11 February 2013
EMA/CHMP/780915/2012
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment Report

Isomarv medium

International non-proprietary name: Insulin human

Procedure no. EMEA/H/C/2610

Applicant: Marvel Life Sciences Ltd. UK

Day 120 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still on going at the time of the withdrawal of the application.

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	**Isomarv medium**
INN (or common name) of the active substance:	Insulin human
Applicant:	Marvel LifeSciences Ltd Congress House, 2nd floor, Lyon Road, Harrow, Middx HA1 2EN, United Kingdom
Applied Indication:	Indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis.
Pharmaco-therapeutic group (ATC Code):	Anti-diabetic agent (A10A C01)
Pharmaceutical form and strength:	suspension for injection 100 IU/ml

LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve, subscripts denote the time interval
AUC0-EoC	Area under the GIR-time curve from time zero to end of clamp
AUMC	Area under the first moment of the concentration-time curve
ß-HCG	beta human chorionic gonadotropin
BBRC	Bombay Bio-Research Centre
BLQ	Below limit of quantification
BMI	Body mass index [kg/m2]
bpm	Beats per minute
BUN	Blood urea nitrogen
CDSCO	Central Drugs Standard Control Organisation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent total plasma clearance after extra-vasal (s.c.) administration
Cmax	Maximum concentration of drug
CPMP	Committee for Proprietary Medicinal Products
CRF	Case report form
CRA	Clinicak Research Associate
CRO	Contract Research Organisation
CV	Coefficient of variation
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EMA/EMEA	European Medicines Agency
F	Fraction of the administered dose systemically available
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIR	Glucose infusion rate
GIRmax	Maximum rise in glucose infusion rate
GLP	Good Laboratory Practice
Gmean;	Geometric mean
GMP	Good Manufacturing Practice
h, hr(s)	Hour(s)
HbA1c	Glycosylated haemoglobin
HBsAG	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HCV	Hepatitis C virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IU	International Units (of insulin dose)
kcal	kilocalorie
kel	Terminal elimination rate constant [1/h]
L	Litre
LLOQ	Lower limit of quantification
ln	Loge (transformed)
log	Logarhithmus
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

mg	Milligram
mL	Millilitre
mmHg	Millimetres of mercury
MPV	Mean platelet volume
MRT	Mean residence time
NABL	National Accreditation Board for Testing And Calibration Laboratories
ng	Nanogram
OTC	Over the counter
PD	Pharmacodynamic(s)
pH	Hydrogen ion concentration
PK	Pharmacokinetic(s)
PT	Prothrombin time
PTT	Partial thromboplastin time
QA	Quality assurance
RBC	Red blood cell count
SAE	Serious adverse event
S.c., s.c.	Subcutaneous(ly)
SD	Standard deviation
SEQ	Sequence
T1D	Type-1 diabetes
T1/2, t1/2	Apparent terminal elimination half-life
T50¸ t50	Time to (early/late) half maximum
Td¸ td	Duration of action defined as the time passed from early t50 to late t50
Tmax¸ tmax	Time at which the drug Cmax is obtained
Tonset, tonset	Onset of action, defined as the time from 0 h until the mean baseline level
UK	United Kingdom
VDRL	Venereal Disease Research Laboratory
VZ/F	Volume of distribution associated with the terminal elimination phase after extra-vascular administration
WBC	White blood cell count
WHO	World Health Organisation
X-ray	Radiography

1. RECOMMENDATION

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the application for Isomarv medium in the treatment of “Patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis” is **not approvable** since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions (Section VI).

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

- Process validation has not been adequately demonstrated for the drug substance manufacturing process.
- Reprocessing of the manufacturing process should be unambiguously justified by data or removed from the dossier.
- For all biological materials the option of “change of source or supplier” is proposed. Similar biological activity of the materials should be ensured.
- The specifications for the drug substance and drug product do not reflect the presented data and do not support consistent quality.
- Several issues have been identified in the study report of the new pharmacological study BBRC/CLN/08/001 including statistical errors, unclear calculations and inconsistent or missing information seriously questioning the reliability of the study results.
- The original study protocol, the statistical analysis plan and bioanalytical reports for the study BBRC/CLN/08/001 as well as the summary report of the study site auditing for the new studies conducted in BBRC and CCDRD have not been submitted.
- The immunogenic potential of Marvel insulin needs further evaluation.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

For the drug substance manufacturer, updated GMP certificates should be provided.

A GMP Certificate should be provided for the manufacturer performing microbiological testing of the drug substance at release and during stability.

GCP inspection(s)

A product-specific GCP inspection of the CRO Bombay Bio-Research Centre (BBRC) is deemed necessary before licence approval. A prior inspection by MHRA in 2010 revealed critical findings in respect to data processing and management (details in section 2.4). Also in the present application there are also strong hints that there may be severe deficiencies in data management, e.g. statistical errors and inconsistent information in the pivotal PK/PD study BBRC/CLN/08/001.

A request for GCP Inspection has been adopted for stud BBRC/CLN/08/001. The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the D120 LOQ and will be needed by Day 121.

2. EXECUTIVE SUMMARY

2.1. Problem statement

Diabetes mellitus is a metabolic disease resulting from inadequate insulin secretion and/or insulin action, leading to chronic hyperglycaemia. The therapeutic approaches for the treatment of diabetes mellitus are multifaceted, including different oral antidiabetic agents or insulin injections. Insulin is a natural hormone produced in ß-cells in islets of Langerhans in pancreas and has a long history of clinical use. For therapeutic purposes insulin was originally extracted from animal pancreas, but in course of time new methods have been developed to manufacture human recombinant insulin or insulin-analogues using recombinant DNA technology. Insulin is mostly administered via the subcutaneous route.

The Applicant has applied for 3 separate Marketing Authorisation Applications (MAA) for “Solumarv (soluble) insulin”, “Isomarv (isophane) insulin” and “Combimarv (biphasic) insulin”. These insulin formulations are synthesized by recombinant DNA technology and have the identical chemical sequence and structure to human insulin. This application is for Isomarv medium and is being made on the basis of Article 10(4) similar biological application of Directive 2001/83/EC. Biosimilarity is being claimed with Humulin I (isophane = long-acting), Eli Lilly and Company Ltd (UK).

This is the second application from Marvel LifeSciences Ltd concerning the above insulin formulations. The first MAA was submitted in 2007 and was withdrawn in the same year after CHMP raised major objections in the D120 List-of-Questions regarding the conducted clinical trials and their results. These early trials were performed before the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005) was published and hence they did not comply with the requirements of the Guidance. After withdrawal of the first MAA the company sought scientific advice from CHMP and conducted new clinical trials for the purpose of this current application.

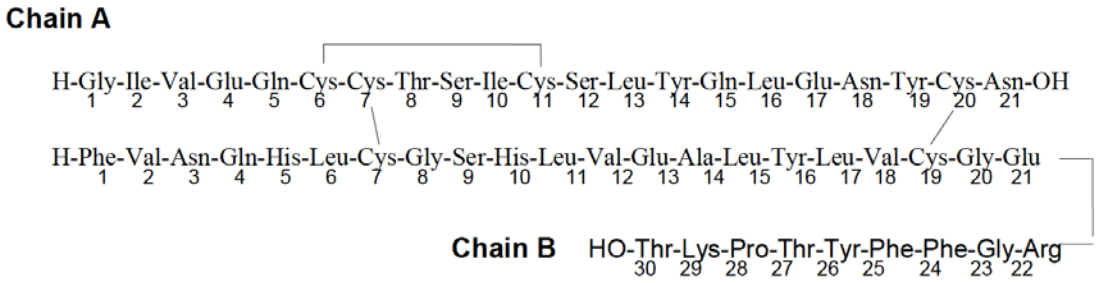
2.2. About the product

Marvel LifeSciences Ltd. has developed the human recombinant insulin product Isomarv medium 100 IU/ml, insulin suspension for injection (Isophane), synthesised by recombinant DNA technology using transformed *Escherichia (E.) coli* bacteria.

The respective ATC code is A10AB01.

The Applicant states that this Marvel insulin formulation is already marketed in 20 countries.

Marvel insulin has the identical chemical sequence and structure as human insulin:



Insulin is a natural hormone produced in ß-cells in islets of Langerhans in pancreas. The most important stimulus for its release into the blood is a rising serum glucose level. Insulin exerts its glucose lowering activity in certain tissues (e.g. muscle and fat cells) through activation of insulin receptor, leading to a variety of actions: Increase in GLUT 4, increase in synthesis of protein, glycogen and lipid, decrease in gluconeogenesis, proteolysis and lipolysis. Insulin has a short half-life in the circulation of about 4-6 minutes.

The therapeutic indication of Marvel's insulins, as for other insulins, is "For the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis". The insulin dosage should be adapted to the individual requirement of the patients. As a guide, the usual daily dose is between 0.3 to 1.0 IU/kg. Marvel's insulins are supposed to be marketed in EU as cartridge to be used with suitable injection pens.

2.3. The development programme/compliance with CHMP guidance/scientific advice

This application is being made on the basis of Article 10(4) similar biological application of Directive 2001/83/EC. The reference medicinal product, which is authorised in the EU, is Humulin I 100 IU/ml suspension for injection. The Marketing Authorisation Holder of the reference medicinal product is Eli Lilly and Co Ltd.

It should be noted that this is the second application from Marvel LifeSciences Ltd for a Marketing Authorisation for three insulin formulations applied for in separate MAAs. Before the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005) was published in 2006, the applicant conducted clinical trials for the proof of biosimilarity between test and reference insulin and the first MAA was submitted in March 2007 (Insulin Human Long Marvel).

When the first MAA was submitted in 2007, the early clinical studies performed in 2002/2003 (PK/PD) and 2005/2007 (clinical efficacy and safety) had been designed based on national scientific advices and did not incorporate all the elements subsequently laid out in the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005). The CHMP raised major objections and the applicant withdrew the MAA in December 2007.

After withdrawal of the first MAA, the company sought scientific advice from CHMP in 2008 and 2010 for the purpose of the current application:

1. EMEA/CHMP/SAWP/368924/2008 (EMEA/H/SA/1118/1/FU/1/2008/SME/I), (Denoted CHMP 2008). Subject: Immunogenicity study
2. EMEA/CHMP/SAWP/650767/2008 (EMEA/H/SA/1118/1/FU/1/2008/SME/II), (Denoted CHMP 2008/FU/1). Subject: Nonclinical (NC), Immunogenicity study specifics
3. EMEA/CHMP/SAWP/95035/2011No (EMEA/H/SA/1118/1/FU/2/2010/SME/II), (Denoted CHMP 2011/FU/2). Subject: Scope of data, reappraisal of 2007 MAA , E&S past and prospective phase 3 studies and PK/PD HV& T1D

The scientific advices were incorporated in the plan of the new studies and the Company conducted three additional PK/PD studies in T1DM patients and an additional study to address the immunogenicity concerns.

The following is an overview of all old and new clinical trials conducted by the applicant:

- Old clinical studies (before 2007):
    - Three double blind, randomized, crossover bioequivalence PK (insulin)/PD (Clamp) studies in healthy volunteers. Study codes:
        - FARMOVS 232/2002 (short-acting insulin; healthy subjects)
        - FARMOVS 21/2003 (isophane insulin; healthy subjects)
        - FARMOVS 439/2002 (biphasic insulin; healthy subjects)
    - A 6-month safety and efficacy (HbA1c) study in patients with Type I or Type II diabetes with a further 6-month open-label extension (investigation of immunogenicity). Study codes: 411-BK-03-01-0000 and 411-BK-03-01-0001
- New clinical studies (after 2007):
    - Three bioequivalence PK (insulin)/PD (Clamp) in Type I diabetic patients. Study codes:
        - BBRC/CLN/07/001 (short-acting insulin; T1D patients)
        - BBRC/CLN/08/001 (isophane insulin; T1D patients)
        - BBRC/CLN/08/002 (biphasic insulin; T1D patients)
    - A new 6-month double blind, randomized immunogenicity study in both Type I and Type II diabetes patients with a 6 months open-label extension. Study code: 411-MA-08-01-0000

2.4. General comments on compliance with GMP, GLP, GCP

GMP:

GMP certificates were provided for the drug substance manufacturers, however updated GMP certificates should be provided

For the manufacturer of the drug product, a GMP certificate is presented. The certificate refers to manufacture of aseptically prepared human medicinal products as lyophilisates and small volume liquids with the following manufacturing operations: purchase of starting materials, control operations regarding supervision of production processes, batch release, and storage.

A GMP certificate has been provided confirming compliance with GMP for the site performing quality control of the finished product.

GLP:

The three new *in vitro* studies (Marvelreport2008v2) were performed at the Division of Chemical Pathology, University of Cape Town, South Africa according to Good Laboratory Practice (GLP). The Laboratory is accredited by the South African National Accreditation system, the official national accreditation body of the Department of Trade and Industry, Republic of South Africa.

The toxicity studies were carried out by Jai Research Foundation (JRF) in Gujarat, India. This laboratory complies with the standards of GLP and has a certificate of Endorsement of compliance with the OECD principles of GLP from The Netherlands.

An immunogenicity study was carried out and according to the Toxicology Tabulated Summary (2.6.7) this study was performed in accordance to GLP. However, no such information could be found in the study report.

GCP:

At the time of the first application in 2007, the CHMP raised concerns about the GCP-compliance of the study 411-BK-03-01-000 and a GCP inspection of the CRO and/or the most important centre(s) was deemed appropriate.

Concerning the new studies the applicant has assured that the Indian CRO, BBRC (Bombay Bio-Research Centre) and the additional engaged CRO Spectrum monitored the new Clamp and PK studies BBRC/CLN/08/001 performed at BBRC. The CRO Spectrum, as well as an independent German auditor who reviewed BBRC both concluded that BBRC met the international GCP standards as a part of the selection process of the CRO BBRC.

The German (Berlin based) CRO, CCDRD monitored the new phase III immunogenicity study 411-MA-08-01-0000 with frequent site auditing.

However, a summary report of the study site auditing for the new studies conducted in BBRC and CCDRD has not been presented and should be submitted subsequently.

An inspection in February 2010 on behalf of the MHRA regarding four other clinical trials conducted in 2007 and 2008 at the study site Bombay Bio-Research Centre (BBRC) pointed at serious concerns about the integrity of data generated by this facility, especially concerning data processing and data management. There were also inspections on behalf of the WHO before 2010 which revealed findings but details are not available.

The new study BBRC/CLN/08/001 in this current application was performed between June 2008 and October 2008 at the same study site. Several issues have been identified in the study reports of these studies including statistical errors, unclear calculations (statistical analysis plan has not been provided) and inconsistent or missing information. A new GCP inspection of this Indian CRO is deemed necessary.

2.5. Type of application and other comments on the submitted dossier

- *Biosimilar application*

This Marketing Authorisation Application (MAA) concerns a Centralised Procedure according to Regulation (EC) No 726/2004, Mandatory Scope (Article 3(1)), Annex 1 (Biotech medicinal product).

This application submitted by the company Marvel LifeSciences Ltd concerns the following recombinant human insulin formulation:

- Isomarv medium 100 IU/ml, insulin suspension for injection in a cartridge (Isophane)

This application is being made on the basis of Article 10(4) similar biological application of Directive 2001/83/EC. Comparability is being claimed with Eli Lilly and Company Ltd (UK) Humulin I.

The structure of the submitted dossier is generally acceptable. However, frequent inaccuracies and calculation errors could be found in the statistical analyses which raise concerns about the validity of the submitted data. In addition, the original study protocols, statistical reports and the bioanalytical validation reports of the newly conducted BBRC studies have not been submitted.

3. SCIENTIFIC OVERVIEW AND DISCUSSION

3.1. Introduction

This MAA is a re-submission of Marvel Lifesciences Ltds application for Isomarv medium which is an intermediate acting insulin preparation containing a recombinant human insulin as active substance. The first application has been withdrawn in 2007.

Isomarv (100 IU/ml Suspension for Injection (Isophane)) is an intermediate acting insulin preparation, for use in the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis. The clinical route of administration is sub-cutaneous.

This is a Centralised Procedure (according to Regulation EC No 726/2004, Annex (point 1, Biotech Medicinal Product). The legal basis for this application is a similar biological application (Directive 2001/83/EC as amended, Article 10(4)). The reference medicinal product, which is authorised in the EU, is Humulin I 100 IU/ml suspension for injection. The MAH for Humulin I is Eli Lilly and Co Ltd and the reference product was first authorised in the UK on 16 February 1987 (Humulin I vials) and on 23 November 1990 (Humulin I cartridges). The applicant claims physico-chemical and biological comparability with the reference product and has provided results of an abbreviated pre-clinical and clinical programme comparing Isomarv with the reference product.

Isomarv is a sterile suspension for injection. 1.0 ml contains 100 IU human insulin produced in *E.coli* by recombinant DNA technology. The product is presented in glass cartridges equipped with a moveable rubber plunger and closed with an aluminium capped rubber disc (nominal volume 3ml). The cartridge also contains a glass bead to enable mixing of the suspension. The cartridge is intended to be used with a re-usable pen device to be comparable to the reference product, Lilly's Isophane Insulin Injection.

The name given to the product is Isomarv medium 100 IU/ml, Insulin suspension for injection in a cartridge (Isophane). The product is referred to as Isophane Insulin Injection, 100 IU/ml in the dossier.

3.2. Quality aspects

Drug Substance

Manufacturing process

The manufacturing process consists of fermentation, harvest and purification steps.

