated, as all of the data points (100%) for Dazparda for IGF-1R and IR-dependent mitogenicity fell within the QR of EU reference product NovoRapid.

In vitro potency of Dazparda lots and NovoRapid lots were tested using In-Cell Western assay, which was developed and targeted to assess IR-B phosphorylation through CHO-K1 cells overexpressing IR-B. All points for Dazparda with respect to *in vitro* potency fell within the quality range of NovoRapid. Hence, the *in vitro* potency was considered similar between Dazparda and NovoRapid. Of note, only representative dose-response curves were provided for Dazparda and NovoRapid which does not allow for a full assessment. Potency results were generated using gradient dilution for each test sample, resulting in several gradient diluted concentrations, as presented in the dose-response curves.

Overall, the *in vitro* methods selected to represent the pharmacology part of this biosimilar application were considered acceptable and "n" appears sufficient for the number of Dazparda and NovoRapid lots included in the different studies. Method validation reports were submitted and assessed as part of the quality dossier and no concerns were identified. All the methods were satisfactorily qualified for the intended purpose. The QR for the reference product EU NovoRapid (and the US NovoLog) was defined for all conducted *in vitro* assays and is considered sufficiently justified in section 2.1 in Analytical Biosimilarity Report of Insulin Aspart Injection. Similarity was shown since 100% of the test batches were included in the corresponding QR.

Pharmacokinetics

Distribution, metabolism, excretion, pharmacokinetic drug interaction and other pharmacokinetic studies were not required in support of similar biological applications.

Absorption and exposure of Dazparda compared to NovoLog and NovoRapid were evaluated during the repeat-dose toxicity study in rats to provide preliminary toxicokinetic information. Overall, the systemic exposure of insulin aspart for Dazparda, NovoLog and NovoRapid at doses of up to 50 U/kg/day were comparable.

The Applicant stated that the toxicokinetic (TK) portion of the study was designed to provide preliminary TK information to facilitate the comparison and interpretation of safety findings. Thus, sparse sampling scheme was utilized in the TK portion of the study with limited number of animals, which may have impacted the individual variation and contributed to the small differences observed between Dazparda, NovoLog and NovoRapid.

The bioanalytical methods were considered GLP compliant and adequately validated to support the bioanalyses of insulin aspart, anti-insulin aspart antibodies in the 4-week repeat-dose toxicology study in rats.

Toxicology

According to existing guidance, no *in vivo* single-dose, repeat-dose, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance and other toxicity studies are required. Nevertheless, the Applicant submitted a 4-week repeat-dose study in rats comparing Dazparda to US-approved NovoLog and EU-licensed NovoRapid.

In a 28-day repeat-dose GLP study with a 14-day recovery period Dazparda, NovoLog or NovoRapid was given to rats by daily s.c. injection at dose levels of 10 and 50 U/kg/day and resulted in treatment-related increased body weight gain and food consumption which were likely compensatory to reduced glucose levels. One mortality was noted in a female rat in the 50 U/kg/day NovoRapid group found dead on dosing Day 14, approximately two hours post-dose. The cause of death was likely associated with exaggerated pharmacology i.e. hypoglycaemia. No remarkable changes on clinical observations, ophthalmology, clinical pathology or anatomic pathology parameters were seen in the main or recovery animals when comparing Dazparda, NovoLog and NovoRapid groups.

The NOAEL was 50 U/kg/day in animals administered with Dazparda, NovoLog or NovoRapid, which is supported. In general, findings were comparable whether animals were given Dazparda, NovoLog or

NovoRapid and were consistent with the pharmacological action of both products. All findings were of small magnitude and had no toxicological relevance. Importantly, considering that the human equivalent dose (HED) for the dose levels used in this study (HED 1.61 U/kg/day for 10 U/kg/day; HED 8.06 U/kg for 50 U/kg/day, respectively) is much higher than the dose used in Dazparda phase 1 study (0.2 U/kg) and actual dose levels in practice (1 U/kg by considering 60 kg of human body weight, NovoRapid label), the findings observed in this study are likely to be an exaggerated effect of high exposure. Hence, the safety profile of Dazparda, NovoLog and NovoRapid was considered comparable in Sprague-Dawley rats.

The package label of the NovoRapid reference product listed glycerol as an excipient whereas the certificate of analysis of Dazparda did not specify the content of glycerol. Likewise, section 3.2 Vehicle Identification of the study report listed zinc ion, disodium hydrogen phosphate and glycerine as components of the vehicle which did not match the corresponding certificate of analysis. The apparent differences in composition between vehicle, Dazparda and NovoRapid were noted. The Applicant clarified that the formulations of Dazparda and NovoRapid were identical and the vehicle of the control group did not differ from the vehicle used in Dazparda and NovoRapid. However, the Applicant did not provide adequate documentation of the formulations of the vehicle and NovoRapid used in the repeat-dose study to substantiate their claim. As the *in vivo* study is only considered supportive for a marketing authorisation application for a biosimilar medicine this issue was not pursued any further.

Of note, the Applicant submitted three amendments to the final report. Amendment No 3 to the final report included several other amendments pertaining to the final report but also amendments to the immunogenicity report No 18110 (Amendment No 2 to study report No 18110) and the study plan of study No S14051. Amendment No 1 to the immunogenicity report No 18110 dated 11th of April 2019 could not be located in the dossier. As the *in vivo* study was only considered supportive for a marketing authorisation application for a biosimilar medicine the issue of the missing amendment was not be pursued any further.

Dazparda is considered to be of no particular hazard to the environment and no special precautions in terms of use and disposal are needed.

A quality question was raised for the drug product. In its response the Applicant summarised several non-clinical toxicity studies (*in vitro* and *in vivo*) that evaluated the potential toxicity and the impact on safety and efficacy of the product. Overall, the thorough non-clinical assessment concludes that patient exposure to Dazparda insulin aspart injections presented minimal toxicological concern. This is supported.

2.4.7. Conclusion on the non-clinical aspects

The conducted *in vitro* pharmacology studies suggested adequate non-clinical evidence of biosimilarity between Dazparda and the EU-approved reference product NovoRapid with respect to receptor binding affinity (IR-A, IR-B and IGF-1R), receptor phosphorylation (IR-A, IR-B and IGF-1R), metabolic activity (glucose uptake, glycogen formation and lipogenesis) and mitogenic potential (IGF-1R and IR-dependent), as requested by guideline. Additionally, biosimilarity was also seen for *in vitro* IR-B potency.

Based on a 4-week repeat-dose toxicity study in rats the assessment of systemic exposure and the safety profile of insulin aspart for Dazparda, NovoLog and NovoRapid at doses of up to 50 U/kg/day can be considered comparable. Bioanalytical methods were adequately validated to support the bioanalyses of insulin aspart and anti-insulin aspart antibodies in the 4-week repeat-dose toxicology study in rats. In addition, method validation reports for the conducted *in vitro* pharmacology studies were submitted and assessed as part of the quality dossier and no concerns were identified.

Hence, the provided non-clinical data package is considered sufficient to support the marketing authorisation application for Dazparda.

In conclusion, the *in vitro* non-clinical data supported biosimilarity of Dazparda to the EU-approved reference product NovoRapid. The *in vivo* study showed that Dazparda, US-approved NovoLog and EU-licensed NovoRapid at doses of up to 50 U/kg/day can be considered comparable.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

- **Tabular overview of clinical studies**

Table 2 – Clinical Study for MAA submission

Study/Phase	Objectives	Subject Population	Endpoints	Location of Study Report
PK/PD similarity study (GL-ASP-1008)	The primary objective of the study was to evaluate PK and PD equivalence of GL Aspart with both EU-authorized NovoRapid and US-licensed NovoLog in healthy male subjects. The secondary objectives were to compare the PK and	Healthy male adults	Primary Pharmacokinetic Endpoints: • Area under the insulin aspart concentration curve from 0 to 12 hours ($AUC_{ins.0-12h}$), • maximum observed insulin aspart concentration ($C_{ins.max}$) Primary Pharmacodynamic Endpoints:	5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Study/Phase	Objectives	Subject Population	Endpoints	Location of Study Report
	PD parameters of the three insulin aspart products and to evaluate the single dose safety and local (i.e., injection site) tolerability of the three insulin aspart products		• Area under the glucose infusion rate curve from 0 to 12 hours ($AUC_{GIR.0-12h}$) • maximum glucose infusion rate within 12 hours post dose (GIR_{max}) Secondary Pharmacokinetic Endpoints: • Areas under the insulin aspart concentration curve during the time intervals 0 to 2 hours and from 0 hours to infinity ($AUC_{ins.0-2h}$, $AUCins._{0-inf}$) • $t_{ins.max}$, time to maximum observed insulin aspart concentration • $t_{50\%-ins(early)}$, time to half-maximum insulin aspart concentration before $C_{ins.max}$ • $t_{50\%-ins(late)}$, time to half-maximum insulin aspart concentration after $C_{ins.max}$ • $t^{1}/_{2}$, terminal elimination half-life calculated as $t^{1}/_{2}=\ln 2/\lambda z$ • λz, terminal elimination rate constant of insulin aspart Secondary Pharmacodynamic Endpoints: • Area under the glucose infusion rate curve (AUC_{GIR}) during the time interval 0 to 2 hours ($AUC_{GIR.0-2h}$) • $t_{GIR.max}$, time to maximum glucose infusion rate • $t_{GIR.50\%-early}$, time to half-maximum glucose infusion rate before GIR_{max} • $t_{GIR.50\%-late}$, time to half-maximum glucose infusion rate after GIR_{max} Time to onset of action	

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Bioanalytical methods.

The analyte insulin aspart was quantified with a UPLC-MS/MS method following MSIA (Mass spectrometric immunoassay) extraction and with bovine insulin as the internal standard. The method was validated to quantify from 70 (LLOQ) to 5000 (UPLOQ) pg/mL of insulin aspart in human plasma.

The bioanalytical method was validated with regards to the following method parameters: selectivity and matrix effect, selectivity in haemolysed blood (1%) and lipidaemic matrix, dilution integrity up to 50000 pg/mL, carry-over effect, robustness, freeze-thaw stability of aspart in matrix (human plasma); long-term stability of aspart in matrix at -80C (210 days), stability of aspart in processed sample at RT and under autosampler conditions; stability of aspart in the primary, the intermediate and in the working stock solution. The bioanalytical method was able to quantify Dazparda and NovoRapid in a accurately, precise and comparable manner**.** The comparability was calculated from the determined mean concentrations at LLOQ and the three QC levels for the respective insulin, see table 6. At all concentrations, the ratio of mean concentrations was within the acceptance limits of 0.800 to 1.20.