A vial from the WCB stock is used for the inoculation of a culture broth, which is then used to yield a seed culture. This culture is used as inoculum for the production fermentor. In the production fermentor biomass is produced by means of a fed batch process. The expression of the recombinant insulin precursor is induced by controlling the glucose concentration. The cells are harvested. The insulin precursor, which is present in the form of inclusion bodies, is isolated, followed by disruption of

the cell walls. The inclusion body slurry is dissolved. After refolding, the primary precursor is enzymatically digested to form a secondary precursor followed by several chromatographic separations, enzymatic digestion and precipitations steps. Finally, the recombinant human insulin is crystallized.

Manufacturing process controls and the respective acceptance criteria and acceptance ranges have been provided. Batch size or scale has been defined but is inconsistent. It is documented that reprocessing is performed. However, reprocessing should be unambiguously justified by data, or removed from the dossier. This is brought out as a Major Objection. For each step of reprocessing the requirements should be established that dictates whether a reprocessing shall be performed or not. The extent (i.e. number of cycles) of reprocessing that is allowed, should be established and documented. The claim of the company to reprocess batches that does not fulfil the in process specification would indicate that the process is not under control and this cannot be accepted.

Control of Materials

Control of materials mainly relies on vendor's certificate of analysis and is limited to identification testing and testing of particular quality attributes for selected raw materials. For some raw materials certificates of analysis are provided. For all biological materials the applicant includes the option of "change of source or supplier". Therefore it has to be demonstrated, that similar biological activity of the material is ensured. Suitable specifications have to be established to ensure adequate quality of these materials, which must also comprise viral safety requirements. Process validation data should be provided to substantiate that there is no impact on drug substance quality. Due to viral safety issues the applicant should consider to completely switch to the use of recombinant materials which are currently only intended to be used as an alternative to materials of animal origin (Major Objection).

Construction of the insulin expression plasmid has been described in satisfactory detail. Adequate information is provided for the generation of the producer cell, the master cell bank (MCB) and subsequently the working cell bank (WCB). For testing of MCB and WCB satisfactory results were achieved. The stability of cells is further verified by analysis of end of production-cells. The Company has adequately described the preparation of a future WCB.

Process controls and Intermediates

The applicant presents some critical parameters of the fermentation and the purification manufacturing process as well as investigational results from which the respective acceptable ranges of the critical parameters have been deduced. However, the rationale used for identification of critical steps and the definition of critical process parameters covering the entire manufacturing process needs further clarification.

Stability of the intermediate has been studied and results indicate that the inclusion bodies are stable at the recommended storage temperature.

Process validation

Validation data for the fermentation process has been presented using three validation batches and presenting data of additional batches manufactured according to the proposed manufacturing process. Validation data for the purification process focus on the presentation of performance of few distinct manufacturing steps only. Only a few acceptance criteria have been reported and due to the lack of acceptance criteria for the process parameters presented, the discussion of the results is of limited value. The average release data leads to the conclusion that the drug substance complies with the proposed release specification. However, validation of the manufacturing process cannot rely on compliance with the release specification alone. Consequently reproducibility and robustness of the proposed manufacturing process is not considered demonstrated. This constitutes a Major Objection.

Since a number of hold steps has been identified in the proposed manufacturing process, information should be provided on validation of hold time. The proposed hold times should be justified by providing appropriate stability studies. The defined maximum lifetime of the several resin materials used in the manufacturing process should also be justified by data.

Drug Substance Characterisation

Characterisation studies were performed. The primary, secondary and tertiary structure of insulin was studied in comparison to the Ph.Eur. CRS, the USP reference material and an in-house standard. By using a variety of adequate methods the correct amino acid composition and sequence, a similar distribution of the secondary structures, an accurate molecular mass for the intact protein as well as for the two chains A and B and an accurate secondary and tertiary structure was confirmed for the recombinant biosimilar insulin . The isoelectric point was determined.

No impurities of different size (e.g. aggregates) could be detected in the insulin samples when tested by SDS-PAGE under reducing conditions. Analysing the same samples by use of SEC combined with DLS detection resulted in a distinct peak of aggregates.

No forced degradation studies were performed in order to examine the impact of degradation on the impurity profile of biosimilar insulin However, by using a modified RP-HPLC method a detailed impurity profile of biosimilar insulin could be obtained including product related substances. It is considered essential to control the product related impurities specific for biosimilar insulin through individual specification limits and using an adequate analytical method. This is reflected in a Major Objection.

Limited data for removal of the potential cell substrate derived impurities, such as endotoxins, host cell proteins and host cell DNA are provided for three batches and show removal to values below the detection limits. Control of endotoxins and host cell protein is implemented in the DS specification with acceptable limits.

The maximum amount of ethanol in the final product is specified in line with the legal requirements. Some process-related impurities were found in the drug substance. For these impurities either consistent removal by the proposed manufacturing process should be demonstrated or acceptance criteria included in the drug substance specification.

Specification

The specification is based on the Ph Eur requirements and lacks justification of the acceptance criteria in terms of manufacturing experience and levels used in the clinical trials and the comparability exercise which is a requirement of ICH Q6B and ”Guideline on similar biological medicinal products containing Biotechnology-derived proteins as active substance: quality issues (EMEA/CHMP/BWP/49348/2005). However, control of drug substance in compliance with the Ph Eur Monograph is not considered sufficient. This is particularly true with respect to control of the impurity profile of the rec human insulin Since the Ph Eur method for related substances is not suitable to separate these specific impurities, an alternative analytical method has to be used. Product-related impurities specific for the manufacturing process should be specified with a reasonable acceptance limit and using an appropriate analytical method. This constitutes a Major Objection. In addition it is not clear from the specification provided whether the tests are performed in accordance with the Ph Eur as no references are made. Method descriptions and validations should be submitted where Ph Eur methods are not used.

Although there is a long history of manufacture of the drug substance, batch data from only three drug substance batches are presented for justification of specification. This is far too limited and not considered sufficient to support the specification. A number of acceptance limits has been set by simply using the respective limits as defined in the Ph Eur monograph. Each acceptance criterion should be

established and justified based on data obtained from batches used in non-clinical and/or clinical studies, and by data from lots used for the demonstration of manufacturing consistency, data from stability studies and any other relevant development data. For some parameters the justification has only included a narrative reference to the robust manufacturing process. This is not acceptable. For justification of specification, in particular for product-related impurities specific for the manufacturing process, a statistical evaluation of relevant historical batches should be provided.

The information provided for the Ph Eur reference standard is considered inadequate. There is no information for any in-house reference standard compared against the Ph Eur standard, nor any characterisation of any in-house reference standard.

Stability

The applicant proposes a defined retest period when stored at -20°C. In accordance with the requirements of the Ph Eur monograph light sensitivity of the drug substance should be considered when storing the drug substance. Since retest periods are not allowed for biological active substances, a shelf life should be established. Before a final assessment of the proposed storage period the applicant should clarify which packaging material and package sizes will be used for the production.

Biosimilarity to the reference product

Comparability exercises were performed including drug substance from batches of biosimilar material and batches of the Eli Lilly reference product material which has been extracted from products obtained on the market. The structural comparability of the biosimilar insulin and the reference product was studied by applying numerous analytical state-of-the-art methods, such as NMR, Dynamic Light Scattering (DLS), IEF, SDS PAGE, Fluorescence spectroscopy, far and near UV, peptide mapping with UPLC-UV and UPLC-MS (ESI-Q). Comparable primary, secondary and tertiary structure could be demonstrated and identical molecular masses and size distributions were obtained. Identification and Assay by HPLC (as per Ph Eur), HMWP (SE-HPLC), related proteins (HPLC as per Ph Eur), total zinc, m-cresol content have been analysed Although all results met the acceptance criteria of the monograph quantitative differences between the two products are apparent. Particularly, the content of zinc is significantly higher in the reference product when compared with the biosimilar insulin. As the zinc content may have an impact on the formation of the isophane crystals and in consequence on the clinical performance this difference should be considered in the evaluation of the clinical studies.

Although the comparison of the impurity profiles is based on limited data only, the biosimilar product is assumed to have a consistent higher amount of impurities. Due to the limited data available, it cannot be finally concluded whether the quantitative differences are significant. The total amount of impurities is still below the pharmacopoeial acceptance limit of total <2% when applying the RP-HPLC method as described by the monograph. However, the compendial method is not suitable to separate all relevant impurities from the main and further comparative data covering the entire impurity profile by using a modified RP-HPLC method are not presented. However, further studies are considered necessary to characterise especially the impurity profile of the drug product and to identify the product-related substances by using appropriate analytical techniques.

In order to demonstrate comparable degradation profiles, forced degradation studies are considered necessary in addition to the accelerated stability studies.

As the panel of analytical methods used is more or less limited to Ph .Eur. methods, the comparability studies should be extended. State of the art methods not included in the Ph. Eur. monograph allowing in depth analysis should be used, such as DSC or Mass spectrometry investigation.

In summary, for the drug substance substantial structural similarity between the biosimilar insulin and the reference product is suggested, but the qualitative and quantitative impurity profile of the

biosimilar insulin is not identical to the reference product. In particular it has to be considered that the compendial method is not suitable to separate all relevant impurities from the main. Due to the limited data available, a final conclusion on comparability cannot be drawn prior to an assessment of data/information requested by the LoQ.

Drug Product

Isomarv medium is a sterile suspension for injection containing 100 IU human insulin/mL. The formulation contains m-cresol, phenol, glycerol, protamine sulphate, zinc oxide, disodium hydrogen phosphate, hydrochloric acid and water for injections as excipients. Protamine sulphate acts as complexing agent in the presence of zinc and phenol and m-cresol leading to the formation of insulin protamine crystals resulting in a prolonged action of insulin.

The drug product is presented in 3 mL glass cartridges closed with aluminium capped rubber disks and equipped with moveable rubber plungers. Each cartridge contains a glass bead to enable mixing of the suspension. The drug product will be administered by the patient after incorporating the cartridge into a re-usable pen purchased on the market. The vendor and the brand name of a potential device are mentioned in the SPC. However, further information on this medical device is not presented. Issues remain in relation to the suitability of the pen device. A copy of the certification (CE), the indication of suitable needles for the pen system and considerations on how to prevent mix-up of different insulin preparations are missing.

Manufacture

The manufacturing process consists of dissolving of the ingredients, mixing, pH adjustment, filtration and filling (including cartridge assembly, sealing and labeling) of the drug product. The procedures are conventional for this type of formulations.

The manufacturing process has been adequately described. A flow chart is presented. Critical steps of the manufacturing process have been addressed.

The in-process controls of each step have been described and respective test and acceptance criteria have been given. However, the control of the formation of the insulin-protamine crystals is currently missing and should be included. Furthermore, although the isophane coefficient for each batch of protamine sulphate is routinely determined by use of a tritrimetric method the respective IPC is missing. In addition, information on holding times should be provided (e.g. holding time from the end of sterile filtration until the beginning of the filling process should be indicated) and should be validated or supported by media fills.

Process validation has been provided based on data of three validation batches. The three consecutive validation batches comply with the predefined in-process control acceptance criteria and the proposed release specification. One other concern deals with the action performed if IPC limits are not met.

Excipients

Most of the excipients are compendial and comply with Ph Eur. However, the quality of the water for injections needs to be confirmed. Due to the heterogeneous nature of protamine sulphate a consistent quality should be ensured for future batches and results from a number of batches showing that ingredients consistently meet the requirements should be provided. In addition the applicant is requested to perform an extended physicochemical characterisation and based on the outcome of this, update the control of protamine sulphate as appropriate.

Control of Drug product

The drug product release and shelf-life specifications are mainly based on the Ph Eur monograph which is not considered to be in line with the requirements of ICH Q6B and the ”Guideline on similar biological medicinal products containing Biotechnology-derived proteins as active substance: quality issues” (EMEA/CHMP/BWP/49348/2005). The proposed acceptance criteria for the drug product specification should be established and justified based on analytical data obtained from batches used in non-clinical and/or clinical studies and data obtained from the biosimilar comparability exercise (quality, safety and efficacy). Taken this into account and given the results of batch data, results from stability and comparability studies, the proposed specification raises concerns. Tightening the limits, in particular of the insulin impurities is considered essential and this is being raised as a Major Objection.

The analytical methods have in general been adequately described. Validation of the analytical methods has been provided for m-cresol and zinc.

Analytical batch data have been provided for full scale production batches. The results demonstrate compliance with the specification at the time. The production scale batches have been used in clinical studies, stability studies, validation studies, toxicity studies and comparability studies

Stability

A defined shelf life at 2-8 °C is claimed and a proposed in-use shelf life at 25°C. However, in the SmPC it is stated that the cartridges should not be stored above 30°C when “in use”. This recommendation is not in accordance to the testing conditions of the in use stability studies. Prior to a final agreement the results of the ongoing stability studies should be provided and the issue on the storage instructions in the SmPC should be resolved.

Biosimilarity to the reference product

A comparability study has been provided for the finished product with the reference product. This includes biosimilarity exercises in relation to formulation, presentation, specification and quality comparison side-by-side with Humulin I.
The panel of analytical methods used is more or less limited to Ph Eur methods and this is not considered sufficient. With regard to the quantitative and qualitative impurity profile further studies, using state of the art technologies, are needed. Due to the limited data available, a final conclusion on comparability cannot be drawn prior to an assessment of data/information requested in the List of Questions. However, the available data indicate that Isomarv is slightly less pure compared to the reference product although still well within the Ph Eur limits. The possible impact of the differences seen has not been commented upon by the Company. In conclusion, there is insufficient data to evaluate biosimilarity with the reference products.

Further comparison of the biological activity of the Marvel and Eli Lilly products is considered essential prior to the assessment of comparability. An appropriate specific cell-based assay should be used for the comparative determination of the biological activity.

The impurity profile of the drug substance and drug product should be further investigated and comparability with the reference product discussed. In addition, it should be demonstrated that the batches used to evaluate comparability is representative of the intended commercial drug substance and product.

Viral safety

Several materials of biological origin are routinely used in the purification process for production of the drug substance. Measures to control viral safety of the animal derived materials are at present not considered adequate.

Conclusions on the chemical, pharmaceutical and biological aspects

Five major objections have been identified which currently preclude a Marketing authorisation. A major objection has been raised with respect to reprocessing of the manufacturing process. Appropriate validation of the drug substance manufacturing process has not been presented since only limited validation data, not covering all process steps, has been provided. Therefore similar biological activity of the materials should be ensured. The drug substance and the drug product specifications are compliant with the requirements of the Ph Eur monograph but this is not considered sufficient with respect to control of the specific impurity profile of the rec human insulin.

In conclusion, based on the review of the data on quality, the CHMP considers that the Marketing Authorisation Applications for Isomarv medium is currently not approvable since several major objections and a high number of other concerns have been identified.

3.3. Non clinical aspects

Pharmacology

In vitro PD studies

Evaluation of the primary pharmacodynamics of Marvels soluble insulin in comparison to reference insulin from Eli Lilly was performed in seven *in vitro* assays. Four studies (MarvelreportAug05) were already submitted in the 2007 application. In these studies, binding to the insulin receptor and the cellular response to insulin-receptor binding (phosphorylation of the insulin receptor and several signal transducers and glucose uptake) were investigated which all can be regarded as indicators of intrinsic activity. Table 1 gives an overview of the previously performed *in vitro* PD studies (MarvelreportAug05).

Table 1: Overview of previously performed PD in vitro studies.

Study Number	Study Type	Test System	Pharmacokinetics Active / IC_{50} (ng / ml)	Pharmacodynamic
MarvelreportAug05	Ligand displacement	CHO-T Cell	IC_{50} = 10^{-10} M	Receptor binding affinity
MarvelreportAug05	Phosphorylation	CHO-T Cell	Active conc. 0.01 ng/ml Half maximal 1 ng/ml (172 pmol/l)	Insulin stimulated tyrosine phosphorylation in insulin receptor beta subunit and IRS protein
MarvelreportAug05	Kinase activation	CHO-T Cell	0.01 - 0.1 ng/ml	Akt, GSK3α, -ß, MAP-kinase activation
MarvelreportAug05	^{3}H-2-Deoxyglucose uptake	3T3-L1 adipocyte	Dose dependency from 0.01 to 10 nM IC_{50} = 0.1~1 nM	Insulin-stimulated glucose uptake

Concentration-response curves were provided for insulin receptor binding, phosphorylation of the insulin receptor, AKT, GSK3 and MAP kinase, and for insulin-stimulated glucose uptake in 3T3-L1 adipocytes. For all experiments Marvel soluble insulin produced a similar dose-response profile as the

reference product. Results of these studies have only been provided in duplicate, and in part raw data are lacking in the study report which does not allow a statistical analysis. The Western blot experiments can only been seen as supportive (see discussion on non-clinical aspects for details).

In the 2007 application there was a lack of experiments on the affinity of Marvels soluble insulin on binding to the IGF-1 receptor and tests on intrinsic activity.

To address the issue concerning the IGF-1 receptor in this application three further *in vitro* pharmacodynamic studies have been provided (Marvelreport2008v2) comparing Marvel soluble insulin and Eli Lilly insulin (Humulin S, EU-sourced) including assays for a competitive IGF-1 receptor binding study, a receptor autophosphorylation study and a ligand-stimulated DNA synthesis study. The experiments were performed under the same supervision of Prof. T.S. Pillay as in MarvelreportAug05 in a GLP conform laboratory in Cape Town, South Africa. Table 2 gives an overview of the additionally performed *in vitro* studies and the results:

Table 2: Overview of additionally performed PD in vitro studies.