Table 3 - Comparability summary

		LLOQ 70.0 pg/mL	QCL 200 pg/mL	QCM 1000 pg/mL	QCH 4000 pg/mL
Mean Concentration Found (pg/mL)	Gan & Lee	75.6	196	1080	3960
	NovoRapid	78.5	202	1110	4490
	Novolog	77.7	188	979	4090
Comparability	Gan & Lee vs NovoRapid	0.963	0.969	0.968	0.882
	NovoRapid Vs Novolog	1.01	1.08	1.13	1.10
	Novolog Vs Gan & Lee	1.03	0.959	0.911	1.03

Comparability acceptance 0.8 to 1.2

$$Comparabilty = \frac{Mean\ QC\ Concentration\ of\ Compound\ 1}{Mean\ QC\ Concentration\ Compound\ 2}$$

LLOQ - Lower limit of quantitation Quality Control Sample
QCL - Low Quality Control Sample
QCM - Medium Quality Control Sample
QCH - High Quality Control Sample

Bioanalysis of Gl aspart and NovoRapid in the clinical study GL-ASP-1008. In the clinical study GL-ASP-1008, 2442 samples (including 66 back-up samples) were analysed with the validated bioanalytical method in 55 analytical runs. During analysis 13 runs failed (11 runs due to QC failure and 2 runs due to sample extraction). The standard bioanalytical acceptance criteria were applied with regards to in-study QC samples and back-calculated calibration standards. The 175 ISR samples evaluated had a pass rate of 94.9%.

Bioanalysis of C-peptide in the clinical study GL-ASP-1008. The analyte C-peptide was quantified using a sandwich enzyme immunoassay, ECLIA test kit for C-peptide from Roche Diagnostics. The assay was validated to quantify C-peptide in serum from 0.20 to 32.00 ng/ml, with a LLOQ of 0.20 ng/ml and a LOD of 0.07 ng/ml. Stability of C-peptide in serum at RT (3 days) and at -80C (468 days) was shown.

Biosimilarity of Dazparda and NovoRapid

Study design of pivotal PK/PD similarity study GL-ASP-1008

This study was a Phase 1, single-center, randomized, double-blind, single dose, three-period, crossover, 12-hour euglycemic glucose clamp study conducted in healthy male subjects to evaluate the equivalence with regard to the primary pharmacokinetic (PK) and pharmacodynamic (PD) endpoints of GL Aspart (100 U/mL, insulin aspart in pre-filled pens) to the reference products NovoRapid (100 U/mL, insulin aspart in pre-filled Flexpen, bulk) and NovoLog, see figure 10. In each period of treatment, a single sc. dose of 0.2 U/kg of the respective aspart was administered. In addition to euglycaemic glucose clamp measurement of the glucose infusion rate (GIR), PK-samples for each subject was taken pre-dose (0 min) and at 5 min, 10 min, 20 min, 30 min, 40 min, 50 min, 60 min, 75 min, 90 min, 105 min, 120 min, 150 min, 180 min, 210 min, 240 min, 300 min, 360 min (6 hr), 420 min, 480 min, 600 min, 720 min (12 hr)) post-dose, to provide a full 12 hr plasma PK-profile of the respective aspart analogue. Samples were also taken pre-dose (-4 an 0 min) and post-dose (1hr, 2 hr, 4 hr, 8 hr and 12 hr) to determine the PD-marker of endogenous insulin, C-peptide.

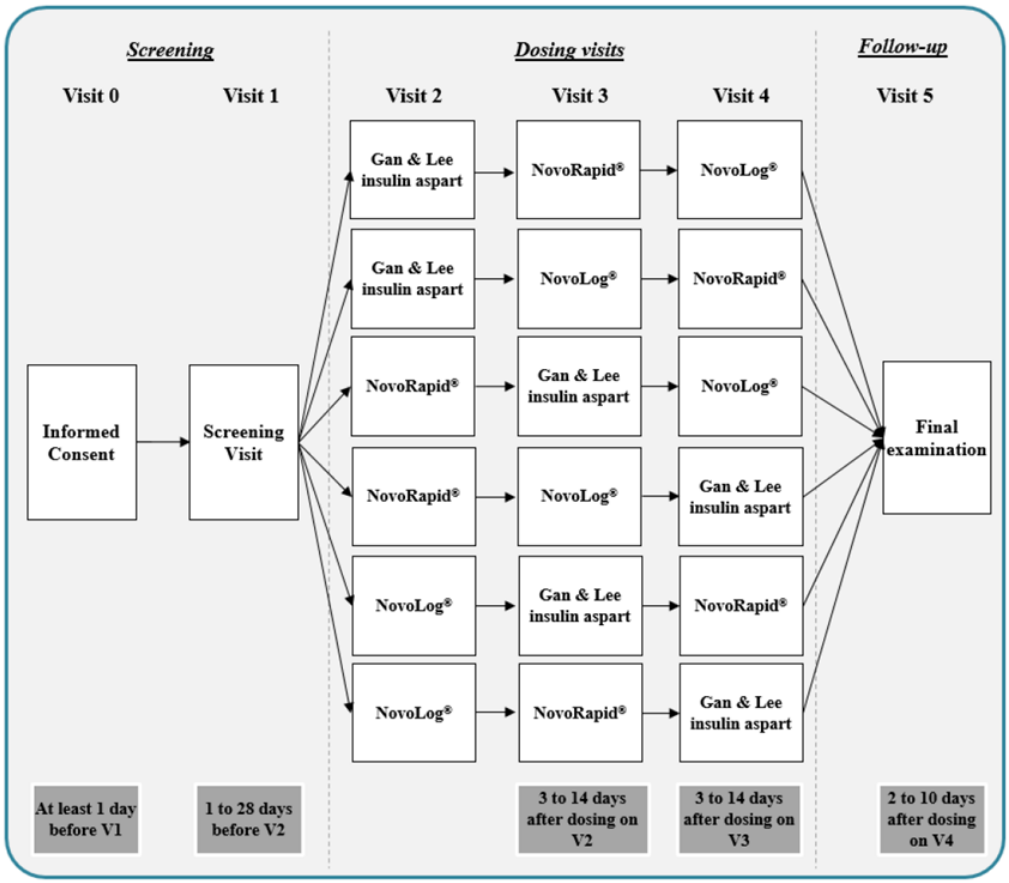

Figure 1 - Schematic overview of the chronological structure of the trial

Study objectives:

Primary study objective:

- To evaluate pharmacokinetics (PK) and pharmacodynamics (PD) equivalence of Dazparda with both EU (NovoRapid) and US reference product (NovoLog), in healthy male subjects

Secondary study objectives:

- To compare the PK and PD parameters of the three insulin aspart products
- To evaluate the single dose safety and local (i.e., injection site) tolerability of the three insulin aspart products.

Study endpoints:

Primary PK Endpoints

- $AUC_{ins.0\text{-}12h}$, area under the insulin aspart concentration curve from 0 to 12 hours
- $C_{ins.max}$, maximum observed insulin aspart concentration within 12 hours post dose.

Secondary PK Endpoints

- $AUC_{ins.0\text{-}2h}$ and $AUC_{ins.0\text{-}inf}$, area under the insulin aspart concentration curve at different intervals from 0 to 2 hours and 0 hours to infinity
- $t_{ins.max}$, time to maximum observed insulin concentration
- $t_{50\%\text{-}ins(early)}$, time to half-maximum insulin aspart concentration before $C_{ins.max}$

- $t_{50\%\text{-ins(late)}}$, time to half-maximum insulin aspart concentration after $Ci_{ns.max}$
- $t_{½}$, terminal elimination half-life calculated as $t_{½} = \ln 2/\lambda z$
- λz, terminal elimination rate constant of insulin aspart.

Primary PD Endpoints

- $AUC_{GIR.0\text{-}12h}$, area under the glucose infusion rate curve from 0 to 12 hours
- GIR_{max}, maximum glucose infusion rate within 12 hours post dose.

Secondary PD Endpoints

- $AUC_{GIR.0\text{-}2h}$, area under the glucose infusion rate curve from 0 to 2 hours
- $t_{GIR.max}$, time to maximum glucose infusion rate
- $t_{GIR.50\%\text{-}early}$, time to half-maximum glucose infusion rate before GIR_{max}

Subject Disposition, Demographic and Baseline Characteristics:

In total, 36 subjects were randomized to one of the treatment sequences and completed the trial. Thirty-six healthy male subjects aged from 19 to 64 years (mean: 36.2 years), BMI from 18.8 to 28.6 kg/m^2 (mean: 24.31 kg/m2) and fasting plasma glucose from 4.11 to 5.50 mmol/L (mean: 5.051 mmol/L) were exposed to the insulin asparts.

Statistical methods

All statistical analyses were performed using SAS and Pharmacokinetic parameters were calculated using WinNonlin (Certara USA Inc., Princeton, New Jersey, USA), version 8**.** The logarithm-transformed primary PK-endpoints were analysed using a mixed-effects model ANOVA with sequence, period and insulin as fixed effects and subject within sequence as random effect. If the exponentially transformed 90% CIs (Confidence Interval) of the geometric mean ratios of $AUC_{ins.0\text{-}12h}$ and $C_{ins.max}$ fell within the limits of 80.00% to 125.00%, then biosimilarity was concluded.

The primary PD analysis based on untransformed endpoints was analysed using a mixed-effects model ANOVA with sequence, period, and IMP as fixed effects and subject within sequence as random effect. For primary analysis of the primary PD endpoints, $AUC_{GIR.0\text{-}12h}$ and GIR_{max} data were assumed to follow a normal distribution, hence these parameters were not logarithmically transformed.

Three sensitivity PD analyses (Clamp Performance Sensitivity PD Analysis, C-Peptide Sensitivity PD Analysis, Hypoglycaemic Event (DRM) Sensitivity PD Analysis) were conducted.

PK analysis in PK/PD similarity study GL-ASP-1008

Primary PK Endpoints

The analysis of PK-endpoints in the GL-ASP-1008 study included all 36 study subjects. For the final PK-endpoint analysis one subjects PK profile was excluded from the NovoRapid group due to an elevated baseline insulin level. The overlaid mean insulin aspart plasma concentration time profiles after treatment by s.c. administration of either 0.2 U Dazparda or 0.2 U NovoRapid is shown in Figure 2.

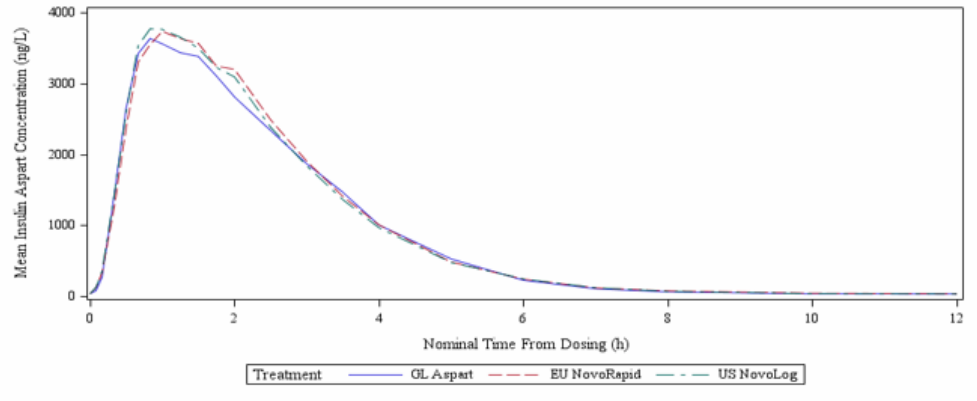

Figure 2 - Mean insulin aspart concentration-time profil after s.c. administration of treatment GL aspart, NovoRapid and NovoLog (0.2 U/kg) – Linear scale (mPPC-PK)

The PK-parameters for each subject, relevant for the PK-endpoint analysis, were determined using non-compartmental analysis (NCA). Descriptive statistics of the primary PK endpoints, $AUC_{ins,0-12hr}$ and $C_{ins,max}$ for Dazparda (GL aspart) and NovoRapid are shown in table 7.

Table 4 - Descriptive statistics of the primary pharmacokinetic endpoints (mPPS-PK)

Parameter (Unit)	Treatment	N	Arithmetic Mean	SD	CV%	Min	Median	Max	GeoMean	GeoCV%
$AUC_{ins\ 0-12h}$ (h*ng/L)	GL Aspart	36	10697.8	1999.24	18.7	7260	10488.4	14667	10515.9	19.0
	EU NovoRapid	35	10999.4	2111.19	19.2	7489	10517.2	15423	10808.4	19.1
	US NovoLog	36	10924.2	1801.64	16.5	7420	10629.5	14916	10782.2	16.5
$C_{ins.max}$ (ng/L)	GL Aspart	36	4103.1	950.51	23.2	2220	4095.0	5980	3991.3	24.6
	EU NovoRapid	35	4197.4	1049.62	25.0	2350	3910.0	6520	4074.2	25.2
	US NovoLog	36	4287.5	1115.57	26.0	2230	4290.0	6460	4138.9	28.1

The primary pharmacokinetic endpoints, $AUC_{ins,0-12hr}$ and Cins.max , of Dazparda versus NovoRapid were compared using ANOVA analysis, see Table 5. The results of the ANOVA analysis for Dazparda and NovoRapid shows that for both primary PK endpoints, the 90% CIs of the ratio of $AUC_{ins,0-12hr}$ and Cins.max of insulin aspart are within the limits of 80.00% to 125.00% for demonstrating biosimilarity.

Table 5 - Treatment comparison of the primary endpoints for insulin aspart, GL aspart versus NovoRapid (mPPS-PK)

		Geometric LS-Means [1]						
Endpoint	Analysis [2]/ Transformation	N	GL Aspart	N	EU NovoRapid	Ratio of LS-Means (%) [3]	SD of the Ratio [4]	90% CI of the Ratio (%) [5]
$AUC_{ins.0-12h}$ (h*ng/L)	Primary (Log-transformed) [6]	36	10516	35	10833	97.08	13.30	(94.50, 99.73)
$C_{ins.max}$ (ng/L)	Primary (Log-transformed) [6]	36	3991.3	35	4083.8	97.74	30.60	(91.90, 103.94)

Secondary PK Endpoints

The secondary PK endpoints, $AUC_{ins.0-2h}$, $AUC_{ins.0-inf}$, $t_{ins.max}$, $t_{50\%-ins(early)}$, $t_{50\%-ins(late)}$, $t_{½}$, and λz were determined by NCA and analysed by descriptive statistics, see table 6.

Table 6 - Descriptive statistics of the secondary pharmacokinetic endpoints (mPPS-PK)

Parameter	Treatment	N	Arithmetic Mean	Standard Deviation	CV%	Min	Median	Max	Geometric Mean	Geometric CV%
$AUC_{ins.0-2h}$ (h*ng/L)	GL Aspart	36	5457.2	1321.14	24.2	2835	5761.6	7524	5289.9	26.4
	EU NovoRapid	35	5576.7	1483.74	26.6	2195	5356.8	8453	5368.9	29.6
	US NovoLog	36	5696.6	1427.84	25.1	3087	5834.3	7775	5506.8	27.7
$AUC_{ins.0-inf}$ (h*ng/L)	GL Aspart	36	10702.7	2004.02	18.7	7259	10488.3	14698	10520.0	19.1
	EU NovoRapid	35	11008.9	2118.88	19.2	7489	10517.9	15427	10816.6	19.2
	US NovoLog	36	10932.1	1806.45	16.5	7426	10632.8	14914	10789.4	16.6
$t_{ins.max}$ (h)	GL Aspart	36	1.250	0.6909	55.3	0.50	1.000	3.50	1.102	53.0
	EU NovoRapid	35	1.360	0.6494	47.7	0.67	1.250	4.00	1.244	43.7
	US NovoLog	36	1.180	0.4601	39.0	0.50	1.000	2.07	1.097	40.2
$t_{50\%-ins(early)}$ (h)	GL Aspart	36	0.475	0.1374	28.9	0.28	0.450	0.92	0.457	28.4
	EU NovoRapid	35	0.497	0.1305	26.3	0.25	0.467	0.88	0.481	26.1
	US NovoLog	36	0.480	0.1366	28.5	0.28	0.450	0.77	0.462	28.3
$t_{50\%-ins(late)}$ (h)	GL Aspart	36	3.039	0.9883	32.5	1.48	2.975	5.17	2.877	35.4
	EU NovoRapid	35	3.072	0.9319	30.3	1.63	2.950	6.67	2.951	29.0
	US NovoLog	36	3.061	0.9721	31.8	1.55	3.075	5.93	2.912	33.2
λ_z (1/h)	GL Aspart	36	0.9679	0.26367	27.2	0.444	0.9231	1.731	0.9324	28.8
	EU NovoRapid	35	0.9686	0.30757	31.8	0.459	0.9092	1.833	0.9222	32.9
	US NovoLog	36	0.9809	0.33559	34.2	0.446	0.9514	1.998	0.9277	35.0
$t_{1/2}$ (h)	GL Aspart	36	0.774	0.2348	30.3	0.40	0.751	1.56	0.743	28.8
	EU NovoRapid	35	0.790	0.2609	33.0	0.38	0.762	1.51	0.752	32.9
	US NovoLog	36	0.790	0.2714	34.3	0.35	0.729	1.55	0.747	35.0

Further analyses of treatment comparisons for secondary PK Endpoints for Dazparda versus NovoRapid is presented in table Table 7. The secondary PK-endpoints, $AUC_{ins.0-2h}$ and $AUC_{ins.0-inf}$, were analysed as primary PK-endpoints. The comparability analysis confirmed equivalence between Dazparda and NovoRapid based on the results of the statistical analysis, see table below. Furthermore, Hodges and Lehmann estimate with the 90% CI indicated that there is no significant difference in $t_{ins.max}$ between Dazparda and NovoRapid.

Table 7 - Treatment comparison of secondary PK endpoints for GL aspart versus NovoRapid

Parameter	Treatment/Comparison	N	LS-Mean	LS Mean Ratio	90% CI
$AUC_{-ins\ 0-2h}$ (h*ng/L)	GL Aspart	36	5289.9	-	(92.24; 104.34)
	EU NovoRapid	35	5391.9	-	
	GL Aspart vs EU NovoRapid	-	-	98.11	
$AUC_{-ins\ 0h-inf}$ (h*ng/L)	GL Aspart	36	10520	-	(94.46; 99.69)
	EU NovoRapid	35	10841	-	
	GL Aspart vs EU NovoRapid	-	-	97.04	

2.5.2.2. Pharmacodynamics

Mechanism of action

The active substance in Dazparda is insulin aspart, a rapid-acting insulin analogue. As with all insulins, insulin aspart exerts its pharmacodynamic effects through binding to the insulin receptor at target tissues including liver, skeletal muscle, and adipose tissue.

Primary and Secondary pharmacology

The pharmacodynamics (PD) of Dazparda was evaluated in study 1008. The primary PD objectives of the study were to evaluate biosimilarity with regard to the total and maximum PD response during one dosing interval ($AUC_{GIR.0\text{-}12h}$ and GIR_{max}) of Gan & Lee Pharmaceuticals insulin aspart with NovoRapid in healthy male subjects.

PD endpoints were derived from glucose infusion rates (GIR) measured by the euglycemic glucose clamp device (Clam part) over the 12-hour sampling period. The glucose clamp device automatically calculated the appropriate adjustments of the i.v. GIR using an algorithm based on the actual measured blood glucose concentration and the grade of variability in the preceding 1 minute. The GIR necessary to keep the blood glucose concentration at the target level was recorded every minute throughout the glucose clamp. The euglycemic glucose clamp is a validated method in which the GIR needed to ensure a constant blood glucose at a pre-determined level is used as a surrogate marker for the PD effect of a glucose-lowering drug. During the entire glucose clamp period, a target blood glucose level of 81 mg/dL (4.5 mmol/L) was strived for.

PD results

In total, 36 subjects were included in the trial and randomised to one of the 6 treatment sequences. All 36 randomised subjects completed the whole trial period.

Pharmacodynamic endpoints were derived from GIRs measured by the ClampArt device over a period of 12 hours following an s.c. injection of 0.2 U/kg of Dazparda, NovoRapid, or NovoLog.