Study Number	Study Type	Test System	Pharmacokinetics Active / IC_{50} (ng/ml)	Pharmacodynamic
Marvelreport2008v2	Competitive binding study	NIH-3T3	Similar between T and R when tested from 10^{-11} to 10^{-5} M	Binding affinity
Marvelreport2008v2	Receptor autophosphorylation	NIH-3T3	Similar between T and R when tested from 10^{-11} to 10^{-6} M	IGF-1 receptor tyrosine phosphorylation
Marvelreport2008v2	Ligand-stimulated DNA synthesis	Human fibroblast	Similar between T and R when tested from 10^{-11} to 10^{-6} M	Ligand-stimulated DNA synthesis using radiolabelled ^{3}H-thymidine

In general, all studies show a good similarity of Marvel soluble insulin and Humulin S throughout all assays and are considered to be adequate. Concerning Western blot experiments (IGF-1 receptor phosphorylation) the same applies as stated above and therefore these experiments can only be seen as supportive. No raw data have been provided in the study reports of all experiments (densitometric values, immunoblots, and scintillation counts; see discussion on non-clinical aspects for details).

In vivo PD studies

In accordance with the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005) no *in vivo* pharmacodynamic or pharmacokinetic studies are necessary. Nevertheless, one *in vivo* pharmacodynamic study to compare Marvel insulin with Humulin insulin preparations (short, mixed and long, all EU-sourced) against a standard of human insulin from the US Pharmacopoeia was conducted in mice in compliance with the procedure “Biological trials of insulin. Method C” (British Pharmacopoeia 1988). The primary pharmacodynamic parameter assessed in this study was glycaemic control; forty minutes after injection blood samples were taken and plasma glucose levels were determined. Standard samples (S) and Test preparations (T) of insulin were

prepared in two concentrations, 0.12 IU/ml and 0.36 IU/ml. Doses of 0.3 ml were administered to the mice subcutaneously according to a twin crossover design as illustrated below.

Table 3. Crossover study design (taken from study report).

	Group 1	Group 2	Group 3	Group 4
Day 1	S1	S2	T1	T2
Day 2	T2	T1	S2	S1

No differences were detected when a comparison of received weighted average values of the biological activity (blood glucose lowering effect) of the insulin preparations was made for analogues dosage forms using Pirson's criterion (p=0.95). There is some discrepancy regarding the data presented for this study which the applicant is asked to clarify (see LoQ). In conclusion, the data from this study can be regarded as supportive of biosimilarity of the short acting Marvel and Humulin insulin preparations. The reliability of these results concerning the longer acting insulins is questionable (see discussion on non-clinical aspects).

Another study was conducted in rats to qualify the impurity with glycaemic control being the primary pharmacodynamic parameter investigated. The study is discussed in the section on Impurities.

Additionally, data on serum glucose levels are available from dose range findings studies of three acute subcutaneous toxicity studies in rats and three local tolerance studies in rabbits but are not comparative in nature. The studies are discussed in the respective Toxicology sections.

No data have been provided for studies on Secondary PD, Safety pharmacology and PD drug interactions according to the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005) and is therefore agreed.

Pharmacokinetics

No animal pharmacokinetic studies were performed in support of this application. This is in line with the recommendations of the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005) and is therefore agreed.

Toxicokinetic data are available from a 7-day rat study comparing Marvel insulin with the respective Humulin preparations (see Toxicology section).

Toxicology

Single dose, repeat-dose and local tolerance toxicity studies were performed by JAI Research Foundation (JRF) in Gujarat, India according to GLP. One immunogenicity study, is stated to be GLP conform in the Toxicology Tabulated Summary (2.6.7). However, no information on GLP compliance could be found in the study report (), see discussion on non-clinical aspects for details.

Single dose toxicity and local tolerance studies

Three single dose toxicity studies in rats and three local tolerance studies in rabbits have been provided by the Applicant. These studies were already provided in the 2007 application and were conducted comparing all three preparations, soluble (Biosulin R vs. Humulin S), isophane (Biosulin N vs. Humulin I) and biphasic (Biosulin 30:70 vs. Humulin M3) insulins sourced from the EU. Taken together, it can be concluded that acute toxicity and local tolerance of the test and reference insulin preparations are comparable.

Repeat-dose toxicity studies

Two 28-day repeat-dose toxicity studies (JRF 6207 and JRF 7410) and one separate 7-day TK study (JRF 9543) in rats have been performed. Study JRF 6207 was already submitted in the 2007 application. In this study a non-EU sourced Humulin R preparation was used as reference. Study JRF 7410 addressed this issue using Humulin S obtained from the UK. Antibodies against human insulin or host cell proteins were not determined (see discussion on non-clinical aspects for details). Toxicokinetics were determined in a separate study. This was also agreed upon a scientific advice given by the EMA in 2008 (EMEA/CHMP/SAWP/368924/2008) and is acceptable. The studies were performed with soluble insulin preparations only and not with isophane and biphasic formulations. In the same scientific advice in 2008 mentioned above it was concluded that pharmacokinetic comparison of the reference product for these longer acting and biphasic insulins should be provided, however if available, such information can be acquired from clinical data, this is fully endorsed.

The second repeat-dose toxicity study (JRF 7410) performed by the applicant with EU-sourced Humulin as comparator yielded similar results as study JRF 6207. In general, it can be concluded that Marvel soluble insulin and the respective Humulin insulin preparations showed only slight and similar toxicities in the dose ranges tested (NOAEL = 270 IU/Kg/day). No severe toxicities or other signs of hypoglycaemia even in the high dose were observed. This is attributed to the fact that higher doses in the acute toxicity studies of 500 IU/kg or above caused lethargy and/or mortalities already after a single dose. Consequently, lower doses were anticipated for the repeat-dose studies with 270 IU/kg/day being the highest dose. This is acceptable.

The 7-day rat TK study was conducted separately by the same laboratory (JRF) comparing soluble Marvel insulins with Eli Lilly insulins (Humulin S, EU-sourced). In conclusion, the kinetics of test substance and the reference substance are comparable with each other, showing nearly similar TK parameters without any biologically significant difference under conditions and procedures followed in the present study. The results can be considered as supportive to state biosimilarity between the two preparations of fast acting insulins.

Immunotoxicity

The occurrences of antibodies against human insulin or host cell proteins were not determined in the pivotal 28-day rat repeat-dose toxicity studies as claimed by the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005). In a scientific advice given by the EMA in 2008 (EMEA/CHMP/SAWP/368924/2008) it was concluded that “immunogenicity can be assessed in a separate study if the animal species and the level of impurities (insulin-related and non-insulin-related) are similar to the species and level used in the pivotal toxicity study. If comprehensive clinical data are available, additional non-clinical studies can be waived.” At the time point of submission clinical data were available but left the possibility that Marvel insulin is more immunogenic than the comparator. Hence, animal data could be useful to address differences in immunogenicity further. Although human insulin is a foreign protein for rodents and thereby will cause a stronger immune response in these

species than in humans, any differences in the intensity of the immune response could hint to additional immunogenic components in the Marvel insulin.

There is one impurity, The possibility exists that this impurity might lead to increased immunogenicity.

The applicant tried to address this issue by conducting an immunogenicity study by directly comparing biosimilar insulin with the impurity).

Immunization with biosimilar insulin or the impurityalone did not cause a measurable antibody response against the antigens tested. In conclusion, under these experimental conditions antibody titres of biosimilar insulin and the impurity were comparable, however the discriminatory nature of the assay has not been shown by the applicant, furthermore, no data sheets/certificates of analysis of the used batches were provided in the study report. The contents of the impurities and biosimilar insulin used is not stated (see discussion on non-clinical aspects for details).

Studies on impurities

In an additional study on impurities -the impurity and the biosmilar insulin were compared. In general, insulin and the impurity show similar effects with a dose-dependent response. No information about the two insulin preparations like certificates of analysis, raw data and statistical analysis have been provided in the study report making it difficult to completely assess the study. However, the CHMP is of the opinion that the overall influence, if any, of the impurity, is minor and can be neglected.

No data have been provided for studies on Genotoxicity, Carcinogenicity and Reproductive and developmental toxicology according to the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005)and is therefore agreed.

Ecotoxicity / environmental risk assessment

Recombinant human insulin is a naturally occurring protein and is rapidly degraded in the body with a half-life in plasma of about 5-6 minutes. As insulin is a protein, it will denature and be inactivated when not maintained in a suitable environment. Therefore, it will not present an environmental risk factor. The absence of an environmental risk assessment is endorsed and is in line with Guideline since proteins and peptides are included in compounds that are stated to be exempted from the requirement of an ERA.

Discussion on non-clinical aspects

Pharmacology

Experiments in MarvelreportAug05, which was already submitted in the 2007 application, have been performed in duplicate only which does not allow a statistical analysis of the results and hence none is provided. The time point chosen to show insulin-stimulated receptor and kinase phosphorylation was 5 minutes. The rationale to choose 5 minutes was not explained by the applicant. It is clear to the CHMP and shown in the literature that at 5 minutes a strong phosphorylation of the insulin receptor and its downstream targets takes place. However, it would have been of interest to see also other time points e.g. at 15, 30 and 60 minutes to claim comparability over a longer time of exposure mimicking an *in vivo* situation more realistically. In general, analysis of Western blots by densitometry seems not to be the appropriate method to get reliable quantitative results. Already slight overexposures of the blots can lead to great variations of the densitometric results. In this context the CHMP also considers important, if densitometric analysis is performed, that at least values are normalized to the

unphosphorylated protein (e.g. phosphorylated Akt vs. unphosphorylated Akt) and/or a housekeeping gene to exclude differences in loading and blotting of the gel/membrane. The provided Ponceau Red staining can only serve as additional qualitative proof but not as a quantitative parameter itself. In conclusion, the Western blot experiments can only be seen as supportive. The insulin receptor binding assay and the glucose uptake assay are quantitative measures and are suitable assays covering the requirements of the guideline. However, these experiments have only been conducted in duplicate and results are only displayed as relative values as percentage of maximal. No absolute values (raw data) could be found in the study report. From the provided data differences in maximum responses cannot be judged. To claim biological activity and comparability of the two insulins the applicant should provide the fluorescence intensity values of the insulin receptor affinity assay and scintillation counts for the glucose uptake assay (see LoQ).

In the additional performed three *in vitro* studies of Marvelreport2008v2 a good similarity of Marvel soluble insulin and Humulin S throughout all assays was shown and they are considered to be adequate. However, concerning Western blot experiments (IGF-1 receptor phosphorylation) the same applies as stated above and therefore these experiments can only be seen as supportive. Additionally, the raw data (densitometric values, immunoblots, and scintillation counts) of all experiments should be provided (see LoQ).

Comparative *in vivo* studies would not be anticipated to be sensitive enough to detect any non-equivalence not identified by *in vitro* assays, and are normally not required as part of the comparability exercise. Nevertheless, one *in vivo* study in mice was performed to show the biological activity of various dosage forms (Marvel insulin preparations and Humulin insulin preparations, EU-sourced) as consistent with the requirements of British Pharmacopoeia (1988). In conclusion, the data from this study can be seen as supportive of biosimilarity of the short acting Marvel and Humulin insulin preparations. The reliability of these results concerning the longer acting insulins is questionable. Blood glucose levels were determined forty minutes after injection of all three formulations. It is unlikely that sufficient blood glucose lowering can be detected after injection of the mixed and long acting insulins after forty minutes only. In the study report no raw data on blood glucose levels are presented, making it impossible to judge and compare the blood glucose lowering effect of the different insulin preparations. There is also some discrepancy regarding the data presented for this study which the applicant is asked to clarify (see LoQ). In addition, the standard short acting insulin of the US Pharmacopoeia is also used to compare the long acting insulins, no long acting insulin preparations were used as standards. Although this is a clear shortcoming, it does not influence the general conclusions on the product.

Toxicology

No concerns arise from the single dose, repeat-dose, and local tolerance toxicity studies. The toxicokinetic profile of Marvel soluble insulin and Humulin S appears to be similar in the dose range tested and are supportive to state biosimilarity between the two preparations of fast acting insulins.

However, the occurrence of antibodies against human insulin or host cell proteins were not determined in the pivotal repeat-dose toxicity studies as claimed by the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005). In a scientific advice given by the EMA in 2008 (EMEA/CHMP/SAWP/368924/2008) it was concluded that “immunogenicity can be assessed in a separate study if the animal species and the level of impurities (insulin-related and non-insulin-related) are similar to the species and level used in the pivotal toxicity study. If comprehensive clinical data are available, additional non-clinical studies can be waived.” In a clinical program some adverse events suspicious for hypersensitivity reactions were observed, predominantly in the Marvel insulin groups.

These impurities are a unique feature of Marvel insulin what can be explained by a different production process. The possibility exists that this impurity might lead to increased immunogenicity. The applicant specifically addressed the immunogenicity of the impurity by conducting an immunogenicity study where biosimilar insulin was directly compared to this impurity. It is not clear or shown that this assay is discriminatory (and validated) and is able to detect differences in antibody levels. Furthermore, as human insulin is an antigen in animal species antibody production will be strong anyway and a detection of differences between insulin and the impurity is difficult. Nevertheless, if differences become obvious in a mouse/rat study such as significantly increased antibody titres in the Marvel insulin group for instance, this can be of value for the interpretation of clinical outcomes. In view of the potential hypersensitivity reactions observed in the Marvel insulin groups it would be desirable to have data on insulin antibodies in blood samples from the 28-day rat repeat-dose toxicity study (preferably from study JRF 7410 were a batch containing the impurity was used or alternatively from the TK study JRF 9543) to clarify possible influence of the impurity (or other impurities) on the immune system (see LoQ). The immunogenicity study, which was performed is stated to be GLP conform by the Applicant. However, no information on GLP compliance could be found in the study report. In addition, no data sheets/certificates of analysis of the used batches were provided in the study report. . Parts of the study report are confusing; the applicant should comment and provide the missing information on certificates of analysis and GLP compliance (see LoQ).

Conclusion on non-clinical aspects

Taken together, pharmacodynamic studies have shown a good similarity between Marvel soluble insulin and the Humulin reference insulin products. However, to claim comparability of the test and reference product, it is deemed necessary to provide raw data of all studies submitted (see LoQ).

The provided immunogenicity study addressing this issue is not considered to be appropriate to show differences in antibody production between insulin and the impurity. In view of the potential hypersensitivity reactions in the clinical trials it is deemed necessary to address immunogenicity of Marvel insulin further. Therefore, if available, insulin antibody levels in the blood samples from the 28-day rat repeat-dose toxicity study should be provided and/or their absence should be justified (see LoQ).

In general, in many parts of the Non-clinical Overview and the Pharmacology and Toxicology Written Summaries minor (copy-paste) mistakes were detected. Also in the above mentioned immunogenicity study parts of the study report are confusing and no data sheets/certificates of analysis of the used batches was provided and GLP compliance was not stated in the study report (see LoQ).

3.4. Clinical aspects

Tabular overview of clinical studies

The following table shows a summary of all conducted old and new clinical studies:

Table 2.7.6- 1 Listing of Clinical Studies

Type of study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK/PD	FARMOVS 232/2002		To compare the PK (AUC, C_{max}) and PD ($AUC_{0\text{-end of clamp}}$ of GIR) of Marvel's soluble rh-insulin vs. Humulin S®, using the manual euglycaemic clamp technique.	Single centre, single-dose, randomised, open, crossover, active control	Marvel's soluble recombinant human insulin (rh-insulin), 100 IU/mL (vs. Humulin S®); s.c. single 0.2 IU/kg dose of rh-insulin per treatment period	24	Healthy male, adult volunteers	Single dose	Complete; Full
PK/PD	FARMOVS 439/2002		To compare the PK (AUC, C_{max}) and PD ($AUC_{0\text{-end of clamp}}$ of GIR) of Marvel's biphasic (30/70%) rh-insulin vs. Humulin biphasic (30/70%)®, using the manual euglycaemic clamp technique.	Single centre, single-dose, randomised, open, crossover, active control	Marvel's biphasic (30% soluble/70 % isophane) rh-insulin, 100 IU/mL [vs. Humulin biphasic (30/70%)®]; s.c. single 0.2 IU/kg dose of rh-insulin per treatment period	24	Healthy male, adult volunteers	Single dose	Complete; Full
PK/PD	FARMOVS 21/2003		To compare the PK (AUC, C_{max}) and PD ($AUC_{0\text{-end of clamp}}$ of GIR) of Marvel's isophane rh-insulin vs. Humulin I®, using the manual euglycaemic clamp technique.	Single centre, single-dose, randomised, open, crossover, active control	Marvel's isophane rh-insulin, 100 IU/mL (vs. Humulin I®); s.c. single 0.2 IU/kg dose of rh insulin per treatment period	24	Healthy male, adult volunteers	Single dose	Complete; Full
PK/PD	BBRC/ CLN/07/001		To compare the PK (AUC, C_{max}) and PD ($AUC_{0\text{-end of clamp}}$ of GIR and GIR_{max}) of Marvel's soluble rh-insulin vs. Humulin S®, using the manual euglycaemic clamp technique in Indian T1D patients.	Single-centre single-dose, randomised, double-blind, crossover, active control	Marvel's soluble rh-insulin, 100 IU/mL (vs. Humulin S®); s.c. single 0.2 IU/kg dose of rh-insulin per treatment period	22	Type I diabetic (T1D) adult Indian male and non-pregnant female patients	Two single doses each (1 for PD, 1 for PK)	Complete; Full
PK/PD	BBRC/		To compare the PK (AUC,	Single-centre	Marvel's isophane rh-	48	T1D adult Indian	Two single	Complete;