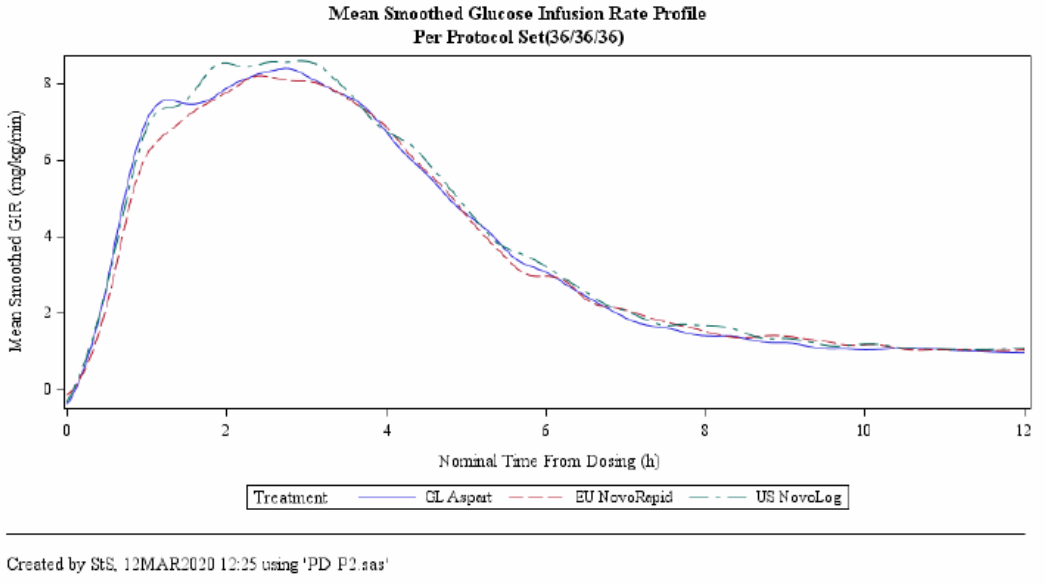

Figure 11-2 Mean of Smoothed Glucose Infusion Rate Profiles after s.c. Administration of GL Aspart, NovoRapid and NovoLog (0.2 U/kg) (PPS)

Figure 3 - Overlaid mean smoothed GIR profiles of GL aspart, NovoRapid, and NovoLog.

An overview of the descriptive statistics of the primary PD endpoints by treatment are displayed in Table 8.

Table 8 – Descriptive Statistics of the Primary Pharmacodynamic Endpoints (PPS)

Parameter	Treatment	N	Arithmetic Mean	SD	CV%	Min	Median	Max	GeoMean	GeoCV%
$AUC_{GIR.0\text{-}12h}$ (mg/kg)	GL Aspart	36	2638.7	912.97	34.6	1245	2584.0	5249	2486.4	36.7
	EU NovoRapid	36	2598.1	753.22	29.0	1443	2499.0	5002	2507.5	26.8
	US NovoLog	36	2737.4	1044.14	38.1	1342	2567.1	6399	2575.1	35.8
GIR_{max} (mg/kg/min)	GL Aspart	36	9.969	3.3641	33.7	3.89	10.169	16.73	9.332	40.3
	EU NovoRapid	36	9.589	3.1582	32.9	4.46	9.220	18.75	9.104	33.9
	US NovoLog	36	10.239	4.6400	45.3	4.14	9.400	26.83	9.406	42.7

Cross-reference: EOT Table 14.2.7.1

The results of the primary and secondary PD analysis of the primary PD endpoints for treatment comparison of Dazparda and NovoRapid are presented in Table 9.

Table 9 – Treatment Comparison of the Primary Pharmacodynamic Endpoints, GL Aspart versus NovoRapid, Primary and Secondary PD Analysis (PPS)

		LS-Means [1]								
Endpoint	Analysis/ Transformation	N	GL Aspart	N	EU NovoRapid	Ratio of LS Means (%) [2]	SD of the Ratio [3]	95% CI of the Ratio (%) [4]	Guideline for Equivalence Limits (%)	CI Contained within
$AUC_{GIR.0\text{-}12h}$ (mg/kg)	Primary (Untransformed) [5]	36	2638.7	36	2598.1	101.56	28.10	(96.88, 106.26)	(80.00, 120.00)	Yes
	Secondary (Log-transformed) [6]	36	2486.4	36	2507.5	99.16	29.01	(92.57, 106.22)	(80.00, 125.00)	Yes
GIR_{max} (mg/kg/min)	Primary (Untransformed) [5]	36	9.97	36	9.59	103.97	41.61	(98.38, 109.81)	(80.00, 120.00)	Yes
	Secondary (Log-transformed) [6]	36	9.33	36	9.10	102.50	38.07	(93.93, 111.86)	(80.00, 125.00)	Yes

Note 1: The Least Squares (LS) Means reported for the Primary PD Analysis were estimated based on fitting a mixed-effect ANOVA model to the untransformed data, while the LS-means for the Secondary PD Analysis were estimated by fitting the model to the log-transformed data and back transforming by exponentiation.
Note 2: Ratio of the LS-means are the GL Aspart over EU NovoRapid multiplied by 100%.
Note 3: The standard deviation (SD) was estimated using the delta method.
Note 4: CI: Confidence intervals for the ratios. For the Primary PD Analysis, CIs were determined according to Fieller's Theorem. For the Secondary PD Analysis the model was based on log-transformed data, and the CI limits were back-transformed from the ANOVA results by exponentiation and multiplied by 100%.
Note 5: Primary PD Analysis EOT Table 14.2.9.1 and program source PDP A1 Fieller.sas.
Note 6: Secondary PD Analysis EOT Table 14.2.9.2 and program source PDP A2 Log.sas.
Cross-reference: EOT Table 14.2.9.1, and EOT Table 14.2.9.2

The results of the Primary PD Analysis according to Fieller's Theorem demonstrate that for both primary PD endpoints ($AUC_{GIR.0\text{-}12h}$ and GIR_{max}) the equivalence limits (95% CI of the LS-mean treatment ratio of untransformed data within the limits 80.00% to 120.00%) were met. Thus, PD equivalence of Dazparda and NovoRapid was achieved.

The results of the Secondary PD Analysis with log-transformed data showed similar results and also met the equivalence limits (95% CI of the LS-mean treatment ratio of log-transformed data within the limits 80.00% to 125.00%).

For the comparison Dazparda and NovoRapid, 2 Sensitivity PD Analyses were conducted:

- C-Peptide Sensitivity PD Analysis (excluding Dazparda profile of Subject 053)

- Hypoglycemic Event (DRM) Sensitivity PD Analysis (excluding Dazparda profile of Subject 040).

All Sensitivity PD Analyses were conducted with untransformed data (Fieller's Theorem) and log-transformed data. Results are compiled in Table 10.

Table 10 – Treatment Comparison of the Primary Pharmacodynamic Endpoints, GL Aspart versus NovoRapid, Sensitivity Analyses (PPS)

		LS-Means [1]								
Endpoint	**Analysis [2]/ Transformation**	**N**	**GL Aspart**	**N**	**EU NovoRapid**	**Ratio of LS Means (%) [3]**	**SD of the Ratio [4]**	**95% CI of the Ratio (%) [5]**	**Guideline for Equivalence Limits (%)**	**CI Contained within**
$AUC_{GIR.0\text{-}12h}$ (mg/kg)	C-Peptide Sensitivity PD Analysis (Untransformed) [6]	35	2624.8	36	2598.1	101.03	28.31	(96.36, 105.71)	(80.00, 120.00)	Yes
	C-Peptide Sensitivity PD Analysis (Log-transformed) [7]	35	2472.2	36	2507.5	98.59	29.13	(91.97, 105.69)	(80.00, 125.00)	Yes
	Hypoglycemic Event (DRM) Sensitivity PD Analysis (Untransformed) [8]	35	2630.1	36	2598.1	101.23	27.61	(96.54, 105.94)	(80.00, 120.00)	Yes
	Hypoglycemic Event (DRM) Sensitivity PD Analysis (Log-transformed) [9]	35	2476.9	36	2507.5	98.78	29.44	(92.09, 105.96)	(80.00, 125.00)	Yes
GIR_{max} (mg/kg/min)	C-Peptide Sensitivity PD Analysis (Untransformed) [6]	35	9.89	36	9.59	103.13	41.77	(97.64, 108.86)	(80.00, 120.00)	Yes
	C-Peptide Sensitivity PD Analysis (Log-transformed) [7]	35	9.26	36	9.10	101.68	38.06	(93.11, 111.04)	(80.00, 125.00)	Yes
	Hypoglycemic Event (DRM) Sensitivity PD Analysis (Untransformed) [8]	35	9.91	36	9.59	103.34	37.56	(97.79, 109.14)	(80.00, 120.00)	Yes
	Hypoglycemic Event (DRM) Sensitivity PD Analysis (Log-transformed) [9]	35	9.28	36	9.10	101.92	37.74	(93.42, 111.20)	(80.00, 125.00)	Yes

Note 1: The Least Squares (LS) Means reported for the Sensitivity PD Analyses (untransformed) were estimated based on fitting a mixed-effect ANOVA model to the untransformed data, while the LS-means for the Sensitivity PD Analyses (log-transformed) were estimated by fitting the model to the log-transformed data and back transforming by exponentiation.
Note 2: Profiles excluded from this analysis are provided in Appendix 16.2.3.2.

Note 3: Ratio of the LS-means are the GL Aspart over EU NovoRapid multiplied by 100%.
Note 4: The standard deviation (SD) was estimated using the delta method.
Note 5: CI: Confidence intervals for the ratios. For the analyses using untransformed data, CIs were determined according to Fieller's Theorem. For the analyses using log-transformed data, the CI limits were back-transformed from the ANOVA results limits by exponentiation and multiplied by 100%.
Note 6: C-Peptide Sensitivity PD Analysis (Fieller) EOT Table 14.2.11.4 and program source PDP A4 Sensitivity C-peptide Fieller.sas.
Note 7: C-Peptide Sensitivity PD Analysis (ANOVA) EOT Table 14.2.11.5 and program source PDP A5 Sensitivity C-peptide Log.sas Fieller.sas.
Note 8: Hypoglycemic Event (DRM) Sensitivity PD Analysis (Fieller) EOT Table 14.2.12.4 and program source PDP A6 Sensitivity Hypo Fieller.sas.
Note 9: Hypoglycemic Event (DRM) Sensitivity PD Analysis (ANOVA) EOT Table 14.2.12.5 and program source PDP A7 Sensitivity Hypo Log.sas.
Cross-reference: EOT Tables 14.2.11.4 and 14.2.11.5, EOT Tables 14.2.12.4 and 14.2.12.5

Analysis of the Secondary Pharmacodynamic Endpoints

Descriptive statistics of the secondary PD endpoints are presented in an overview in Table 11.