Type of study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
	CLN/08/001		C_{max}) and PD ($AUC_{0\text{-end of clamp}}$ of GIR and GIR_{max}) of Marvel's isophane rh-insulin and Humulin I®, using the euglycaemic clamp technique. In Indian T1D patients.	single-dose, randomised, double-blind, crossover, active control	insulin, 100 IU/mL (vs. Humulin I®); s.c. single 0.2 IU/kg dose of rh insulin per treatment period		male and non-pregnant female patients	doses each (1 for PD, 1 for PK)	Full
PK/PD	BBRC/ CLN/08/002		To compare the PK (AUC, C_{max}) and PD ($AUC_{0\text{-end of clamp}}$ of GIR and GIR_{max}) of Marvel's biphasic rh-insulin vs. Humulin biphasic (30/70%)® in Indian T1D patients.	Single-centre single-dose, randomised, double-blind, crossover, active control	Marvel's biphasic (30% soluble/70% isophane) rh-insulin, 100 IU/mL [vs. Humulin biphasic (30/70%)®]; s.c. single 0.2 IU/kg dose of rh-insulin per treatment period	48	T1D adult Indian male and non-pregnant female patients	Two single doses each (1 for PD, 1 for PK)	Complete; Full
Efficacy &Safety	411-BK-03-01-0000		To prove the equivalence of a test formulation containing rh-insulin to a reference product of the same type (Humulin®) for the treatment of diabetes.	Multicentre (N=27, Europe), randomised, double-blind, parallel group, active control	Marvel recombinant human insulin, 100 IU/mL, s.c. for free combination of regular and NPH insulin or fixed combination of 70% NPH insulin plus 30% regular insulin.	Enrolled: 243 T1D (123 test, 120 ref); 283 T2D (142 test, 141 ref).	Adult male and female patients with type 1 (T1D) or type 2 diabetes mellitus (T2D)	24 weeks	Complete; Full
Efficacy &Safety	411-BK-03-01-0001		Follow-up period to study 411-BK-03-01-0000 to investigate the potential for immunogenicity (antibodies) of the test insulin only and the impact of antibodies on PK/PD and safety	Multicentre (N=24, Europe), open follow-up period, uncontrolled	Marvel rh-insulin, 100 IU/ml, s.c. for free combination of regular and NPH insulin or fixed combination of 70% NPH insulin plus 30% regular insulin.	All treated patients: N=409 T1D: 196 patients. T2D: 213 patients.	Adult male and female patients with T1D or T2D who have completed study 411-BK-03-01-0000	24 weeks	Complete; Full
Safety &Efficacy	411-MA-08-01-0000		To evaluate the incidence of possible newly developed	Multicentre (N~30,	Marvel rh-insulin, 100 IU/ml, s.c. for free	Planned: N=500	Adult male and female patients	28 weeks double	Ongoing; Interim

Type of study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
			insulin antibodies of the test formulation containing rh-insulin vs. a reference product of the same type (Humulin®) up to week 28 and then for 28 weeks treatment with the test product only. To evaluate the clinical relevance of antibodies on insulin dose, glucose control, body weight and safety.	randomised, double-blind, parallel group; active control	combination of regular and NPH insulin or fixed combination of 70% NPH insulin plus 30% regular insulin.	Enrolled: N=478 (244 test, 234 ref);	with T1D or T2D	blind, then 28 weeks open treatment with test drug only	

Clinical pharmacology

The two PK/PD studies FARMOVS 21/2003 and BBRC/CLN/08/001 have been submitted. The following is a summary of these two clinical studies:

<u>Old study FARMOVS 21/2003 (intermediate insulin; healthy subjects):</u>

Title: Comparison of the pharmacodynamics and pharmacokinetics of a recombinant human insulin product with Humulin I, using the euglycaemic clamp technique and a bioequivalence approach.

Design: This was a single centre, single-dose, randomised, open-label, cross-over, glucose clamp trial in healthy male subjects.

Test insulin: Recombinant human insulin (Human Insulin N), Cartridge containing 100 IU/mL human insulin (Human insulin assay according to CoA: 102.0 IU/mL**Reference insulin:** Humulin I, Cartridge containing 100 IU/mL human insulin (Human insulin assay according to CoA: 105.3 IU/mL), Batch Number: FF3J76G, Expiry Date June 2005, Manufacturer: Eli Lilly and Company Limited, UK**Investigator, study site:** Dr Francois Burger, FARMOVS-PAREXEL Clinical Research Organisation, Kampuslaan Suid, Campus of the University of the Free State, 9301 BLOEMFONTEIN, SOUTH AFRICA

Study period: 29 October 2003 to 16 January 2004

Objectives: *<u>Primary</u>*: To compare the $AUC_{(0\text{-end of clamp})}$ of GIR of a recombinant insulin (Marvel LifeSciences Ltd.) and Humulin I (Eli Lilly). *<u>Secondary</u>*: To compare the pharmacodynamics and pharmacokinetics of a recombinant human insulin (Marvel LifeSciences Ltd.) and Humulin I (Eli Lilly). Safety: To assess the safety profile after single doses of recombinant human insulin (Marvel LifeSciences Ltd.), as evaluated by standard safety parameters.

Population: Healthy males between 18 and 55 years of age, minimum body Criteria for inclusion: Weight of 60 kg, BMI between 18 and 28 kg/m2, non-smokers or past-smokers, HbA1c <6.4 %.

Sample size and patient disposition: 31 healthy subjects were screened, 24 male subjects were randomised and all subjects completed the study. Data of subject 22 at 5 h 15 min post-dose RHI was not included in the PK analysis due to abnormally high exogenous insulin and data of the last time-point for subject 24 was excluded from PD analysis due to improper handling of the tap of the glucose infusion at the end of clamp procedure leading to a high blood glucose (TP 2, RHI).

PK evaluation: *Secondary endpoints*: $AUC_{0\text{-end-of-clamp}}$ ($AUC_{0\text{-EoC}}$) of insulin, $AUC_{0\text{-}4}$, $AUC_{0\text{-}8}$ of insulin, C_{max}, t_{max}, $t_{1/2}$, MRT, CL/F and V_Z/F

PD evaluation: *Primary endpoints:* $AUC_{0\text{-end-of-clamp}}$ ($AUC_{0\text{-EoC}}$) of GIR. *Secondary endpoints:* $AUC_{0\text{-}4}$, $AUC_{0\text{-}8}$ of GIR, GIR_{max} and its t_{max}, t_{onset}, earlyt$_{50}$, late t_{50} as well as t_d

Treatments: Each subject received one dose of 0.2 IU/kg recombinant human insulin per trial period; either the reference product (Humulin I) or the test product, after an overnight fast of 10 hours.

Method of administration and sampling: In this manual euglycaemic clamp study each subject received one dose of 0.2 IU/kg recombinant human insulin s.c. through Autopen delivery device per trial period; either the reference product (Humulin I) or the test product, after an overnight fast of 10 hours. Each trial period was separated by a washout period of either 7 or 8 days. After administration of study medication, infusion of a 20% glucose solution was started when the blood glucose fell below 10% of the subject's mean baseline level within 30 minutes after study drug administration or at a decrease of 5% from mean baseline level after 30 minutes. The rate of glucose delivery (20% glucose solution) was adjusted in a feedback manner to maintain the blood glucose level at the volunteer's mean fasting blood glucose level, calculated from the four glucose values before administration.

Blood glucose: Whole blood samples (0.3 mL) for the determination of blood glucose were taken at -60, -30, -15 and 0 minutes before study drug administration and every five minutes up to five hours thereafter. From five hours until the end of the clamp period, blood glucose samples were taken every 10 minutes. If it was not possible to obtain a sample for the determination of blood glucose on the exact protocol time due to clotting of a cannula or something similar (missing sample), this event was not documented as a deviation. A maximum of 45 mL of blood was collected per trial period.

Serum insulin and C-peptide: Venous blood (4 mL) was scheduled to be collected at -60, -30, -15 minutes before dosing, and at 1 h, 2 h, 2 h 30 min, 3 h, 3 h 15 min, 3 h 30 min, 3 h 45 min, 4 h, 4 h 15 min, 4 h 30 min, 4 h 45 min, 5 h, 5 h 15 min, 5 h 30 min, 5 h 45 min, 6 h, 6 h 15 min, 6 h 30 min, 6 h 45 min, 7, 8, 9, 10, 11, 12, 14, 16 and 24 h post-dosing. However, the last sample was drawn at the end of the clamp procedure regardless of the scheduled protocol time. The maximum clamp duration was 19 h 20 min. A maximum of 124 mL of blood for serum insulin and 62 mL for serum C-peptide was collected per trial period.

New study BBRC/CLN/08/001 (intermediate acting insulin; T1D patients):

Title: Comparison of the Pharmacodynamics and Pharmacokinetics of Marvel LifeSciences Ltd.'s Isophane Test Insulin, With Reference Product Humulin I (Isophane) of Eli Lilly and Company Limited, UK in 48+2 Adult Human Type-I Diabetic Indian Male and Female Patients Using the Euglycemic Clamp Technique and a Bioequivalence Approach.

Design: A mono-centre, double blind, randomised, 2-treatment, 2-sequence, single-dose, crossover, manual euglycemic clamp study in adult T1D Indian male and female subjects under near fasting conditions with light meals at 3 and 6 h during the clamp without relevant impact on glucose.

Test insulin: Isophane Insulin Manufactured by: Marvel LifeSciences Ltd. Dosage Type: S.c. injection Formulation strength: 100 IU/mL**Reference insulin:** Humulin I (Isophane insulin) Manufactured by: Eli Lilly and Company Limited, UK, Dosage Type: S.c. injection, Formulation strength: 100 IU/mL,Batch Number: A404874L Manufacturing Date: Not known, Expiry Date: 08/2009.**Investigator, study site:** Dr. Anilkumar Chopde, BBRC, Plot No. 35, Deonar Ancillary Industrial Plots, Govandi, 400 043 Mumbai, India. Study site: Bombay Bio-Research Centre Plot No. 35, Deonar Ancillary Industrial Plots, Govandi, 400 043 Mumbai, India.

Study period: 01 August 2008 to 04 October 2008

Objectives: ***Primary Objectives:*** *Pharmacodynamics (PD)***:** To demonstrate biosimilarity of Marvel's isophane rh-insulin (test) with the isophane Humulin I of Eli Lilly (reference), based on the AUC of glucose infusion rate (GIR) and plasma C-peptide concentrations. *Pharmacokinetics (PK):* To compare the complete concentration-time profile (AUC) of Marvel´s isophane insulin (test) with Eli Lilly's isophane Humulin I (reference). ***Secondary Objectives****: PD***:** To compare the PD time-effect profile

including AUC0-1, AUC0-2, AUC0-4, AUC0-6, AUC0-8, GIR_{max}, t_{max} of GIR, t_{onset}, early and late t_{50} and t_d of Marvel´s isophane test insulin versus Eli Lilly´s Humulin I (reference. ***PK*:** To compare Cmax, tmax, t1/2, MRT, CL/F and VZ/F of Marvel´s isophane test insulin with the isophane reference product Humulin I of Eli Lilly. ***Safety*:** To assess the safety profile after a single dose of isophane test versus reference insulin, evaluated with standard safety parameters.

Population: Adult Indian/Asian male and female T1D non-smoking subjects ≤50 years of age, without evidence of disease and a body mass index (BMI) between 18.0–24.9 kg/m2 (both inclusive), glycosylated haemoglobin (HbA1c) ≤6.5% and screening laboratory values, ECG and 2D echocardiography, blood pressure, pulse rate and body temperature within normal limits or considered to be of no clinical significance. Subjects had to have no positive human insulin antibody test. The inclusion criteria do, however, not include any details on how type 1 diabetic subjects were to be identified.

Sample size and patient disposition: 50 subjects planned and enrolled, all analysed in safety population, 48 analysed in the per-protocol population for PK and PD. The two subjects 09 and 11 were withdrawn due to difficulty of a recannulation and finding a prominent vein. The sample size was primarily based on the previous phase-I study conducted by the sponsor and the intra-individual CVs obtained for the AUC of GIR. To achieve a statistical power of 80%, a sample size of at least 48 subjects was calculated to demonstrate equivalence between the formulations, based on the formal bioequivalence range of 80 to 125 % for AUC and "test/reference" mean ratio between 0.95 and 1.05.

PK evaluation: *Primary endpoint:* AUCs of insulin (AUC0-t and AUC0-∞). *Secondary endpoints*: C_{max}, t_{max}, $t_{1/2,}$ MRT, CL/F and V_Z/F .

PD evaluation: *Primary endpoints:* $AUC_{0\text{-end-of-clamp}}$ ($AUC_{0\text{-EoC}}$) of GIR and C-peptide concentrations. *Secondary endpoints:* $AUC_{0\text{-}1}$, $AUC_{0\text{-}2}$, $AUC_{0\text{-}4}$, $AUC_{0\text{-}6}$, $AUC_{0\text{-}8}$ of GIR, GIR_{max} and its t_{max}, t_{onset}, early and late t_{50} as well as t_d.

Safety evaluation (secondary): AEs and local tolerability, physical examination, ECG recordings, vital signs, routine laboratory safety (biochemistry, haematology, urine analysis), HbA1c and human insulin antibody test.

Treatments: Subjects were switched to study insulin from the 1st day to completion of the study that was four days before initiation of Clamp 1 on Day 5. The objective was to monitor the suitability of study insulin in the subjects and to restrict the interference of the subject's own insulin with the study insulin. On clamp days 5 and 15 and PK days 9 and 19 the subjects were fasted overnight (water was allowed). After priming (or tapering) with i.v. insulin and at least 30 min stable blood glucose level (80-99 mg/dl) at the clamp days 5 and 15, Isophane insulin doses of 0.2 IU/kg were injected by the s.c. route of administration for the test and reference product. A total of four single-dose s.c. injections, two single doses for test and reference product, were administered according to the random plan at the euglycaemic clamp Days 5 and 15 and the PK assessment Days 9 and 19.

Sampling: ***PD-Sampling***: pre-dose -01.50, -01.00, -00.50 h, then at 0.50, 1.00, 1.50, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.25, 4.50, 4.75, 5.00, 5.17, 5.33, 5.50, 5.67, 5.83, 6.00, 6.17, 6.33, 6.50, 6.67, 6.83, 7.00, 7.25, 7.50, 7.75, 8.00, 9.00, 10.00 h relative to s.c. injection during clamping and at 12.00 h on Days 5 and 15. ***PK-sampling***: pre-dose -0.33 h and at 1.00, 3.00, 4.00, 4.50, 5.00, 5.25, 5.50, 5.75, 6.00, 6.25, 6.50, 6.75, 7.00, 7.50, 8.00, 9.00, 10.00, 11.00, 12.00, 16.00 and 24.00 h relative to s.c. injection on Days 9 and 19.

The Applicant did not provide any information on the analytical procedures used to determine serum insulin and C-peptide at the new site in Thane, India (laboratory of Dr. Ulhas Vaidya). This is not acceptable, see LoQ.

Pharmacokinetics

Results

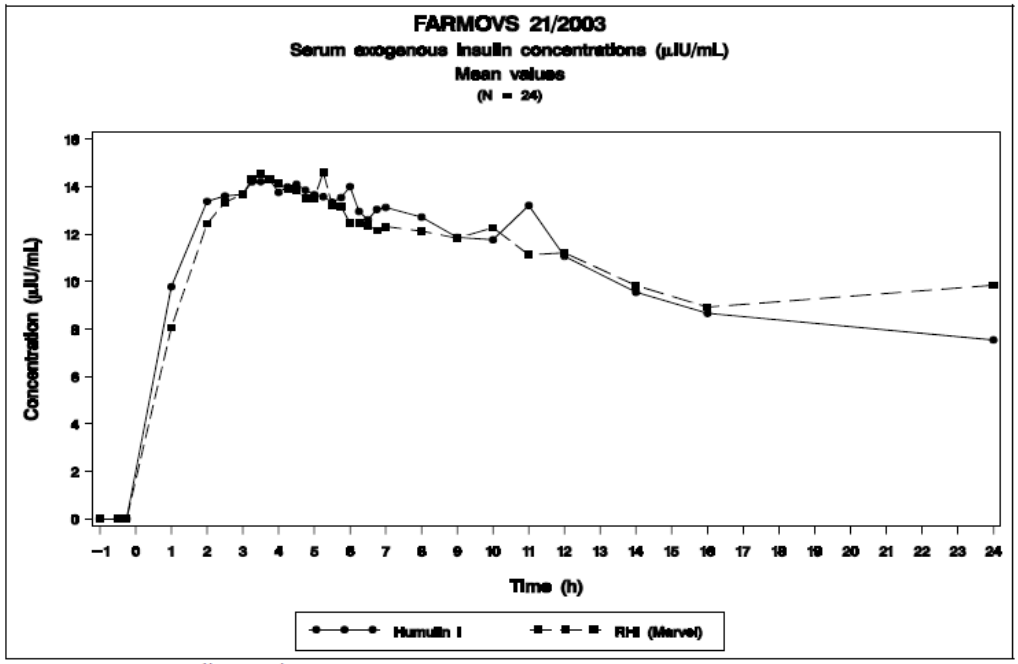
Old study FARMOVS 21/2003 (intermediate acting insulin; healthy subjects):

This study was primarily designed to be a pharmacodynamic study using the euglycaemic clamp technique. However, the concentrations of serum insulin measured in this study were used to address the pharmacokinetics as well. The PK results are summarised as follows:

Variable	Humulin I®	Isphane Marvel	Ratio	95% CI	90% CI
$AUC_{0\text{-}EoC}$	173.5 (188.8 ± 80.08)	175.8 (185.5 ± 60.53)	101.3	84.6 – 121.3	87.3 – 117.6
$AUC_{0\text{-}8}$	88.38 (97.63 ± 47.87)	89.09 (93.30 ± 29.01)	100.8	85.0 – 119.5	87.5 – 116.1
$AUC_{0\text{-}4}$	40.18 (44.16 ± 21.12)	40.03 (41.77 ± 12.66)	99.6	84.7 – 117.2	87.1 – 114.0
C_{max}	16.05 (17.29 ± 7.35)	16.65 (17.16 ± 4.23)	103.7	90.1 – 119.4	92.3 – 116.5
t_{max}*	5.02 (5.76 ± 3.17) *Median: 4.88*	4.66 (5.38 ± 3.62) *Median: 4.00*	93.0 –0.31	65.3 – 132.4 –3.38 – 1.75	69.3 – 124.6 –3.00 – 0.88
$T_{1/2,z}$	14.40 (53.86 ± 132.3)	11.1 (15.23 ± 16.37)	79.1	47.7 – 131.2	52.0 – 120.2
V_Z/F	694.2 (905.6 ± 563.1)	751.6 (820.4 ± 365.0)	112.0	83.2 – 150.8	87.6 – 143.2
MRT	7.96 (8.02 ± 0.95)	8.08 (8.11 ± 0.74)	101.5	96.6 – 106.6	97.4 – 105.7

Tables with geometric means (arithmetic means ±SD), geometric mean ratios and 95% + 90% CIs
*, Non-parametric CIs for the respective median differences are also provided
Units: AUC [µIU*h/mL], C_{max} [µIU/mL], V_Z/F [L], all time units in [h]

Figure 12-1 Mean Serum Exogenous Insulin Concentrations per Treatment



Data Source: Appendix IX, Figure 5

New study BBRC/CLN/08/001 (intermediate acting insulin; T1D patients):

PK Ratios With 90% CIs From Ln-transformed Data (Acceptance Range: 80–125%)

PK Parameters		Test Gmean* (SD)	Reference Gmean* (SD)	% Ratio Test/Ref.	90% CI lower-upper
C_{max}	[ng/mL]	2.52 (0.92– 7.41)	2.45 (0.80–13.07)	102.86	92.84–115.69
AUC_{0-t}	[ng*h/mL]	30.14 (9.41–61.48)	29.75 (8.98–55.77)	101.31	94.63–108.58
AUC_{0-inf}	[ng*h/mL]	32.64 (10.28–62.62)	32.24 (9.22–64.51)	101.24	95.11–107.72
T_{max}*	[h]	5.50 (1.00–24.00)	6.13 (1.00–24.00)	89.80	63.19–103.51
$T_{1/2}$*	[h]	2.62 (0.33– 5.93)	2.42 (0.51– 4.68)	108.26	86.47–123.69
MRT*	[h]	14.56 (10.61–27.22)	15.22 (8.84–24.02)	94.86	91.48–104.75
V_Z/F	[L]	0.046 (0.009–0.455)	0.046 (0.019–0.210)	100.00	81.02–119.48

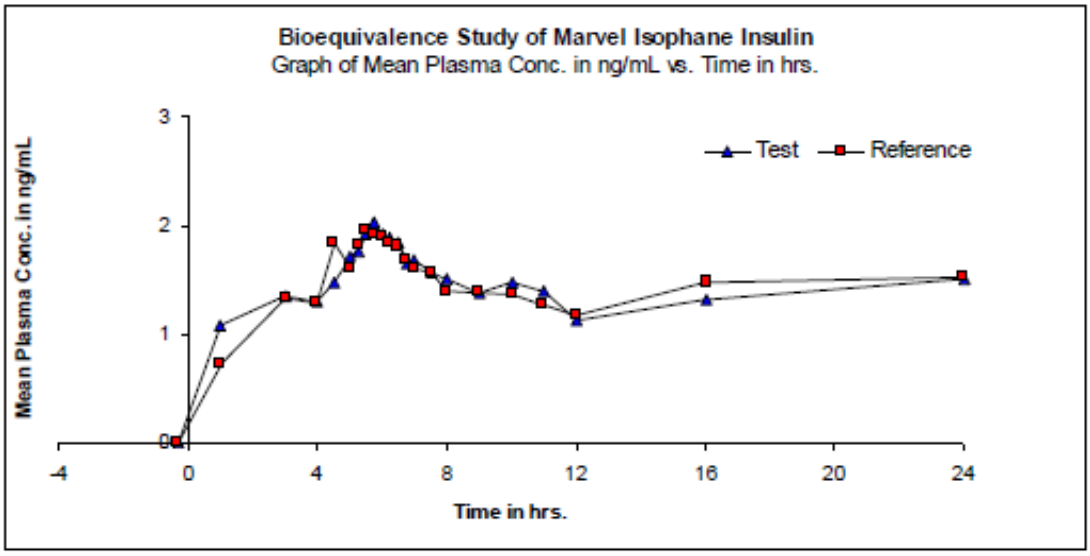
*, Medians used for ANOVA

Table 5: Summary Statistics for PK Parameters

Parameters	Test Product							
	C_{max} [ng/mL]	T_{max} [h]	AUC_{0-t} [ng*h/mL]	$AUC_{0-\infty}$ [ng*h/mL]	$t_{1/2}$ [h]	CL/F [L/h]	V_Z/F [L]	MRT [h]
Mean	2.78	7.77	32.576	35.399	2.62	0.019	0.066	15.898
Gmean	2.52	5.44	30.14	32.64	2.32	0.017	0.046	15.378
Median	2.56	5.50	35.348	38.135	2.62	0.015	0.042	14.555
SD	1.322	7.079	11.773	12.898	1.21	0.011	0.075	4.325
%CV	47.58	91.10	36.14	36.43	46.29	57.50	114.43	27.20
Minimum	0.92	1.00	9.409	10.278	0.33	0.008	0.009	10.609
Maximum	7.41	24.00	61.481	62.619	5.93	0.064	0.455	27.219
Parameters	Reference Product							
	C_{max} [ng/mL]	T_{max} [h]	AUC_{0-t} [ng*h/mL]	$AUC_{0-\infty}$ [ng*h/mL]	$t_{1/2}$ [h]	CL/F [L/h]	V_Z/F [L]	MRT [h]
Mean	2.86	8.80	32.562	35.441	2.42	0.020	0.056	16.065
Gmean	2.45	6.78	29.75	32.24	2.23	0.017	0.046	15.664
Median	2.475	6.125	35.829	38.595	2.42	0.016	0.043	15.343
SD	2.011	7.077	12.247	13.656	0.932	0.013	0.043	3.708
%CV	70.29	80.40	37.61	38.53	38.50	63.55	75.84	23.08
Minimum	0.80	1.00	8.976	9.220	0.51	0.008	0.019	8.836
Maximum	13.07	24.00	55.766	64.511	4.68	0.056	0.210	24.022

Mean = Arithmetic Mean Gmean = Geometric Mean

Figure 108: Arithmetic Mean Figures of Plasma Insulin Concentrations with Expanded Scale on Y-Axis



Data Source: Section 14.5.1 - 2

Table 6: Results of Pharmacokinetic Analyses for Primary and Secondary Parameters

Primary Parameters	Gmean Test	Gmean Reference	Ratio	Lower 90% CI	Upper 90% CI	p-Value
$LnAUC_{0-\infty}$	32.64	32.24	101.24	95.11	107.72	0.745
$LnAUC_{0-t}$	30.14	29.75	101.31	94.63	108.58	0.741
Secondary Parameters	**Gmean Test**	**Gmean Reference**	**Ratio**	**Lower 90% CI**	**Upper 90% CI**	**p-Value**
LnT_{max}*	5.50	6.13	89.80	63.19	103.51	0.103
LnC_{max}	2.52	2.45	102.86	92.84	115.69	0.588
$LnT_{1/2}$*	2.62	2.42	108.26	86.47	123.69	0.754
LnV_Z/F	0.046	0.046	100.00	81.02	119.48	0.889
LnMRT*	14.56	15.34	94.86	91.48	104.75	0.600

Data source: Table 31 and Appendix 16.1.9; Gmean, geometric mean
*, Medians used for ANOVA

Table 31: Pharmacokinetic Evaluation

Primary Parameters	Gmean Test	Gmean Reference	Ratio	Lower 90% CI	Upper 90% CI	p-Value
$LnAUC_{0-\infty}$	32.64	32.24	101.24	95.11	107.72	0.745
$LnAUC_{0-t}$	30.14	29.75	101.31	94.63	108.58	0.741
Secondary Parameters	**Gmean Test**	**Gmean Reference**	**Ratio**	**Lower 90% CI**	**Upper 90% CI**	**p-Value**
LnT_{max}*	5.50	6.13	89.80	63.19	103.51	0.103
LnC_{max}	2.52	2.45	102.86	92.84	115.69	0.588
$LnT_{1/2}$*	2.62	2.42	108.26	86.47	123.69	0.754
LnV_Z/F	0.046	0.046	100.00	81.02	119.48	0.889
LnMRT*	15.38	15.66	94.86	91.48	104.75	0.600

Data source: Appendix 16.1.9

Onset of action (test / reference): tonset (0.78 ±0.59 vs. 0.63 ±0.60 h), early t50 (2.61 ±1.15 vs. 2.67 ±1.18 h), late t50 (7.84 ±3.45 vs. 8.00 ±3.55 h) and td (4.22 ±0.59 vs. 4.37 ±0.60 h).

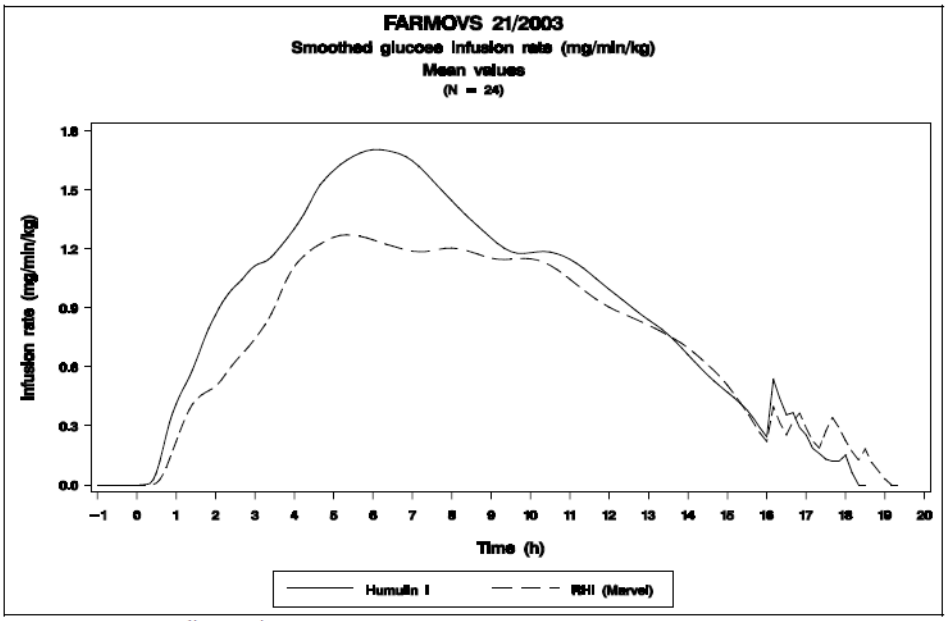
Pharmacodynamics

Results

Old study FARMOVS 21/2003 (intermediate acting insulin; healthy subjects).

Summary of PD Parameters (AUC of GIR), original curve and table based on 95% CI:

Figure 11-1 Smoothed Glucose Infusion Rate (mg/min/kg): Mean Values



Data Source: Appendix IX, Figure 25

Table 11-1 ANOVA for Primary Pharmacodynamic Endpoint

Variable	Arithmetic Means		Point estimate (95% CI)*
	Humulin I	RHI (Marvel)	RHI (Marvel)/Humulin I
$AUC_{(0\text{-end of clamp})}$ of GIR (mg/kg)	1017.660	844.853	83.0% (56.5; 109.5)%

Data Source: Appendix VIII, Table 13

*Point estimate and 95% confidence interval for the ratio of treatment means, based on untransformed data.

Table 11-2 ANOVA for Secondary Pharmacodynamic Endpoints

Variable	Arithmetic Means		Point estimate (95% CI)*
	Humulin I	RHI (Marvel)	RHI (Marvel)/Humulin I
$AUC_{(0\text{-}4h)}$ of GIR (mg/kg)	173.966	116.486	67.0% (27.8; 106.1)%
$AUC_{(0\text{-}8h)}$ of GIR (mg/kg)	556.647	408.541	73.4% (43.8; 103.0)%
GIR_{max} (mg/min/kg)	1.993	1.707	85.7% (60.8; 110.6)%
t_{max} of GIR (h)**	5.687**	6.688**	0.61h (-1.25; 2.17)h**
t_{onset} (h)**	1.124**	0.857**	0.44h (-0.07; 1.94)h**
Early $t_{50\%}$ (h)**	2.491**	3.525**	0.98h (-0.13; 1.93)h**
Late $t_{50\%}$ (h)**	12.860**	13.986**	0.71h (-0.40; 1.82)h**
t_d (h)**	9.097**	9.321**	-0.09h (-1.35; 1.33)h**

Data Source: Appendix VIII, Table 13

*Point estimates and 95% confidence intervals for the ratio of treatment means, based on untransformed data.
** Point estimates and 95% confidence intervals for the respective median differences (test-reference) from non-parametric data analysis, reported in hours.

New study BBRC/CLN/08/001 (intermediate acting insulin; T1D patients):

Summary of PD Parameters (AUC of GIR):

GIR Ratios With 90% and 95% CIs From Untransformed Data (Acceptance Range: 80–125%)

PD parameters	Test Mean* (SD)	Reference Mean* (SD)	% Ratio Test/Ref.	90% CI lower-upper	95% CI lower-upper
GIR_{max} [mg/kg]	30.956 (12.43)	30.716 (11.32)	100.68	95.08–106.05	93.99–107.14
AUC_{0-1} [mg*h/kg]	17.420 (9.28)	17.011 (7.37)	102.40	94.26–110.06	92.96–111.64
AUC_{0-2} [mg*h/kg]	37.588 (18.17)	38.213 (16.43)	98.36	91.27–104.74	89.93–106.08
AUC_{0-4} [mg*h/kg]	85.904 (39.61)	86.458 (36.23)	99.36	92.53–105.52	91.28–106.81
AUC_{0-6} [mg*h/kg]	136.639 (61.22)	137.467 (56.86)	99.40	93.19–105.01	92.01–106.18
AUC_{0-8} [mg*h/kg)	187.194 (82.58)	188.366 (76.96)	99.38	93.70–104.52	92.62–105.59
AUC_{0-EoC} [mg*h/kg]	233.311 (102.12)	235.144 (95.66)	99.22	93.70–104.30	92.64–105.36
T_{max} of GIR [h]$^{\&}$	5.59 (0.67–9.75)	5.50 (1.33–9.33)	101.64	85.64–111.22	83.09–113.76

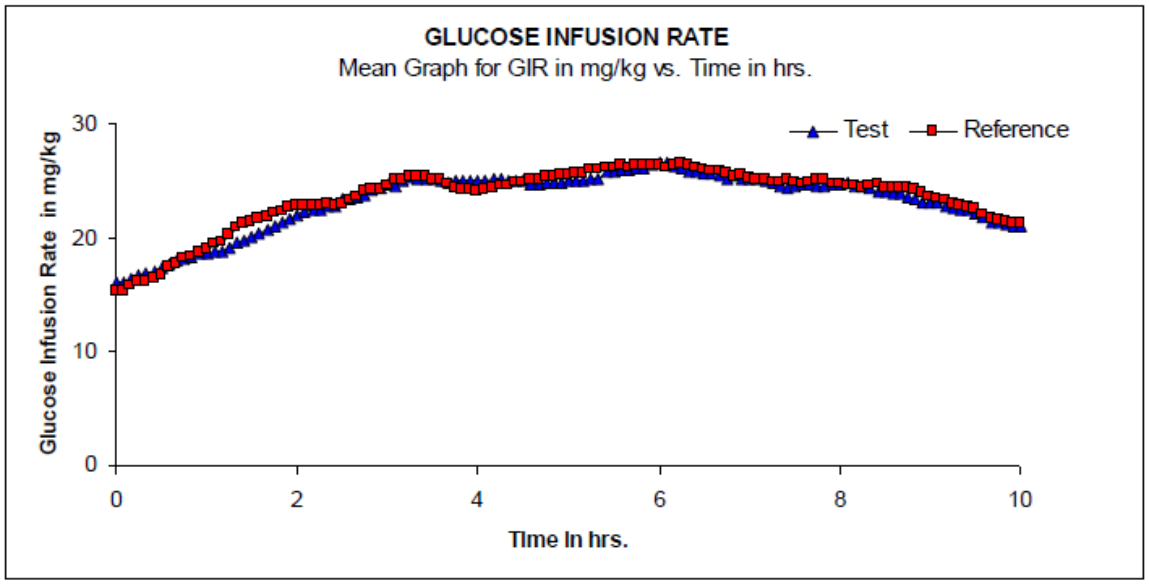
*, Arithmetic mean; $^{\&}$, Medians (ranges) as used in the ANOVA