Table 11 – Descriptive Statistics of the Secondary Pharmacodynamic Endpoints (PPS)

Parameter	**Treatment**	**N**	**Arithmetic Mean**	**SD**	**CV%**	**Min**	**Median**	**Max**	**Geometric Mean**	**Geometric CV%**
$AUC_{GIR.0\text{-}2h}$ (mg/kg)	GL Aspart	36	627.8	315.36	50.2	146	627.7	1440	540.6	65.0
	EU NovoRapid	36	574.9	260.07	45.2	187	513.8	1347	518.3	50.4
	US NovoLog	36	638.8	356.98	55.9	145	586.0	1842	552.4	60.3
$t_{GIR.max}$ (h)	GL Aspart	36	2.681	1.0596	39.5	0.85	2.750	4.85	2.443	48.9
	EU NovoRapid	36	2.917	0.9189	31.5	0.93	2.817	4.82	2.753	38.0
	US NovoLog	36	2.743	0.9913	36.1	1.05	2.600	4.87	2.560	40.5
$t_{GIR.50\%\text{-}early}$ (h)	GL Aspart	36	0.949	0.4905	51.7	0.37	0.783	2.38	0.857	45.5
	EU NovoRapid	36	0.938	0.4120	43.9	0.50	0.833	2.85	0.881	34.1
	US NovoLog	36	0.879	0.3281	37.3	0.42	0.800	2.13	0.829	34.7
$t_{GIR.50\%\text{-}late}$ (h)	GL Aspart	36	4.813	1.0011	20.8	2.17	4.917	6.93	4.703	22.8
	EU NovoRapid	36	5.099	1.0689	21.0	3.37	4.817	8.33	5.000	19.9
	US NovoLog	36	4.956	1.0853	21.9	2.12	4.958	6.93	4.825	24.9
Time to onset of action (h)	GL Aspart	36	0.348	0.1525	43.8	0.05	0.350	0.65	0.309	59.2
	EU NovoRapid	36	0.368	0.1747	47.5	0.05	0.383	0.78	0.320	63.7
	US NovoLog	36	0.378	0.1942	51.3	0.02	0.358	0.82	0.311	89.2

Cross-reference: EOT Table 14.2.7.2

Statistical analysis results of the secondary AUC_{GIR} endpoint $AUC_{GIR.0\text{-}2h}$ for GL Aspart versus NovoRapid are presented in Table 12 (untransformed data) and the non-parametric analysis of $t_{GIR.max}$ is presented in Table 13.

Table 12 – Secondary Analysis of the Secondary Pharmacodynamic Endpoints (Fieller)

Secondary Analysis of Secondary PD Endpoints for Ratio of GL Aspart vs. US NovoRapid
Fieller Confidence Intervals for the Untransformed,
LS-Mean Ratio of GL Aspart vs. US NovoRapid PD Parameters
Per Protocol Set

Parameter	Treatment/Comparison	N	LS-Mean/ LS-Mean Ratio	95%-CI (1)
AUC-GIR 0-2h (mg/kg)	GL Aspart	36	627.80	
	EU NovoRapid	36	574.86	
	GL Aspart vs EU NovoRapid	.	109.21	(104.04;114.31)

Table 13 - Secondary analysis of the Secondary Pharmacodynamic Endpoints (Non-parametric)

Non-parametric Analysis of Time until GIRmax for the Ratio of GL Aspart vs. EU NovoRapid
Per Protocol Set

Parameter	Treatment/Comparison	N	Median/ Estimate of Hodges and Lehmann	95%-CI (1)	p-Value
Time until GIRmax (h)	GL Aspart	36	2.750		.
	EU NovoRapid	36	2.817		.
	GL Aspart vs EU NovoRapid	.	-0.200	(-0.7500; 0.2667)	0.2283

The results of the statistical analysis of $AUC_{GIR.0\text{-}2h}$ confirmed equivalence between Dazparda and NovoRapid and supported the findings from the analysis of primary endpoints. Hodges and Lehmann estimate, along with the 95% CI indicated no meaningful difference in $t_{GIR.max}$ between Dazparda and NovoRapid.

C-peptide

Blood samples for C-peptide determination at visits 2, 3, and 4 were drawn at scheduled times. A C-peptide profile was determined to have a baseline C-peptide level >0.5 nmol/L, which increased by at least 100% from baseline. According to the pre-specified SAP criterion, the corresponding GIR profile was excluded in the C-peptide sensitivity PD analysis.

Mean C-peptide concentrations decreased after dosing and increased from 2 hours post dosing to slightly higher values than at baseline at 8 hours post dosing, reflecting the suppressive effect of the insulin administration on endogenous insulin secretion. This pattern showed that endogenous insulin levels were not markedly increased by glucose infusion and thus did not interfere with clamping results in most subjects.

No clear difference in mean C-peptide profiles was observed between Dazparda, NovoRapid and NovoLog (Figure 4 and Table 14).

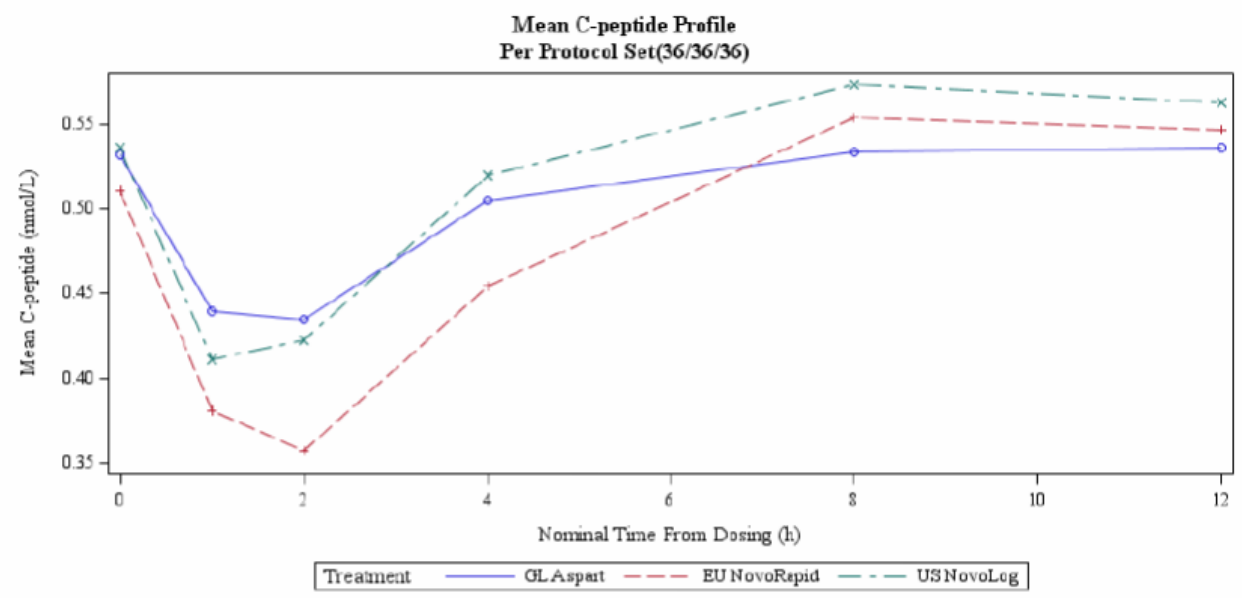

Figure 4– Mean C-Peptide Profiles (PPS)

Table 14 – Descriptive Statistics of the Primary PD Endpointsfor the C-Peptide Sensitivity Analysis

Parameter	Treatment	N	Mean	Standard Deviation	CV%	Min	Median	Max	Geometric Mean	Geometric CV%
$AUC_{GIR.0\text{-}12h}$ (mg/kg)	GL Aspart	35	2628.2	924.06	35.2	1245	2583.8	5249	2472.9	37.1
	EU NovoRapid	36	2598.1	753.22	29.0	1443	2499.0	5002	2507.5	26.8
	US NovoLog	36	2737.4	1044.14	38.1	1342	2567.1	6399	2575.1	35.8
Maximum GIR (mg/kg/min)	GL Aspart	35	9.910	3.3943	34.3	3.89	9.826	16.73	9.264	40.7
	EU NovoRapid	36	9.589	3.1582	32.9	4.46	9.220	18.75	9.104	33.9
	US NovoLog	36	10.239	4.6400	45.3	4.14	9.400	26.83	9.406	42.7

Source: Study GL-ASP-1008 CSR, Table 14.2.11.1.

Quality of clamps

The clamp quality parameters precision (in terms of coefficient of variation, or CV) and deviation from target were calculated based on all raw measurements of the PPS during the 12-hour clamp procedure where GIR was >0 mg/kg/min as pre-defined in the SAP. An overview of clamp quality is displayed in Table 15.

Table 15 -Descriptive Statistics for Quality of Clamp Data (PPS)

Parameter	Treatment	N	Arithmetic Mean	SD	Min	Median	Max	Excluded*
Precision (CV, %)	GL Aspart	36	5.12	1.453	2.7	5.27	8.7	0
	EU NovoRapid	36	4.86	1.484	3.0	4.73	9.7	0
	US NovoLog	36	5.44	2.341	2.4	4.84	13.0	0
Deviation from Target (mg/dL)	GL Aspart	36	0.48	0.399	-0.1	0.42	1.4	0
	EU NovoRapid	36	0.33	0.409	-0.5	0.21	1.7	0
	US NovoLog	36	0.55	0.836	-0.4	0.32	3.7	0

*Excluded: Number of subjects excluded from PD Sensitivity Analysis
Cross-reference: EOT Table 14.4.1

Results in both precision and deviation from target demonstrate that the clamp performance was good and comparable among the tested IMP. All subjects met the precision requirement (CV<15%) and all subjects met the deviation from target requirement (within the range of ±10 mg/dL). No profile was excluded based on clamp quality.

2.5.3. Discussion on clinical pharmacology

The Applicant Gan & Lee Pharmaceuticals Europe GmbH applied for a MA of rapid- and short acting insulin aspart, referred to as Dazparda in the application. Dazparda for subcutaneous injection is a biosimilar product of the reference insulin aspart product NovoRapid. The US aspart reference product was also included in the pivotal clinical study and data of NovoLog was included in the submitted application. Data from NovoLog and comparison with NovoLog are not considered of relevance for the current MAA.

The application is supported by one clinical Phase 1 study GL-ASP-1008, a pivotal PK/PD comparability study. In the pivotal PK/PD comparability study of Dazparda with NovoRapid, the euglycemic clamp technique was applied as recommended in the EMA guideline on insulin biosimilar products: 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). The current application was evaluated primarily according to this regulatory guideline.

Dazparda and the reference product, NovoRapid, were quantified in human plasma using a validated mass spectrometry immunoassay-liquid chromatography-mass spectrometry/mass spectrometry (MSIA-LC-MS/MS) method. The Applicant provided a justification that two deviations according to ICH M10 guideline in method validation did not impact the conducted bioanalysis. It was demonstrated that the bioanalytical method performance was satisfactory and comparable for both Dazparda and NovoRapid. In the clinical study GL-ASP-1008, the samples were measured with the validated MSIA-LC-MS/MS method. The guideline acceptance criteria with regards to back calculated concentration of calibrations standards, QC samples and ISR samples were fulfilled. The C-peptide biomarker was quantified in serum with a validated sandwich enzyme immunoassay. Overall, the bioanalysis was in accordance with regulatory requirements.

The pivotal PK/PD study GL-ASP-1008 using the euglycemic glucose clamp technique was designed to demonstrate PK and PD equivalence of Dazparda with the reference EU aspart product NovoRapid. This Phase 1 study was a randomized, double-blind, 3-way cross-over study conducted in 36 healthy male subjects. In each period of treatment, a single sc. dose of 0.2U/kg of the respective aspart was administered. In addition to glucose clamp measurements for each subject over 12 hrs, PK-samples

was taken to provide a full 12 hr plasma PK-profile for aspart. Furthermore, C-peptide was analysed to assess endogenous insulin secretion in study. The following study parameters, study endpoints and statistical methods were in accordance with the insulin biosimilar guideline for rapid-/short acting insulins: duration of study i.e. 12 hr, dosage of 0.2 U/kg insulin aspart; the primary PK-endpoints, $AUC_{0ins,0-12h}$ and $C_{ins,max}$; the selected secondary PK endpoints; comparability evaluation using ANOVA analysis and the application of standard BE criteria i.e. 90% CI of the ratio test/reference within 80%-125% acceptance range. In conclusion, the methodology and study design of the pivotal biosimilarity study GL-ASP-1008 is in accordance with the EMA guideline on biosimilar products containing insulin or insulin analogues.

The PK analysis in GL-ASP-1008 included all 36 subjects included in the study. One subject (50) was excluded due to elevated baseline insulin. This is acceptable. The primary PK-endpoints $AUC_{0ins,0-12h}$ and $C_{ins,max}$ were determined for each subject using standard NCA analysis. It was demonstrated by statistical analysis, ANOVA, that for both primary PK endpoints $AUC_{0ins,0-12h}$ and $C_{ins,max}$ in the GL-ASP-1008 study of insulin aspart, the similarity limits (90% CI of the geometric LS-mean treatment ratio within the limits 80.00–125.00%) were met. The demonstration of PK-similarity of Dazparda with NovoRapid by application of the conventionally bioequivalence acceptance criteria follows the guidelines recommendation. Analysis of secondary PK endpoint using similar methodology as primary PK endpoints were supportive for the conclusion of PK-similarity between Dazparda and NovoRapid.

In conclusion, it has been demonstrated that Dazparda and NovoRapid have similar human pharmacokinetics.

Pharmacodynamics

The primary PD objectives of study 1008 were to evaluate biosimilarity with regard to the total and maximum PD response during one dosing interval ($AUC_{GIR.0-12h}$ and GIR_{max}). With a high precision (mean CV% of approximately 5) and a mean deviation from target blood glucose of less than 1 mg/dL, the clamp studies were comparable among the tested IMPs and of high quality. Overall, the PD results from the clamp study support the conclusion of biosimilarity between Dazparda and NovoRapid. The results of the secondary analysis of $AUC_{GIR.0-2h}$ confirmed equivalence between Dazpardaand NovoRapid and supported the findings from the analysis of primary endpoints.

C-peptide profiles were comparable between the different treatment groups.

According to the EMA insulin guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1), for primary PD parameters, the 95% confidence intervals of the ratio test/reference should be contained within the pre-defined equivalence margins. The primary PD endpoints, $AUC_{GIR.0-12h}$ and GIR_{max}, were analysed using untransformed data for the main analysis. The results of the statistical analysis demonstrate that for $AUC_{GIR.0-12h}$ and GIR_{max}, the similarity limits (a 95% CI of the LS-mean treatment ratio within the limits of 80.00–120.00%) were met for Dazparda vs. NovoRapid. All confidence intervals contain the value 100%.

All sensitivity analyses on the primary PD endpoints, using either C-peptide corrections or hypoglycaemic events, fell within the prespecified CI limits.

2.5.4. Conclusions on clinical pharmacology

The Applicant has conducted an adequate biosimilarity study comparing the PK and PD profiles between Dazparda and the aspart EU reference product NovoRapid. Both in terms of PK and PD, similarity was demonstrated. Hence, from a PK/PD perspective Dazparda can be used as a biosimilar to NovoRapid.

2.5.5. Clinical efficacy

The Applicant Gan & Lee Pharmaceuticals developed a biosimilar Dazparda (insulin aspart) to improve glycemic control in adults and paediatric patients with type 1 and type 2 diabetes similar to that of EU-authorized NovoRapid a rapid- and short acting human insulin analogue that is produced by recombinant DNA technology utilizing *E.coli* cells as the production organism.

The proposed indication for Dazparda is identical to that of NovoRapid and NovoLog and is to improve glycaemic control in adults and paediatric patients with type 1 and type 2 diabetes. A phase 1 study was conducted to evaluate pharmacokinetics (PK) and pharmacodynamics (PD) equivalence of Dazparda with both EU (NovoRapid) and US reference product (NovoLog), in healthy male subjects.

No efficacy assessment was performed in conducted PK/PD similarity study, and no dedicated efficacy study was conducted for the present application. This is acceptable. In the EMA guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1), it is stated that "There is no anticipated need for specific efficacy studies since endpoints used in such studies, usually HbA_{1c}, are not considered sensitive enough to detect potentially clinically relevant differences between two insulins."

The Applicant has conducted a phase 3 study in China (Study AP-1) in patients with type 2 diabetes to evaluate the effectiveness and safety of Dazparda compared to NovoRapid after 24 weeks of drug administration. High level information in the Risk Management Plan (RMP) stating that similar therapeutic effects were established versus Novorapid, has been provided. This is acceptable.

Furthermore, the Applicant planned an Open-label, Randomized, Multicenter, Phase 3 Study (GL-ASP-3007) to Compare the Immunogenicity, Efficacy, and Safety of Dazparda to NovoRapid (Insulin Aspart Injection) in Adult Subjects with Type 1 Diabetes Mellitus. The EMA 2015 and FDA 2019 draft guidance notified that a comparative clinical immunogenicity study would be considered unnecessary to support a demonstration of biosimilarity or interchangeability for a proposed insulin product if the comparative analytical assessment (CAA) adequately supports a demonstration of "highly similar" as part of the biosimilarity. Therefore, the Applicant cancelled the Phase 3 immunogenicity comparative study GL-ASP-3007.

2.5.6. Discussion on clinical efficacy

The Applicant developed a biosimilar Dazparda (insulin aspart) to improve glycaemic control in adults and paediatric patients with type 1 and type 2 diabetes similar to that of EU-authorized NovoRapid a rapid- and short acting human insulin analogue that is produced by recombinant DNA technology utilizing *E.coli* cells as the production organism.

The proposed indication for Dazparda is identical to that of NovoRapid and NovoLog and is to improve glycaemic control in adults and paediatric patients with type 1 and type 2 diabetes. A phase 1 study was conducted to evaluate pharmacokinetics (PK) and pharmacodynamics (PD) equivalence of Dazparda with both EU (NovoRapid) and US reference product (NovoLog), in healthy male subjects.

No efficacy assessment was performed in conducted PK/PD similarity study, and no dedicated efficacy study was conducted or submitted for the present application. This is acceptable. In the EMA guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1), it is stated that "There is no anticipated need for specific efficacy studies since endpoints used in such studies, usually HbA1c, are not considered sensitive enough to detect potentially clinically relevant differences between two insulins."

2.5.7. Conclusions on the clinical efficacy

No phase 3 efficacy studies have been conducted for the current MA application which is acceptable for a biosimilar rapid-acting insulin.

2.5.8. Clinical safety

The safety results in this submission are presented for the pivotal PK/PD similarity study.

A summary of clinical safety studies included in this submission is presented in Table 16.

Table 16 – Description of Clinical Study

Study	# Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment	Design Control Type	Treatments (Dose, Route, Regimen)	Study Objective (s)	# Subjects by Arm Entered / Completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion Criteria	Key Safety Endpoint(s) and Results	Location of Study Report
GL-ASP-1008	Single center Profil Mainz GmbH & Co. KG, Germany	Date of Study initiation (FSFV): 27 Aug 2019 No. of subjects: Healthy Male Subjects 36 subjects planned, enrolled, and completed the study Date of Study completion (LSLV): 16 Dec 2019	Phase 1, a single-centre, randomized, double-blind, three-treatment, single dose, three-period, crossover, 12-hour euglycemic glucose clamp trial	GL Aspart: 0.2 U/kg, SC NovoRapid: 0.2 U/kg, SC NovoLog: 0.2 U/kg, SC	Primary Objective: The primary objective of the trial was to evaluate PK and PD equivalence of GL Aspart with both EU-authorized NovoRapid and US-licensed NovoLog (reference products) in healthy male subjects.	Randomized: 36 GL Aspart: 36/36 EU NovoRapid: 36/36 US NovoLog: 36/36	The treatment consisted of 3 single dose administrations on 3 individual dosing days, each separated by a wash-out period of 3 to 14 days	36 Male Median Age: 32.5 years Age range: 19-64 years	Healthy Male Subjects	Adverse events (AEs): GL Aspart: 33.3% NovoRapid: 19.4% NovoLog: 27.8% Clinical laboratory parameters: Mild injection site reaction (preferred term: injection site erythema: redness, probably related to GL Aspart administration) was observed for one hour and	5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Study	# Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment	Design Control Type	Treatments (Dose, Route, Regimen)	Study Objective (s)	# Subjects by Arm Entered / Completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion Criteria	Key Safety Endpoint(s) and Results	Location of Study Report
					Secondary Objectives: Secondary objectives were to compare the PK and PD parameters of the three insulin aspart products and to evaluate the single dose safety and local (i.e. injection site) tolerability of the three insulin aspart products.					had the outcome recovered/ resolved. There were no clinically significant findings or changes in safety laboratory test results, vital signs, ECGs, and physical examination results.	