Table 3: Summary Statistics for PD Parameters

Parameters	Test Product											
	GIR_{max} [mg/kg]	T_{max} [h]	AUC_{0-1h} [mg*h/kg]	AUC_{0-2h} [mg*h/kg]	AUC_{0-4h} [mg*h/kg]	AUC_{0-6h} [mg*h/kg]	AUC_{0-8h} [mg*h/kg]	AUC_{0-EoC} [mg*h /kg]	Early t_{50} [h]	Late t_{50} [h]	Onset [h]	Duration o action [h]
Mean	30.956	5.23	17.420	37.588	85.904	136.639	187.194	233.311	2.61	7.84	0.78	4.22
Gmean	28.646	4.595	15.886	34.550	78.666	124.917	171.111	214.082	2.301	6.896	0.570	4.176
Median	29.790	5.585	14.509	31.399	75.646	126.854	176.724	217.559	2.795	8.380	0.625	4.375
SD	12.429	2.299	9.279	18.166	39.612	61.225	82.584	102.124	1.150	3.449	0.592	0.592
% CV	40.15	43.98	53.27	48.33	46.11	44.81	44.12	43.77	43.98	43.98	76.10	14.02
Minimum	8.980	0.67	3.296	8.684	19.459	30.828	42.125	59.707	0.34	1.01	0.08	2.42
Maximum	74.257	9.75	65.326	124.629	256.312	394.678	538.387	678.651	4.88	14.63	2.58	4.92
Parameters	Reference Product											
	GIR_{max} [mg/kg]	T_{max} [h]	AUC_{0-1h} [mg*h/kg]	AUC_{0-2h} [mg*h/kg]	AUC_{0-4h} [mg*h/kg]	AUC_{0-6h} [mg*h/kg]	AUC_{0-8h} [mg*h/kg]	AUC_{0-EoC} [mg*h /kg]	Early t_{50} [h]	Late t_{50} [h]	Onset [h]	Duration o action [h]
Mean	30.716	5.33	17.011	38.213	86.458	137.467	188.366	235.144	2.67	8.00	0.63	4.37
Gmean	28.881	4.711	15.954	35.723	80.682	128.176	175.480	219.077	2.358	7.070	0.436	4.316
Median	28.530	5.500	14.588	32.280	80.136	127.245	173.233	215.947	2.750	8.250	0.420	4.580
SD	11.321	2.367	7.367	16.432	36.231	56.864	76.958	95.656	1.184	3.551	0.604	0.604
% CV	36.86	44.39	43.31	43.00	41.91	41.37	40.86	40.68	44.39	44.39	95.30	13.83
Minimum	15.416	1.33	6.770	16.290	37.949	59.608	77.865	99.888	0.67	2.00	0.08	2.25
Maximum	66.007	9.33	55.342	117.224	244.946	376.960	508.973	634.633	4.67	14.00	2.75	4.92

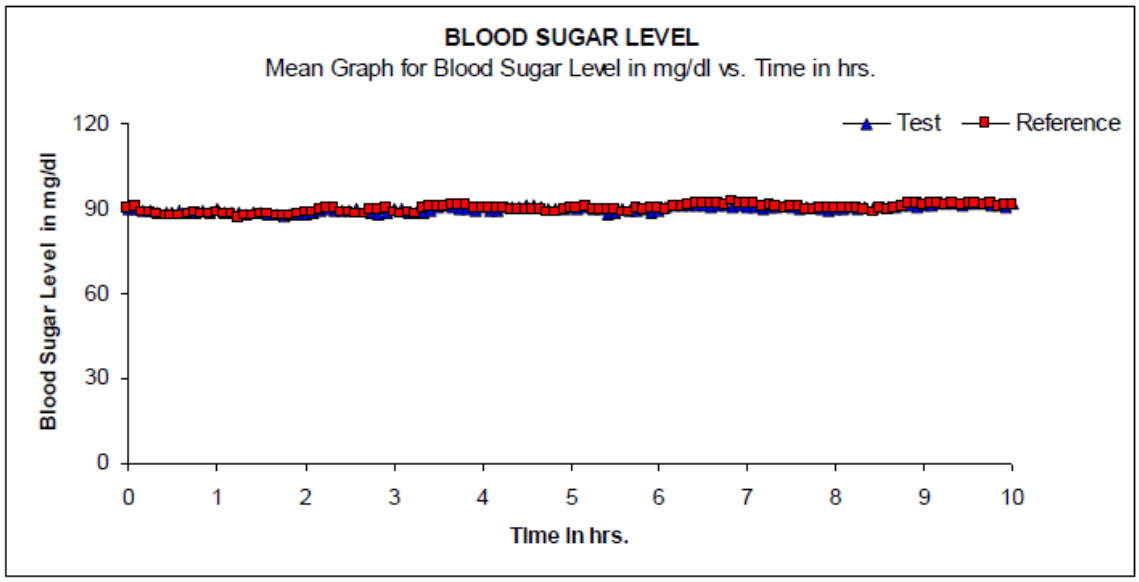
Mean = Arithmetic Mean Gmean = Geometric Mean

Figure 2: Arithmetic Means of GIR Plasma Concentrations During the Clamp Treatment on Days 5 and 15 [N=48]



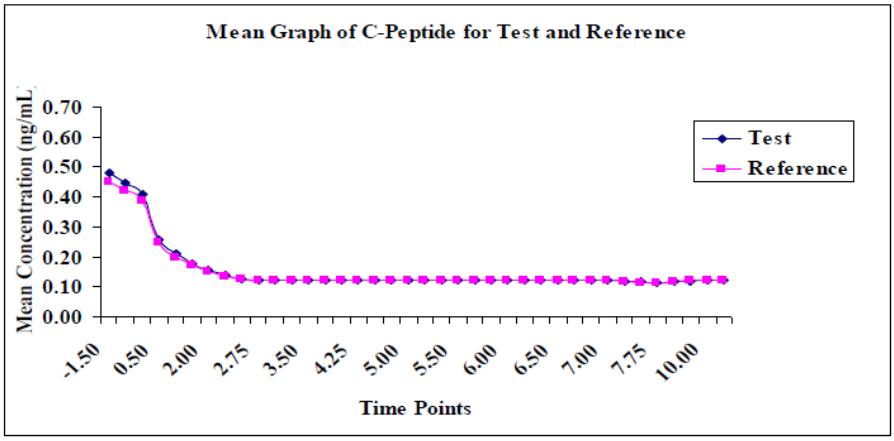
* Expanded Scale on Y-Axis
Data source: Table 9, Table 10 and Figure 7

Figure 3: Arithmetic Means of Plasma Glucose Concentrations During the Clamp on Treatment Days 5 and 15 [N=48]



* Expanded Scale on Y-Axis
Data source: Table 13, Table 14 and Figure 57

Figure 4: Mean Graph of C-Peptide for Test and Reference



Data Source: Figure 106

Onset of action (test / reference): t_{onset} (0.78 ±0.59 vs. 0.63 ±0.60 h), early t50 (2.61 ±1.15 vs. 2.67 ±1.18 h), late t50 (7.84 ±3.45 vs. 8.00 ±3.55 h) and td (4.22 ±0.59 vs. 4.37 ±0.60 h)

C-peptide concentration at screening ranged between 0.23-0.58 and 0.31-0.59 ng/ml for test and reference. Mean baseline **C-peptide** concentrations for the test and reference product at -1.50 h were 0.48 and 0.45 ng/mL). Levels declined within 2.75 to 12.0 h to 0.12 ng/mL for both products and remained at this concentration throughout the study except for time point 7.75 (both 0.11 ng/mL).

Discussion on clinical pharmacology

Pharmacokinetics

In the old study FARMOVS 21/2003, the partial AUCs, $AUC_{0\text{-}EoC}$, C_{max} and MRT values of Isomarv and Humulin I (90% CI; range 80-125%), i.e. the rate and extent of absorption of the two insulins were comparable. Although t½, t_{max} and V_z/F of the test and reference insulins were out of the acceptance range 80-125%, PK bioequivalence in healthy volunteers can still be established based on the rate and extent of absorption. The difference in t_{max} is acceptable, taking into consideration that due to high variability of this parameter an interpretation of t_{max} for an intermediate insulin should be done cautiously. For long-acting insulins with a flat PK profile the comparison of t_{max} may become completely meaningless. However, the t½ of the test insulin (Gmean 14.40 hr) and reference insulin (Gmean 11.1 hr) showed a large difference in the mean values and standard deviations (T/R 53.86 ± 132.3 vs. 15.23 ± 16.37). It is also notable that the serum insulin concentrations at 16 hr post-dose still remained at a high level, deviating from the published data for intermediate-acting insulins. After 16 hr post-dose, only 10 subjects in the test and 9 subjects in the reference group completed the PK measurements up to 24 hr. The serum insulin concentrations of these subjects still remained at a high level, lying widely apart. A possible explanation of these differences could have been the varying, not-standardised study condition in the two groups. This issue should be clarified.

In the new study BBRC/CLN/08/001 the values of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, Cmax, t½ and MRT of Isomarv and Humulin I (90% CI; range 80-125%), i.e. the rate and extent of absorption of the two insulins were comparable. T_{max} was out of the acceptance range 80-125%, however, as mentioned earlier, the interpretation of differences in tmax should be done cautiously due to high variability of this parameter.

MRT was not analyzed by ANOVA in study BBRC/CLN/08/001. The results of the parametrical analysis of MRT have not been presented. As opposed to the study with the short-acting insulin

(BBRC/CLN/07/001) the value of t½ in this study has been given as median and not as mean. This approach should be justified.

It should be noted that the patients in this study received two doses of insulin on the PK days 9 and 19; one dose in the morning and the second dose at 12 hr post-dose (twice daily doses). This approach is comprehensible as these patients were T1D patients and needed more than only one dose of study insulin per day. However, due to this second dose the concentration-time-curve of serum insulin stays at a high level even up to 24 hr post-dose. The applied second dose also makes the calculation of t½ unreliable. It is not clear, if the second dose was standardized for all patients. The course of insulin concentration-time curve shown in Table 5 and Figure 108 up to the first 12 hours is not consistent with the measured PK values as the curve of insulin shows rather a constant plateau until 12 hours. T½ could only be calculated for 32/48 (test medicinal product, TMP) and 31/48 (reference medicinal product, RMP) T1D patients and thus, the mean of each TMP or RMP was substituted for patients with missing data. There were enough PK sampling points beyond Cmax for calculation of the terminal elimination rate, but insulin concentrations continued to be that high in a third of patients, so that an erroneously long half life would have resulted using the non-compartmental approach. In addition, there is a very large difference between the measured t½ value in the old study FARMOVS 21/2003 (healthy subjects: 11 hr) and in this new BBRC study (diabetes patients: 2.6 hr). This large difference was already noticed by CHMP in the Scientific Advice. The applicant responded that a higher cellular uptake in healthy volunteers and the different statistical calculation of t½ (use of median instead of mean) may have been accountable for these differences.

According to the guideline, factors contributing to PK variability e.g. insulin dose and site of injection / thickness of subcutaneous fat should be taken into account. The Applicant should clarify whether insulin was administered at the same injection site and by the same person throughout the study and, if this has not been the case, provide a discussion on the potential impact on the study results

Furthermore, the statistical analyses of the PK data in the new BBRC study raise concern about the reliability and validity of the submitted data due to unclear calculations, inconsistent or missing information of different PK values. The original study protocol and statistical analysis plan have not been submitted.

Furthermore, no analytical reports for the determination of serum insulin and C-peptide in the new study performed by BBRC were provided.

Pharmacodynamics

In the old study FARMOVS 21/2003, despite similar PK profiles, the clamp study failed to confirm similar PD profiles of Isomarv medium and Humulin I. None of the PD parameters was compatible with BE requirements. The applicant has stated that “One of the major reasons for the lack of BE for Long Marvel versus Humulin I was the extremely high variability, as indicated by a much higher SD compared to Rapid or Mix Marvel and their corresponding Humulin formulation, which was already observed for the secondary PK parameters”. The design of this study and the selection of healthy subjects (instead of T1D patients) with interfering endogenous insulin production could indeed have biased the PD results, although, successful clamp studies with NPH insulin preparations in healthy subjects have been reported in the literature (e.g. Starke AA et al. Diabet Med 1989). Overall, Isophane Marvel vs. Humulin I in healthy adults showed a faster absorption, a slower onset of action and a lower and longer effect on blood glucose. A pharmacodynamic comparability between test and reference insulins in healthy adults has not been shown.

In the new study BBRC/CLN/08/001, the PD results in patients with T1DM suggest that the time-action profile of the test insulin Isomarv is similar to that of reference insulin Humulin I since the 95% CIs for the ratio of all AUC and Cmax values of GIR are contained in the 80-125% range. In addition, the

values for T_{max} of GIR are highly similar. However, the clamp procedure in this study lasted only 10 hr. This clamp duration is shorter than clamp duration published in literature for intermediate insulins, which e.g. for NPH insulin or insulin detemir in T2D patients has been given up to 16 hr (Hompesch M et al. in Diabetes Obes Metab 2006) or up to 19 hr (Starke AA et al. in Diabet Med 1989). For an appropriate reflection of PD profile longer clamp duration is considered to be appropriate. It should be noted that the duration of action (td) of Marvel insulin was estimated to be ca. 4.3 h, which is too short for an intermediate-acting insulin. In the old study FARMOVS the duration of action of Isomarv was ca. 9 hr. This discrepancy should be clarified. Furthermore, in the graphical presentation of GIR the unit mg/kg has been used for the glucose infusion rate. This approach is confusing as the correct unit should also contain a time component, i.e. mg/kg/min. Unless this issue could be clarified satisfactorily by the applicant, an adequate interpretation of the submitted PD results remains infeasible.

According to study report the C-peptide concentration at screening ranged between 0.23-0.58 and 0.31-0.59 ng/ml for test and reference. However, these values are the fasting concentrations on clamp days and not the screening values. Furthermore, C-peptide was also chosen as a part of the primary PD objective in the new BBRC study. This approach is not comprehensible as C-peptide should not play a role for the PD or PK results in T1D patients. It is notable that in Table 3 of the new BBRC study (summary of PD parameters) the values of early and late t50% have been derived from Tmax by division respective multiplication by half (early t50 = Tmax * 0.5 and late t50 = Tmax * 1.5). This approach should be clarified.

On clamp days 5 and 15 the patients were fasted overnight but were allowed to have a light meal (24 kcal) at 3 and 6 h during the clamp. Details and glycemic index of this light meal has not been presented and should be submitted subsequently.

The study protocol / study report of the new BBRC study do not include any details on how type 1 diabetes was identified in these patients and on the duration of diabetes. Furthermore, data on the patients' previous insulin therapy should be provided, both expressed as mean daily doses and corrected for body weight, to allow a rough estimate on the insulin sensitivity of the patients in relation to the outcome of the clamp. Furthermore, there is no detailed information on how the patients´ diabetes was treated prior to study days (9 and 19). Carry over from other insulin therapy could be an issue and there is no data presented for the pre-dose sample which would have aided this investigation.

In the old study FARMOVS blood glucose was determined with a Yellow Springs Instruments 2300 S glucose analyser using the glucose oxidase method. In the new BBRC study bedside blood glucose monitoring was done continuously at pre-defined time points after s.c. insulin doses using a glucometer. However, the validity and reliability of the instruments and the measured glucose values have been not been discussed. In addition, no algorithm for GIR adjustments has been provided.

As mentioned above, the original study protocol, statistical report and the bioanalytical validation reports have not been submitted. In addition, as for pharmacokinetic, the statistical analyses of the PD data in the new BBRC study also raise concern about the validity of the submitted data due to unclear calculations, inconsistent or missing information about different PD values.

Conclusions on clinical pharmacology

Pharmacokinetics

In the old study FARMOVS 21/2003, based on a CI of 90%, AUCs, Cmax and MRT were within the traditional acceptance range of 80-125% and hence met BE requirements. Some differences in Tmax and T½ were observed suggesting that Insulin Isomarv is absorbed and eliminated somewhat faster; the difference in Tmax is however considered acceptable and interpretation of Tmax for an

intermediate insulin should be done with caution anyway due to high variability of this parameter for retarded insulin preparations. However, T1/2 of the test and reference insulins was significantly different, with a wide 90% CI of the treatment difference. It is notable that only few patients had insulin measurements at 24 h post-dose and insulin levels stayed high at 16 h post-dose and beyond, which is different from published data in healthy subjects. The Applicant should clarify for how long study conditions were standardized and whether patients were allowed to eat during the clamp study.

In the new study BBRC/CLN/08/001 all PK parameters of Isomarv and Humulin I were comparable (90% CI; range 80-125%). The difference in Tmax is acceptable and interpretation of Tmax should be done with caution due to high variability of this parameter for intermediate and long-acting insulins. The calculation of T1/2 appears unreliable and needs to be further addressed by the Applicant.

Taken together, the old and new studies could support the bioequivalence of insulin PK between Marvel's intermediate-acting insulin and Humulin I, provided that the multiple and serious issues raised in the LoQ could be resolved. Several issues have been identified in the study report BBRC/CLN/08/001 including statistical errors, unclear calculations (statistical analysis plan has not been provided) and inconsistent or missing information, which casts serious doubts on the reliability and validity of the data.