AE = Adverse event; ECG=electrocardiogram; FSFV = first subject first visit; GL=Gan & Lee; (I)U=(international) units; LSLV = last subject last visit; PK/PD = Pharmacokinetic/ Pharmacodynamic; SC=subcutaneous.

2.5.8.1. Data from a Phase 3 trial not submitted

From RMP:

"*Study AP-1:*

This was a phase 3 multicenter, randomized, open-label, positive control, non-inferiority design clinical study conducted in China in order to evaluate the effectiveness and safety of GL Insulin Aspart Injection (Ruixiulin) compared to NovoRapid after 24 weeks of drug administration. A total of 590 type 2 diabetic subjects (ages ≥18 and ≤75 years) in 21 sites were randomized, of which 543 completed the whole trial and 47 subjects dropped out of the study for various reasons. Subjects had been taking metformin only or metformin in combination with sulfonylureas, insulin secretagogues (including short-acting), and glucosidase as an anti-diabetic drug therapy for more than three months without reaching targets. The primary efficacy endpoint was the change from baseline in HbA_{1c} after 24-week treatment of GL Insulin Aspart Injection or NovoRapid. The safety data set (SS) was defined as the full analysis set except subjects who never received treatment. The safety data set was the primary data set for the safety evaluation.

Overall, 588 subjects were included in the SS set, with 439 in GL Insulin Aspart Injection group (441 in full analysis set) and 149 in NovoRapid group. The study indicates that the insulin aspart injection fluid developed by Gan & Lee and NovoRapid treatment methods can enable subjects with type 1 or type 2 diabetes to achieve good blood glucose control. Using HbA_{1c}, fasting blood glucose, and 2-hr post-meal venous blood glucose levels as determination criteria, insulin aspart injection fluid has similar therapeutic effects to NovoRapid for diabetic subjects. There were no differences between the two groups in terms of hypoglycemic event incidence rates, adverse event incidence rates, complete blood

count (CBC), urinalysis (urine test), blood biochemistry tests, blood enzyme tests and ECG. The study demonstrated that three times daily use of insulin aspart injection to treat diabetes is safe and effective and features good tolerance."

2.5.8.2. Patient exposure

Only data from one clinical trial has been submitted (study 1008), and in this trial a single dose of each of the three study drugs was administered to each participant. Hence, no steady state or long-term safety data are provided. The dose for each treatment was 0.2 U/kg.

2.5.8.3. Adverse events

Overall, 35 AEs were reported during the trial. All AEs were treatment emergent, i.e. started after the first IMP dosing. No deaths and no SAEs occurred in this trial. The events were either mild (12 events) or moderate (23 events). No AE was severe. All AEs had the outcome recovered/resolved. At least one AE was experienced by 12 subjects (33.3%) after administration of Dazparda, (14 events), by 7 subjects (19.4%) after administration of NovoRapid (7 events) and by 10 subjects (27.8%) after administration of NovoLog (14 events).

An overview of incidence of AEs is provided in Table 17.

Table 17 -Overview of Incidence of Adverse Events (Safety Analysis Set)

	GL Aspart (N=36)	EU NovoRapid (N=36)	US NovoLog (N=36)
Incidence of Adverse Events	12 (33.3%)	7 (19.4%)	10 (27.8%)
Number of Adverse Events	14	7	14
Incidence of Moderate and Severe (1) Adverse Events	6 (16.7%)	6 (16.7%)	8 (22.2%)
Number of Moderate and Severe (1) Adverse Events	6	6	11
Incidence of Drug Related (2) Adverse Events	7 (19.4%)	6 (16.7%)	7 (19.4%)
Number of Drug Related (2) Adverse Events	8	6	7
Incidence of Deaths	0	0	0
Incidence of Serious Adverse Events	0	0	0
Incidence of Drug Related (2) Adverse Events Leading to Permanent Discontinuation of Study Drug	0	0	0
Incidence of Unblinding of the Study Drug	0	0	0

(1)No severe AEs occurred in this trial.
(2)Drug related AEs: relationship to IMP is possible or probable.
The denominator for percentages is based on the number of subjects in the safety analysis set for each administration.
Cross-reference: EOT Table 14.3.1.1

Table 18 presents a summary of AEs by MedDRA system organ class and preferred term. Most frequent AE based on the PT level was headache (9 events after Dazparda, 5 events after NovoRapid, and 9 events after NovoLog administration).

Table 18 – Summary of Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

		Number (%) of Subjects/Number of Events		
System Organ Class	**Preferred Term**	**GL Aspart (N=36)**	**EU NovoRapid (N=36)**	**US NovoLog (N=36)**
Overall		12 (33.3%)/ 14	7 (19.4%)/ 7	10 (27.8%)/ 14
Gastrointestinal disorders	Overall	1 (2.8%)/ 1	1 (2.8%)/ 1	1 (2.8%)/ 2
	Diarrhoea	1 (2.8%)/ 1	1 (2.8%)/ 1	0
	Nausea	0	0	1 (2.8%)/ 1
	Vomiting	0	0	1 (2.8%)/ 1
General disorders and administration site conditions	Overall	2 (5.6%)/ 2	0	2 (5.6%)/ 2
	Catheter site haematoma	1 (2.8%)/ 1	0	1 (2.8%)/ 1
	Injection site erythema	1 (2.8%)/ 1	0	0
	Vessel puncture site thrombosis	0	0	1 (2.8%)/ 1
Injury, poisoning and procedural complications	Overall	0	1 (2.8%)/ 1	0
	Ligament sprain	0	1 (2.8%)/ 1	0
Metabolism and nutrition disorders	Overall	1 (2.8%)/ 1	0	0
	Hypoglycaemia	1 (2.8%)/ 1	0	0
Musculoskeletal and connective tissue disorders	Overall	0	0	1 (2.8%)/ 1
	Neck pain	0	0	1 (2.8%)/ 1
Nervous system disorders	Overall	9 (25.0%)/ 9	5 (13.9%)/ 5	9 (25.0%)/ 9
	Headache	9 (25.0%)/ 9	5 (13.9%)/ 5	9 (25.0%)/ 9
Respiratory, thoracic and mediastinal disorders	Overall	1 (2.8%)/ 1	0	0
	Nasopharyngitis	1 (2.8%)/ 1	0	0

Unique events for a subject were counted once within each preferred term.
The denominator for percentages was based on the number of subjects in the safety analysis set for each administration.
Cross-reference: EOT Table 14.3.1.2

2.5.8.4. Serious adverse events, deaths, and other significant events

No deaths and no SAEs occurred in this trial.

2.5.8.5. Laboratory findings

For both haematology and clinical chemistry parameters, no substantial differences between treatment groups were observed in study 1008.

2.5.8.6. Immunological events

No assessment of immunogenicity has been provided, and the single-dose application of IMPs in study GL-GLA-CT-1008 does not allow any meaningful evaluation of immunogenicity.

In the integrated summary of immunogenicity, a justification for not conducting a phase 3 safety study is provided. A phase 3 study (AP-1) was conducted and a statement in the RMP that no differences in safety and efficacy were seen was included. This is acceptable.

The analytical studies comparison between Dazparda to NovoRapid demonstrated similarity between the two products with regards to quality attributes which include primary structure, secondary and higher order structure, product related substances and impurities, related protein, aggregates, protein content, excipient, target binding, receptor phosphorylation, mitogenic activity, metabolic activity, and *in vitro* potency. The forced degradation and accelerated stability data also support high analytical similarity.

The toxicity of Dazparda was also evaluated in rats. There were no apparent differences after 4 weeks of once daily subcutaneous administration of either Dazparda or at doses up to 50 U/kg. Serum insulin aspart antibody analysis indicated that there were similar immune responses in the treated rats after 28 days repeated subcutaneous injections of Dazparda or NovoRapid/NovoLog. The No observable adverse effect level (NOAEL) is observed when Dazparda was administered at a dose of 50 U/kg/day.

The safety assessments from the study GL ASP 1008 indicated no safety concern for Dazparda in comparison with EU NovoRapid and US NovoLog. Dazparda, NovoRapid and NovoLog are comparably safe and well tolerated.

A toxicology risk assessment and medical risk assessment have been performed to evaluate impact of the visible particles on patient safety and efficacy. The toxicology report concluded that exposure of patients to Dazparda is unlikely to pose any serious adverse effect and could pose only negligible risk to patient.

Therefore, it was concluded that the visible particles have a low risk of impact on product quality, efficacy and patient safety. Based on the data from this integrated report, "Gan & Lee Pharmaceuticals" believes that the phase 1 study was adequately designed to support biosimilarity and interchangeability designations and that there is no need of Phase 3 study as Dazparda has the same low risk for immunogenicity compared to the reference product.

Injection site reactions:

One mild injection site reaction was reported after Dazparda administration and was probably related to IMP.

2.5.8.7. Discontinuation due to adverse events

No events leading to intervention, including withdrawal of IMP or significant additional concomitant therapy occurred during this trial.

2.5.8.8. Post marketing experience

Dazparda was administered to 25280 users in China between 2020-10-01 and 2022-12-31; 113 adverse events and 88 adverse drug reactions were reported between 2020-05-12 and 2022-12-31. The adverse reaction reporting ratio was 0.35% in exposure period (from 2020-10-01 to 2022-12-31).

2.5.9. Discussion on clinical safety

The safety results in this submission stem from the phase 1 PK/PD BE study 1008 only. Hence, the safety of Dazparda is only evaluated based on single dose administrations and no steady state or long-term safety data are provided.

No assessment of immunogenicity has been provided. It is acceptable as no clinical safety studies are warranted for biosimilar insulins. The single-dose application of IMPs in study GL-GLA-CT-1008 does not allow any meaningful evaluation of immunogenicity. In the integrated summary of immunogenicity, the Applicant justifies the omission of a phase 3 safety and immunogenicity study. Based on these quality and non-clinical data together with the results from the clamp study, there seems no need for a safety study. The appearance of the Dazparda pen is somewhat similar to that of Bysumlog (insulin lispro). The Bysumlog pen is orange, and the Dazparda pen is also planned to be orange, only with another colour of the label. However, in a human factors differentiation study including 75 participants (patients, lay caregivers, HCPs, and pharmacists), no confusion between the Dazparda pen and the Bysumlog pen was observed. Hence, the appearance of the Dazparda pen is considered acceptable.