Pharmacodynamics

The old study FARMOVS 21/2003 failed to show similar PD profiles of the test insulin Isomarv medium and the reference insulin Humulin I in healthy subjects. None of the 95% CIs of the PD parameters was contained in the 80-125% acceptance range. The applicant has stated that "One of the major reasons for the lack of BE for Long Marvel versus Humulin I was the extremely high variability, as indicated by a much higher SD compared to Rapid or Mix Marvel and their corresponding Humulin formulation, which was already observed for the secondary PK parameters". However, successful clamp studies with NPH insulin preparations in healthy subjects have been reported in the literature. It should be noted that comparative clamp studies are extremely labour-intensive (especially manual clamps) and require profound expertise and strict standardisation of study conditions.

The newly conducted BBRC study in patients with T1DM showed highly similar PD profiles of Marvel's intermediate-acting insulin Isomarv and Eli Lilly's Humulin with the 95% CIs of all PD parameters contained within the traditional acceptance range for BE, i.e. 80-125%. However, several issues have been identified for this study relating to the reliability and validity of the study results and the appropriateness of the duration of the clamp study..

Taken together, due to the listed severe uncertainties Isomarv appears not approvable to date.

Clinical efficacy

The efficacy of Marvel insulins is supported by data obtained from 2 double-blind, randomised, controlled, multicenter, phase 3 trials:

- study 411-BK-03-001-0000 (comparison with Huminsulin (RMP), 6 month open-label extension 411-BK-03-001-0001
- study 411-MA-08-001-0000 (comparison with Huminsulin as RMP)

These studies aimed to compare the safety and efficacy of the Marvel Insulins (Insulin Human 30/ 70 Mix Marvel, Insulin Human Long Marvel (Isomarv) and Insulin Human Rapid Marvel (Solumarv) to the equivalent reference licensed products (Huminsulin S, Huminsulin I and Huminsulin M3, Eli Lilly). Both studies included patients with both type 1 and type 2 diabetes.

Study 411-BK 03-001-0000 was already submitted within the previous MAA in 2007. This study was designed as an efficacy study with HbA1c as the primary endpoint. Since such a study is not a formal requirement according to the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005) as well as due to limitations with respect to study design and results it is only regarded as supportive for efficacy. The euglycaemic PK/ PD clamp studies are considered pivotal to demonstrate biosimilarity.

Study 411-MA-08-001-0000 is designed as a safety study investigating immunogenicity in line with the requirements as set out in the a. m. guidance document. Only results with respect to secondary endpoints (HbA1c, weight gain, insulin dose) are set out in the following section. For results on the primary endpoint (anti insulin antibodies) please refer to the clinical safety part.

Study 411-BK-03-01-0000

Methods

Study participants were male and female patients suffering from type 1 or type 2 diabetes mellitus and were on treatment with insulin for at least one year. Patients who satisfied the inclusion and exclusion criteria were randomised to reference (Humulin insulin) or test medication (Marvel insulin). Patients continued on their pre-study existing dosage regimen of a “free” dose of soluble and isophane insulins or the “fixed” dose combination of the biphasic insulin. For each insulin type patients in the test group received Marvel insulins and in the reference group they received Humulin insulins.

The study was originally planned to last for 6 months; after the CHMP Guidance document was published that requires at least 12 months of immunogenicity data, the study was extended with an additional six months follow-up phase (study 411-BK-03-01-0001). The second six month period was designed as an open-label, uncontrolled treatment study.

The objective of the study was to prove the equivalence of a test formulation [regular insulin, intermediate acting insulin, or premixed (70% intermediate acting plus 30% regular insulin)] containing recombinant human insulin to a reference product of the same type (Humulin) for the treatment of diabetes.

The primary endpoint of the present study was the glycosylated haemoglobin (HbA1c) measured after 24 weeks of treatment.

The secondary endpoints of the present study were:

- glycosylated hemoglobin (HbA1c) measured after 12 weeks of treatment
- incidence and severity of hypoglycemia,
- parameters resulting from an 8-point blood glucose profile,
- changes in weight.

The additional endpoint of the present study was the effect of the intensified insulin treatment on inflammatory markers (CRP).

The sample size chosen for this study was based on assumptions of the estimated difference between the test and reference HbA1c values and a maximum tolerable difference of 0.6%, to achieve a significance level of 0.025 at the 95% confidence interval. This calculation yielded an estimated size of 100 patients per treatment group (types 1 and 2 of diabetes and test and reference treatments) who were to be randomised separately. Allowing for a possible dropout rate of 15%, a target total for recruitment of 480 patients was to be randomised.

Statistical analysis was performed on three different patient populations:

- the safety population (all treated patients)
- the full analysis set (FAS, former ITT): all patients as randomized who received study medication at least once and for whom post-baseline control data [HbA1c after 12 (visit 6) and/or 24 weeks (visit 9) of treatment] are available.
- the per-protocol set (PPS): all patients of the full analysis set who were treated for the whole double-blind study phase (24 weeks) without major protocol violations

Summary of Main Efficacy Results

- **Primary endpoint**

The primary endpoint of study 411-BK-03-001-0000 was HbA1c measured after 24 weeks of treatment. The results of the analysis of plasma concentrations of HbA1c are presented in tables below by diabetes sub-type and by type of insulin.

A Comparison between Fixed and Free Types of Insulin in Type 1 and Type 2 Diabetes in Study 411-BK-03-001-0000

Diabetes type	Insulin type	N	Adj. Means (U/ml)		Difference	95% CI
			Marvel	Humulin		
Type 1	Fixed	27	8.43	8.16	0.28	(-0.54, 1.09)
	Free	169	8.53	8.30	0.22	(-0.15, 0.597)
Type 2	Fixed	175	7.73	7.52	0.21	(-0.04, 0.47)
	Free	61	7.33	7.68	-0.35	(-0.85, 0.15)
Pooled	Fixed	202	7.82	7.61	0.21	(-0.05, 0.46)
	Free	230	8.23	8.15	0.08	(-0.22, 0.39)

Adjusted means from ANCOVA adjusted for screening (baseline) values.

HbA1c analysis split by diabetes type, insulin type or pooled (24 weeks DB). The data represent adjusted means, difference and confidence intervals (CIs) adjusted for baseline values

Type 1	N_{Marvel}	$N_{humulin}$	$A1C_{Marvel}$	$A1C_{Humulin}$	Difference	95% CI
Fixed	12	15	8.43	8.16	0.28	(-0.54, 1.09)
Free	83	86	8.53	8.30	0.22	(-0.15, 0.60)
Pooled	95	101	8.51	8.30	0.21	(-0.12, 0.56)
Type 2						
Fixed	87	88	7.73	7.52	0.21	(-0.04, 0.47
Free	25	36	7.33	7.68	-0.35	(-0.85, 0.15
Pooled	112	124	7.65	7.56	0.08	(-0.15, 0.32
All patients						
Fixed	99	103	7.82	7.61	0.21	(-0.05, 0.46
Free	108	122	8.23	8.15	0.08	(-0.22, 0.39

Pooled	207	225	8.05	7.88	0.16	(-0.04, 0.36)

Across subgroups the results are fairly consistent with CIs contained within a 0.6% interval. The subgroup in which the pre-specified non-inferiority margin of 0.6% was exceeded was the group of patients with Type 1 diabetes treated with fixed combination.

Except for one subgroup the pre-defined non-inferiority margin of 0.6% was met. In the subgroup of type 1 diabetic patients treated with the fixed combination the upper range of the 95% CI exceeded 0.6 (CI -0.54, 1.09). This may partly be explained by the low number of patients within this subgroup (n=27). The results of the pooled analysis (type 1 and type 2 diabetes mellitus) showed a difference, the 95% CI of which was within the range of 0.4%, a margin which, according to CHMP SA (see below), would be acceptable for demonstration of clinical equivalence.

The Applicant provided data on HbA1c levels in the FAS of Type 1 diabetics (Table 106 of the study report) but not of Type 2 diabetics. This should be done, see LoQ.

Secondary endpoints

Hypoglycaemia

The percentage of patients treated with the test insulins who reported minor hypoglycaemic episode(s) was slightly higher in type 1 diabetes (61.8% vs. 56.9%) and slightly lower in type 2 diabetes (40.5% vs. 46.7%) as compared with Humulin. Major hypoglycaemic episodes were infrequent under both treatments, a total of 6 patients in each treatment group.

8-point glucose profile

Three parameters were calculated: post-prandial increment, mean glucose level, and glucose range. In both types of diabetes, the mean glucose levels showed a trend consistent with the results of HbA1c in both treatment groups. Under the test insulins, an initial decrease was observed between screening and 12 weeks, followed by an increase between 12 and 24 weeks; in contrast, a continuous decrease was seen under Humulin.

Changes in bodyweight

The mean weight gain was comparable in type 1 diabetic patients: 0.8 vs. 0.6 kg at 24 weeks for the test and reference products, respectively. There was essentially no weight change in type 2 diabetic patients.

The secondary endpoints do not provide additional support to the biosimilarity claim but do not raise major issues either.

Study 411-BK-03-01-0001 (open-label extension of BK-03-01-0000)

Study design

Study 411-BK-03-01-0001 was designed as an extension to study 411-BK-03-01-0000. It was a 6 months open label, uncontrolled, multicentre study in patients with type I and type II diabetes. Subjects entered study 411-BK-03-01-0001 directly from the end of the double-blind treatment phase of study 411-BK-03-01-0000. Subjects were treated with open label Marvel Insulin in a continuation of the treatment regimen used in the original study, i.e. either free combination of regular and isophane insulins, or biphasic 30/70 insulin (fixed combination). The primary objective of study 411-BK-03-01-0001 was to investigate the potential for immunogenicity in accordance with the recommendations of the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins

as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005).

The secondary objective was to provide supportive information regarding the continuing efficacy and safety of Marvel insulin under open, non-controlled conditions and to evaluate the interchangeability when switching from Humulin to Marvel insulin.

Results (efficacy)

Type 1 Diabetes

The mean values of HbA1c for all patients at visits 9, 10, and at the final visit (11) were 8.44 ±1.55, 8.41 ± 1.55, and 8.34 ± 1.58, respectively. This indicates that there was no trend for deterioration of glycaemic control in the course of treatment with the study drug. Patients who switched from from Humulin in study 411-BK-03-01-0000 to Marvel insulin in study 411-BK-03-01-0001 retained the same HbA1c level throughout the additional 6 months treatment phase. No changes in insulin dose requirements were noted.

Type 2 Diabetes

The mean values of HbA1c for all patients at visits 9, 10, and at the final visit (11) were 7.69 ± 1.21, 7.78 ± 1.37, and 7.72 ± 1.35, respectively. This indicates that there was no trend for deterioration of glycaemic control in the course of treatment with the study drug. As was the case for the patients with type 1 diabetes, patients who switched from from Humulin in study 411-BK-03-01-0000 to Marvel insulin in study 411-BK-03-01-0001 retained the same HbA1c level throughout the additional 6 months treatment phase. No changes in insulin dose requirements were noted.

Study 411-BK-03-01-0000 has already been part of the marketing authorisation application for Marvel Insulins in 2007. The key concerns raised by the CHMP within the day 120 list of questions were 1. that the equivalence margin of 0.6% has not been adequately justified and is considered too wide and that 2. consistent trends in glycaemic control favouring the reference products in type 1 diabetic patients were observed (the 95% CI for type 1 diabetic patients was very close to the pre-defined margin of 0.6%). The second concern could be partly explained by baseline differences between Marvel insulin and RMP at baseline (a mean HbA1c of 8.8% versus 8.53%). However, the results of the pooled analysis (type 1 and type 2 diabetes mellitus, post-hoc analysis) showed a difference which was within the range of 0.4%, a margin which may be acceptable for demonstration of clinical equivalence.

Generally, the efficacy results of study 411-BK-03-001-0000 slightly favoured reference over test treatment. However, the study was only powered for a non-inferiority margin of 0.6% in HbA1c, which is considered too wide for. HbA1c results of the extension study 411-BK-03-01-0001 showed no trend for deterioration of glycaemic control in the course of treatment with the study drug. HbA1c values did not rise in patients switched from Huminsulin to Marvel insulin in the open-label extension and no change in insulin dose requirements was noted.

Efficacy studies such as study 411-BK-03-01-0000 as well as its open-label extension are not formal requirements of the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005). Instead, euglycaemic clamp PK/ PD studies for the individual insulin preparationsare considered pivotal to demonstrate similar efficacy since HbA1c is considered too insensitive for this purpose.

Overall, study 411-BK-03-01-0000 does not confirm or contradict biosimilarity of Marvel insulin with Humulin.

Study 411-MA-08-01-0000

Methods

In contrast to study 411-BK-03-0000, study 411-MK-08-01-00 had an initial focus on safety as it investigated the incidence of newly developed anti-insulin antibodies. Please note that all results relating to safety (immunogenicity) are presented in the Clinical Safety section.

This study was a multicentre, randomised, double blind, active-controlled study and included both type 1 and type 2 diabetes patients, in two parallel groups of patients.

The primary objective of the study was to describe the development of insulin antibodies in the test and reference populations (i.e. Marvel insulins and Humulin) and evaluate the clinical relevance of possible newly developed antibodies based on clinically relevant endpoints (dosage of insulin, glucose control, and adverse events).

Secondary efficacy endpoints were glycaemic control as estimated by HbA1c measured after 28 and 56 weeks of treatment (not change from baseline), dosage of insulin, incidence and severity of hypoglycaemia and changes in weight.

Patients had to suffer from type 1 and type 2 diabetes mellitus for at least 6 months before randomization and had to have a negative screening assay for antibodies against insulin. A total number of 476 patients were randomly assigned to either Marvel insulin or Humulin in a double-blind fashion. In pretreated patients treatment proceeded in each patient with the type of insulin regimen (free combination of regular and NPH insulin or fixed combination of 70% NPH insulin plus 30% regular insulin) received before the beginning of the trial. A separate randomization schedule was used for each stratum (fixed combination or free combination). Approximately 50% of the patients were randomized to receive a fixed combination and the remaining 50% received a free combination.

The dosage was individually determined in each patient based on the results from the screening examination. Each patient documented the daily dose of insulin administered in a patient diary.

The duration of double-blind treatment lasted for 28 weeks. Visits were performed 4, 12, 20, and 28 weeks after randomization and, during the open treatment period, 32 and 56 weeks after randomization.

Baseline demographics did not differ between treatment groups. The Applicant should clarify if males and females were equally distributed between groups. Both T1DM and T2DM patients were included. Only about 10 % of patients included had a diagnosis of T1DM and no measures had been taken to ensure that a higher proportion of T1DM patients were to be included. Baseline HbA1c levels were not reported in the study report and should be provided, see **LoQ.**

Summary of main efficacy results

Glycosylated haemoglobin (HbA 1 c) measured after 28 weeks of treatment (not change in HbA1c) : The mean values (±SD) in the respective groups for the PPS were 7.93% (1.49) for the test group and 7.90% (1.39) for the reference group. The 95% confidence interval for the difference between the test and the reference group was between -0.17% and +0.34%.

Table 72 Time course of HbA1c [%] measurement - descriptive statistics, per protocol set

HbA1c	description						
	MD	N	Mean	SD	Min	Median	Max
Week -2 / Entry							
Test	1	195	9.27	2.39	5.9	8.80	23.0
Reference	1	189	9.49	2.36	5.9	9.00	19.5
End of week 12							
Test	4	192	8.12	1.69	5.4	7.80	17.6
Reference	5	185	8.06	1.42	4.8	7.70	13.9
End of week 28							
Test	5	191	7.93	1.49	5.4	7.63	12.7
Reference	5	185	7.90	1.39	5.2	7.80	14.1

The difference in HbA1c values between test and reference met the initially defined non-inferiority margin of 0.4% for the PPS. Although the absolute reductions in HbA1c were larger with reference (and analyses of subgroups showed an inferior antiglycaemic effect for test), the antiglycaemic efficacy can be considered comparable between test and reference treatment. The Applicant is asked to submit data for the safety population, since this may be the more conservative approach within a descriptive analysis.

In addition, the Applicant did not submit a comparison of the evolution of HbA1c from baseline to week 28 as outlined in the Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus (CPMP/ EWP/ 1080/ 00). HbA1c has also not been included as a covariate in the analysis.

Dosage of insulin: The mean daily dose (±SD) of regular insulin was 15.6 IU (11.66) for the test group of patients and 17.1 IU (11.89) for the reference group of patients in the PPS. The mean daily dose of NPH insulin was 24.0 IU (12.61) for the test group of patients and 26.4 IU (13.87) for the reference group.

TT 2 Mean daily dose of trial medication from patients diary, per protocol set

Mean daily dose [IU]	description						
	MD	N	Mean	SD	Min	Median	Max
Regular insulin							
Test	27	169	15.6	11.66	2.1	12.2	67.5
Reference	25	165	17.1	11.89	3.0	13.8	59.9
NPH insulin							
Test	4	192	24.0	12.61	2.0	21.5	63.9
Reference	2	188	26.4	13.87	4.1	23.9	106.8

The Applicant should comment on the fact that patients were included that used a daily dose of 2.0 and 4.1 IU of NPH insulin as these doses are very low. Information on the insulin regimen for the patients using these low doses should be provided, i.e. bolus doses of regular insulin, see LoQ.

Changes in weight: The body weight remained comparable between both treatment groups for the entire duration of treatment: 73.4 (±15.3) kg in the test group vs. 72.1 (±16.2) kg in the reference group at screening; 73.8 (±15.2) kg in the test group vs. 73.2 (±15.6) kg in the reference group after 28 weeks of treatment.