Evaluation of haematology and clinical chemistry parameters revealed no clinically significant changes during the study.

2.5.10. Conclusions on the clinical safety

No clinical studies in subjects with diabetes were submitted for the current MA application, which is acceptable as no clinical efficacy and safety studies are required for authorisation of a biosimilar insulin in the EU.

Immunogenicity of Dazparda was not studied in clinical trials. Antibodies to insulin are very frequent in patients with diabetes but have in general no clinical consequences during treatment with human or analogue insulins. No specific risk for immunogenicity was identified based on the physicochemical and functional characterisation and comparison to the reference product NovoRapid, and from the comparison of the pharmacokinetic and pharmacodynamic profiles, impurity profile and nature of excipients of Dazparda vs. NovoRapid.

2.6. Risk Management Plan

2.6.1. Safety concerns

None.

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

None.

2.6.4. Conclusion

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

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

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

2.7.2. Periodic Safety Update Reports submission requirements

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.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report to the reference product NovoRapid solution for injection in a pre-filled pen, and Ondibta solution for injection in a pre-filled pen that belongs to the same device platform. In addition, the applicant submitted user readability testing report for Instructions for Use that could not have been bridged to the reference product. The bridging report submitted by the applicant has been found acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Dazparda (Insulin aspart) is included in the additional monitoring list as a biological medicine authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Dazparda is developed by the Applicant as a biosimilar for the EU reference product NovoRapid. The Applicant is seeking approval for the same indications as those approved for NovoRapid:

For treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

Quality aspects

The biosimilarity of Dazparda to the EU NovoRapid reference product was assessed using a range of state-of-the-art analytical tests in line with the EMA *Guideline on Similar Biological Medicinal Products containing Biotechnology-derived proteins as active substance (*EMA/CHMP/BWP/247713/2012).

Non-clinical aspects

The non-clinical program aimed at proving similarity between Dazparda and the EU-approved NovoRapid primarily based on *in vitro* pharmacology studies in accordance with requirements presented in 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).

Additionally, a 4-week repeat-dose toxicity study in rats assessing systemic exposure and safety profile after s.c. injection of insulin aspart for Dazparda and NovoRapid (and NovoLog) at doses of 10 and 50 U/kg/day was conducted. However, *in vivo* animal studies are not deemed necessary for biosimilarity assessment of insulin analogues in accordance to the guideline. Hence, the study is only considered supportive.

Clinical aspects

A hyperinsulinaemic clamp study was performed in order to establish biosimilarity. This approach follows 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).

No efficacy assessment was performed in conducted PK/PD similarity study, and no dedicated efficacy study was submitted for the present application. As for safety, a biowaiver for a safety study has been submitted as part of the Integrated Summary of Immunogenicity. This is acceptable as it is in accordance with the above-mentioned guideline.

3.2. Results supporting biosimilarity

Quality aspects

Quality attributes included in the biosimilarity exercise cover: Protein content (assay and total protein), excipient content (zinc, phenol, metacresol), primary structure, pI, secondary and higher-order structure, disulfide linkage, product-related substances and impurities (as assessed by multiple methods, including RP-HPLC, CEX-HPLC, HI-HPLC, LC-MS peptide mapping, SE-HPLC), and biological characteristics, i.e. target binding, phosphorylation, mitogenicity, and metabolic activity (glucose uptake, glycogen synthesis, lipogenesis). The selected panel of QAs is deemed appropriate. For all but some QAs, 100% of Dazparda lots were within the QR. The exceptions are oligomer by non-denaturing SEC-MALS, thermal stability by DSC, and other quality attributes. These outliers are discussed individually.It can also be noted that some impurities showed systematically lower levels for test lots than RMP lots. The Applicant suggests that this may reflect a slightly higher purity of the test product or that the test lots were less aged than the RMP lots at the time of testing. This is acknowledged. The differences in impurity levels are not considered concerning.

Insulin aspart is formulated with Zn^{2+} to induce formation of more stable hexamers. Non-denaturing SEC-MALS was used to measure oligomer Mw and quantify the amounts of hexamer and monomer. All test lots fell within the QR with respect to oligomer size, but there were differences with respect to hexamer and monomer content. As follows below, degradation pathways and impacts on biological QAs were deemed overall similar between test and RMP lots in head-to-head comparative accelerated

stability and forced degradation studies. The differences in oligomer contents are therefore considered to not significantly impact stability, and thus to be acceptable.

The thermal stability curves were obtained by DSC The DLS, FTIR, CD, and fluorescence spectra were found to be similar, showing that there are no large differences in structure.In general, differences in Tm can affect protein function and/or stability. In the case of Dazparda, there appears to be no significant impact on function, as there are no clear differences between clinical, commercial, and RMP lots. Concerning stability, degradation profiles were deemed sufficiently similar between the clinical and commercial lots in comparative accelerated stability studies, and between the commercial and RMP lots in head-to-head accelerated stability and forced degradation studies (see below). Therefore,it is considered that the rather small differences can be accepted.

For several other attributes, small differences were identified and explained, and it is therefore agreed that the differences do not preclude a conclusion of biosimilarity.

Comparative stability studies were carried out to assess similarity in Dazparda and RMP degradation profiles, testing for a wide range of QAs. The studies were performed under accelerated and forced degradation conditions, where the latter included: High temperature, low pH, high pH, oxidation, light exposure, and mechanical agitation.

Under the accelerated condition, trends were overall similar between test and RMP lots.

For most forced degradation conditions, one or more QA showed differences in their rates of change. However, the differences were inconsistently observed among the different conditions and generally quite small. Therefore, they are not considered concerning. With respect to light stress, a difference was observed. However, considering the outcome of the other forced degradation studies, and that the product is to be protected from light, this is not deemed to preclude a conclusion of biosimilarity.

Overall, the comparative stability studies support the conclusion of biosimilarity.

Non-clinical aspects

The conducted *in vitro* pharmacology studies provided adequate evidence of biosimilarity between Dazparda and the EU-approved reference product NovoRapid with respect to receptor binding affinity (IR-A, IR-B and IGF-1R), receptor phosphorylation (IR-A, IR-B and IGF-1R), metabolic activity (glucose uptake, glycogen formation and lipogenesis) and mitogenic potential (IGF-1R and IR-dependent), as requested by guideline. Additionally, biosimilarity was also seen for *in vitro* IR-B potency.

Based on a 4-week repeat-dose toxicity study in rats the assessment of systemic exposure and the safety profile of insulin aspart for Dazparda, Novolog and NovoRapid at doses of up to 50 U/kg/day can be considered comparable. Bioanalytical methods were adequately validated to support the bioanalysis of insulin aspart and anti-insulin aspart antibodies in the 4-week repeat-dose toxicology study in rats. In addition, method validation reports for the conducted *in vitro* pharmacology studies were submitted and assessed as part of the quality dossier and no concerns were identified.

Clinical aspects

PK/PD: In the clamp study, biosimilarity between Dazparda and the reference EU aspart product, NovoRapid, was demonstrated for both PK ($AUC_{0\text{-}12h}$ and C_{max}) and PD ($AUC_{GIR.0\text{-}24h}$ and GIR_{max}).

3.3. Uncertainties and limitations about biosimilarity

Quality aspects

The results of the individual tests of the analytical biosimilarity exercise generally support a conclusion of biosimilarity. All queries were resolved.

Non-clinical aspects

From a non-clinical perspective, biosimilarity between Dazparda and NovoRapid is generally supported based on the provided *in vitro* pharmacology studies.

Clinical aspects

No efficacy assessment was performed in the conducted PK/PD similarity study, and no dedicated efficacy study was conducted for the present application. This is acceptable. In the EMA guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1), it is stated that "There is no anticipated need for specific efficacy studies since endpoints used in such studies, usually HbA_{1c}, are not considered sensitive enough to detect potentially clinically relevant differences between two insulins."

In addition, no formal safety assessment and comparison with NovoRapid has been conducted. The only safety assessment took place as part of the clamp study, in which no differences in safety was demonstrated. The Applicant has submitted an Integrated Summary of Immunogenicity, in which a justification for a biowaiver for a dedicated safety and immunogenicity study is found.

Taken together, it is acceptable that the clinical clamp study GL-ASP-1008, was the only clinical study conducted.

3.4. Discussion on biosimilarity

Quality

The analytical biosimilarity exercise is supportive of a conclusion on biosimilarity.

Non-clinical aspects

From a non-clinical perspective, the provided *in vitro* pharmacology results generally supports biosimilarity of Dazparda and the EU-approved NovoRapid in accordance to the guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1).

Based on a 4-week repeat-dose toxicity study in rats the assessment of systemic exposure and the safety profile of insulin aspart for Dazparda, NovoLog and NovoRapid at doses of up to 50 U/kg/day can be considered comparable. The apparent differences in composition between vehicle, Dazparda and NovoRapid were clarified by the Applicant. However, the Applicant did not provide adequate documentation of the formulations of the vehicle and NovoRapid used in the repeat-dose study to substantiate their claim. As the *in vivo* study is only considered supportive for a marketing authorisation application for a biosimilar medicine this issue was not pursued any further. Bioanalytical methods were adequately validated to support the bioanalysis of insulin aspart and anti-insulin aspart antibodies in the 4-week repeat-dose toxicology study in rats. In addition, method validation reports for the conducted *in vitro* pharmacology studies were submitted and assessed as part of the quality dossier and no concerns were identified. The non-clinical data package is considered sufficient to support the marketing authorisation application for Dazparda.

Clinical

From a clinical perspective, the PK/PD results of clamp study GL-ASP-1008 support biosimilarity between Dazparda and NovoRapid. No phase 3 efficacy studies have been submitted for the current MA application, which is acceptable for a biosimilar rapid-acting insulin. In addition, a dedicated safety and immunogenicity study has been waived based on similar quality, non-clinical, and PK/PD data.

3.5. Conclusions on biosimilarity and benefit risk balance

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

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Dazparda (insulin aspart) 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 Dazparda is favourable in the following indication(s):

Dazparda is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

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 medical prescription.

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.

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

Not applicable.