TT 7 Body weight - Changes versus weight at visit 2, descriptive statistics by visit, per protocol set

	Description						
	ND	N	Mean	SD	Min	Median	Max
Visit 1 / Entry							
Test	0	196	-0.05	1.19	-8.00	0.00	4.00
Reference	1	189	-0.01	1.12	-3.10	0.00	8.00
Visit 2							
Test	0	196	0.00	0.00	0.00	0.00	0.00
Reference	1	189	0.00	0.00	0.00	0.00	0.00
Visit 3							
Test	3	193	0.09	1.58	-7.00	0.00	8.00
Reference	1	189	0.05	1.58	-5.00	0.00	9.00
Visit 4							
Test	3	193	0.38	2.51	-6.50	0.00	14.00
Reference	5	185	0.33	2.23	-8.00	0.00	10.00
Visit 5							
Test	3	193	0.33	2.74	-7.50	0.00	17.00
Reference	2	188	0.71	2.76	-5.00	0.00	11.00
Visit 6 / Final							
Test	2	194	0.32	3.17	-9.00	0.00	11.00
Reference	5	185	1.00	2.94	-5.00	0.30	11.50

It should be taken into account that the evaluation of efficacy parameters in this study is not a formal requirement of the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005) and, hence, these data are considered supportive in this MAA.

In line with the findings of study 411-BK-03-01-0000, results of study 411-MA-08-01-0000 presented for the PPS numerically favour reference treatment with respect to the results on HbA1c. However, both treatments led to a clinically relevant reduction within the double blind treatment period with no increase detectable at week 28. Moreover, the upper limit of the 95% CI for the treatment difference

(+0.34%) in HbA1c was within the non-inferiority margin of 0.4% agreed to by CHMP in the SA procedure EMEA/ H/ SA/1118/1/ FU/ 2008/ SME/ II. It has to be borne in mind that these confidence intervals were calculated for the difference at week 28 and not for the comparison baseline- week 28. Therefore, a definite assessment of this efficacy parameter will take place after submission of additional data.

The other secondary endpoints (hypoglycaemic episodes, weight) do not raise safety concerns as regards Marvel Insulin.

Results of the secondary endpoints in study 411-MA-08-01-000 are presented for the PPS only. The Applicant is asked to submit results of all secondary endpoints for the safety population additionally as this is considered to be the more conservative approach within a descriptive analysis.

This assessment is based on an interim study report including results after completion of the double blind phase. The open label phase will be continued until week 56 thereby meeting the requirement of a study duration of at least 12 month as set out in the Annex to Guideline on similar biological medical products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005). According to this Guidance document it is considered sufficient to present data at the end of 12 months as a post-approval commitment. However, since data will be available by end of April 2012 at the latest, the Applicant is asked to present the results of the open-label extension within the response document. With regard to the results on HbA1c this data will enable assessment a sustained effect on HbA1c.

Discussion on clinical efficacy

As the euglycaemic clamp PK/ PD studies are considered to be the most sensitive approach in establishing similar efficacy of two insulins claimed to be biosimilar, these studies are considered pivotal in this application dossier. In the absence of guidance for the development of biosimilar insulins at the time, study 411-BK-03-01-000 was planned as an efficacy trial, albeit with an unacceptably large non-inferiority margin for HbA1c (0.6%), whereas study 411-MA-08-01-0000 mainly served to investigate immunogenicity. The results of efficacy parameters investigated in studies 411-BK-03-01-0001 and study 411-MA-08-01-0000 are considered supportive only.

Although, in both studies results of HbA1c at week 28 (change from baseline was not investigated) tended to favour reference treatment, the upper limit of the 95% CIs of the treatment differences for the overall study populations were contained within the non-inferiority margin of 0.4% considered acceptable by CHMP (see EMEA/ H/ SA/1118/1/ FU/ 2008/ SME/ II). HbA1c results of the extension study 411-BK-03-01-0001 showed no trend for deterioration of glycaemic control in the course of treatment with the study drug. HbA1c values did not rise in patients switched from Huminsulin to Marvel insulin in the open-label extension and no change in insulin dose requirements was noted. Results from the 56-week extension of study 411-MA-08-01-00 are awaited.

In addition, an additional analysis comparing the difference from baseline in HbA1c between test and reference is requested by the Applicant.

Patients were included in study 411-MA-08-01-0000 that used a daily dose of only 2.0 and 4.1 IU of NPH insulin as these doses are very low. Information on the insulin regimen for the patients using these low doses should be provided, i.e. bolus doses of regular insulin.

Conclusions on clinical efficacy

Clinical efficacy measured as glycaemic control was demonstrated in the phase 3 trials and was comparable to the reference product. The Applicant should clarify some minor points (see LoQ). However, findings on glycaemic control are only supportive since the main comparability exercise regarding efficacy is based on the clamp studies (see section on clinical pharmacology) due to higher sensitivity.

Clinical safety

Patient exposure

The clinical development programme for Marvel insulin consisted of nine clinical trials: six Phase 1 single-dose studies and three Phase 3 studies. From the Summary of Clinical Safety it was somewhat difficult to get an overview of patient exposure. Furthermore, it is questioned whether or not the number of patients presented is correct, as it appears that patients exposed to Marvel insulin in the double-blind treatment phase (411-BK-03-01-000) continuing in the open-label extension phase may have been counted twice. The patient numbers presented below were calculated based on numbers extracted from different tables in the safety summary. The Applicant should confirm if these are indeed the correct patient numbers and if relevant, all tables should be updated accordingly, see LoQ.

Safety evaluation is mainly focussed on the two phase 3 studies. No relevant safety information could be derived from the pharmacology studies in which patients were exposed for a short period of time only.

In study 411-BK-03-01-0000 (BK-03 for short) the safety population (i.e. the number of patients treated with at least one dose) consisted of 243 T1DM and 283 T2DM patients of whom 123 and 142, respectively, received the Marvel product. The remainder received the comparator. In this trial care was taken to include approximately the same number of T2DM and T1DM patients. The mean treatment duration in the comparative phase was 25.1 and 25.5 weeks in the Marvel and comparator group, respectively.

In contrast, study 411-MA-08-01-0000 (MA-08 for short) recruited patients without special regard to the type of diabetes. In consequence, T1DM patients were a minority (around 10% in each treatment group) and were not evaluated separately. In total, 478 patients contributed to the safety set, 244 of these received Marvel insulin and 234 comparator. The mean treatment duration in the comparative phase was 26.4 and 26.9 weeks in the Marvel and comparator group, respectively.

In both trials the patients either received short-acting insulin, NPH insulin or a 70/30 (NPH/regular) mixture, depending on the treatment regimen employed before inclusion.

There was a marked difference in baseline characteristics and in the incidence of adverse events between T1DM and T2DM patients so that these subpopulations were evaluated separately in study BK-03 (and extension). Due to differences in design and population, safety data from both trials were largely evaluated separately for both trials.

Baseline characteristics (e.g. age, gender, race, diabetes duration, baseline HbA1c and BMI) were in general fairly balanced between test and reference product except for gender in Type 1 diabetics of study BK-03 (51% males in the test group and 66% males in the reference group). However, this is expected to play a minor role since Type 1 diabetics in this trial were rather young, thereby still having a low absolute CV risk.

Furthermore, there was an imbalance in background disease in Type 1 diabetics of study BK-03. In particular, cardiac disorders, endocrine disorders, diabetic retinopathy and hypertension were more frequent in the Marvel group. This has to be considered when interpreting the safety results of this subpopulation (see below).

Adverse events

An overview of the adverse events is shown in the following three tables, listing the findings of study MA-08, BK-03 T1DM and BK-03 T2DM, respectively. Information is taken from Tables 0-04 (p.16) and 0-24 (p.67ff) of SCS.

Study MA-08: Summary of treatment emergent adverse events, safety population

Number of -...	Test	Reference
	(N=244)	(N=234)
AEs reported	171	182
Patients with AEs	80	81
Serious AEs	17	17
Patients with SAEs	12	10
Deaths	0	0
Patients withdrawn due to AE	5	1

The reasons for discontinuation of the five patients in the test group were (Table 0-24 of SCS):

- tongue oedema and face oedema
- face oedema
- thrombophlebitis
- breast cancer
- bladder cancer.

In the reference group the patient withdrew due to depression.

It can be derived from the table above that adverse events were fairly balanced between the test and reference group. However, there is a difference in the number of patients who discontinued due to an AE not favouring the test product. Two of them could be due to a hypersensitivity reaction (face and tongue oedema). Potential hypersensitivity is discussed in more details in the following paragraphs.

Study BK-03 Summary of treatment emergent adverse events, safety population, T1DM

Number of -...	Test	Reference
	(N=123)	(N=120)
AEs reported	53	29
Patients with AEs	30	15
Serious AEs	1	2
Patients with SAEs	1	2
Deaths	0	1
Patients withdrawn due to AE	0	2

The two patients in the reference group withdrew due to CV accident and urticaria, respectively.

Study BK-03 Summary of treatment emergent adverse events, safety population, T2DM

Number of -...	Test	Reference
	(N=142)	(N=141)
AEs reported	78	89
Patients with AEs	36	44
Serious AEs	16	16
Patients with SAEs	8	7
Deaths	0	0
Patients withdrawn due to AE	4	2

The four patients in the test group withdrew due to the following reasons (Table 0-24 of SCS):

- combination of digestive complaints, skin reaction and face oedema
- vertigo and restlessness
- deterioration of the diabetes
- skin reaction.

In the reference group the two patients discontinued due to CV accident and pancreatitis, respectively.

Among the Type 2 diabetics of trial BK-03 there was an imbalance in the patients discontinuing due to an AE. Again, two of these AEs were suspicious of hypersensitivity reactions (skin reaction and face oedema).

Furthermore, there were more non-serious AEs in the test group of Type 1 diabetics, but this could be due to the imbalance in baseline disorders (see section on patient exposure and baseline characteristics above).

Regarding the nature of the AEs, there were some numerical imbalances in the incidence of certain events in both trials, e.g. gastrointestinal, renal/urinary and vascular disorders, but a causal relationship to the study drugs (insulin) appears unlikely.

Related AEs

In the more recent trial MA-08 there were markedly more certain or probable related AEs in the Marvel than in the reference group, 11 vs. 2 events in 8 vs. 2 patients. Besides two events of hypoglycaemia in one patient all these events were highly suspicious of hypersensitivity. Events of potential hypersensitivity were also observed in the earlier trial BK-03 and led to discontinuation; these were considered as “possibly related”.

Potential hypersensitivity reactions

Since both Phase III trials gave hints for potential hypersensitivity reaction, the Applicant listed all events of study MA-08 that might be attributed to local or systemic hypersensitivity reactions, regardless of causality assessment.

The selection of events that might indicate allergic reaction was rather wide but appropriate to increase the sensitivity to detect such reactions. E.g., chest discomfort, peripheral oedema, cough, dyspnoea and hypotension may have numerous causes most of which are completely unrelated to hypersensitivity. However, events that are more likely attributable to hypersensitivity reactions such as face, tongue, eyelid or periorbital oedema were clearly more frequent in the Marvel group (5 vs. 1). Furthermore, as already outlined above, these rather unusual events such as face, tongue and eyelid oedema were considered related (possibly, probably or certainly) by the investigator. More unspecific events like cough were not considered related in most cases.

Nevertheless, this finding is still difficult to interpret because the absolute number of events is rather low so that statistical fluctuation may play a role.

To allow further assessment of a potential causal relationship the Applicant is asked to provide full reports of all potential hypersensitivity reactions. The Applicant should also comment whether these events might be due to host cell proteins or to insulin antibodies of the IgE class. Furthermore, the Marvel insulin preparation (but not Humulin) contains an unusual impurity (around 1% of the insulin content. This originates from the different manufacturing procedure of Marvel insulin. Thus, modified insulin could also contribute to immunogenicity. The Applicant is again asked to comment.

Serious adverse events and deaths

Serious AEs were well balanced between test and reference group, see summary tables in the previous section. No deaths occurred in the more recent Phase III trial, and one death occurred in the reference group of the earlier Phase III trial BK-03. There were no deaths in the Phase I and PD/PK trials. In trial BK-03 there were remarkably few SAEs among the T1DM patients. This could be due to the lower incidence of accompanying disease in the (younger) T1DM population.

Two cases of hypoglycaemia and one case of hyperglycaemia were recorded in the Humulin group of trial BK-03 (Table 0-9 of SCS, see below), and two events of hypoglycaemia occurred in the uncontrolled extension period 411-BK-03-01-0001 of this trial. The potential hypersensitivity reactions were mostly considered serious and related. Otherwise the SAEs were considered not related to study medication (e.g. cancer, CV events).

Table 0-9: Pooling of all serious adverse reactions from the Phase 3 studies considered related to treatment

Study number	Treatment	Patient number	Adverse event	Severity	Causal relationship to study medicine	Outcome
411-BK-03-01-000	Marvel	3073	paronychia	Moderate	possible	recovered
			cellulitis	Moderate	possible	recovered
	Humulin	3009	hypoglycemia	Severe	certain	recovered/resolved
			hypoglycemia	Severe	certain	recovered/resolved
		4087	inadequate control of diabetes mellitus	Severe	probable	recovered/resolved
			hyperglycaemia	severe	probable	recovered/resolved
411-BK-03-01-001	Marvel	1223	hypoglycaemia	severe	probable	recovered/resolved
		1285	hypoglycaemia	moderate	probable	recovered/resolved (withdrawn)
411-MA-08-01-000	Marvel	235	face oedema	moderate	certain related	recovered (withdrawn)
		506	face oedema	moderate	probable related	recovered (withdrawn)
			tongue oedema	moderate	probable related	recovered (withdrawn)

In the submitted tables of serious adverse events many events were classified as mild or moderate in severity. The Applicant should clarify how SAEs were defined in the study protocols and whether or not the AEs presented in tables 0-8 and 0-9 (shown above) were in fact serious, see **LoQ.**

Laboratory findings

In all Phase 3 studies laboratory evaluations were performed including haematology, biochemistry, lipid profile and urinalysis these tests provided no indication for adverse drug reactions in patients treated with either Marvel insulins or Humulin nor were there any clinically relevant differences between Marvel insulin and Humulin.

There were no remarkable findings in regard to standard laboratory parameters. Few cases of hypoglycaemia occurred (see section on SAEs above), but this is expected for insulin, and the incidence was fairly balanced between test and reference product.

Antibodies

In the CHMP Scientific Advice, the Applicant was advised to include a sufficient number of subjects with T1DM. Thus, the Applicant should explain the reasons for why more T1DM patients were not included. Also, any measures that could be taken to gain more information regarding the comparative immunogenicity in type 1 diabetics should be discussed**.**

The primary endpoint of new study MA-08 was defined as the incidence of newly developed anti-insulin antibodies (IgG) during the double-blind treatment phase as determined by a screening assay and confirmed by a confirmatory assay. In study MA-08 only patients were included that were initially negative for insulin antibodies. A blood sample for determination of binding antibodies (screening assay) was drawn at every visit. In case of positive screening test the result was confirmed in a

second, confirmatory test. Confirmed positive samples were subject to determination of neutralising antibodies if they had a level of binding antibodies above the (higher) detection limit for neutralising antibodies.

Confirmed positive cases were evaluated for the clinical relevance of anti-insulin antibodies (development of possible insulin resistance) by evaluating the insulin dose, glucose control, and adverse events. The Applicant states that no cases of apparent increase of the dosage of insulin or deterioration of glucose control were registered.

Antibody measurements from the previous study BK-03 were considered unreliable due the use of an insensitive assay and thus are not reported here.

The assay used for the detection of binding antibodies (screening and confirmation) was of commercial source and is in general considered appropriate in design. Acceptable validation was performed. However, because this was not intended by the Applicant, it is not able to discriminate between antibodies against native and modified insulin. Hence, it cannot answer the question whether or not modifiedinsulincould be more immunogenic in patients than native human insulin. Furthermore, it is not designed to detect antibodies of classes other than IgG, e.g. IgE, which could be important for hypersensitivity reactions.

In contrast, the assay for neutralising antibodies is questionable in that it did not measure inhibition of insulin effect but instead determined inhibition of binding to a recombinant insulin receptor in a highly artificial system. The Applicant is asked to comment.

The proportions of patients with newly developed antibodies were 32% vs. 22% for test vs. reference in Type 1 diabetics and 28% vs. 29% for test vs. ref. in Type 2 diabetics (study MA-08). It should be noted that the number of Type 1 diabetics was low (22 vs. 18 patients, test vs. ref.) so that only limited conclusions can be drawn from this subgroup.

Anti-insulin antibodies demonstrating a neutralizing capacity in-vitro were detected in patients (Marvel insulin n= 6, 3.06% and Humulin n=4, 2.11 %). In these patients the comparison of the mean daily dose of insulin, HbA1C, as well as minor and major hypoglycaemic episodes revealed no clinically relevant differences. However, the number of patients was very low, and no firm conclusions can be drawn based on these data.

Regarding the subgroup analysis according to type of treatment, in the Marvel group a somewhat larger number of subjects with the free combination compared to the fixed combination developed new antibodies (36.4% vs. 23.9% respectively), whereas the opposite was true for the Humulin group (22.9% vs. 31.7% respectively). The capacity for building antibodies is not expected to be different between the fixed and free insulin combinations.

The antibody titres increased over time in both treatment groups (what is unsurprising since only antibody-negartive patrients were included in the study MA-08). At the latest time point (28 weeks) the titre was numerically higher in the Marvel than in the reference group (see Figure TF4 below); the confidence intervals were wide but this can be explained by the fact that a large proportion of the patients had no antibodies at all. Follow-up immunogenicity data from the extension phase of study MA-08 should be provided pre-marketing.

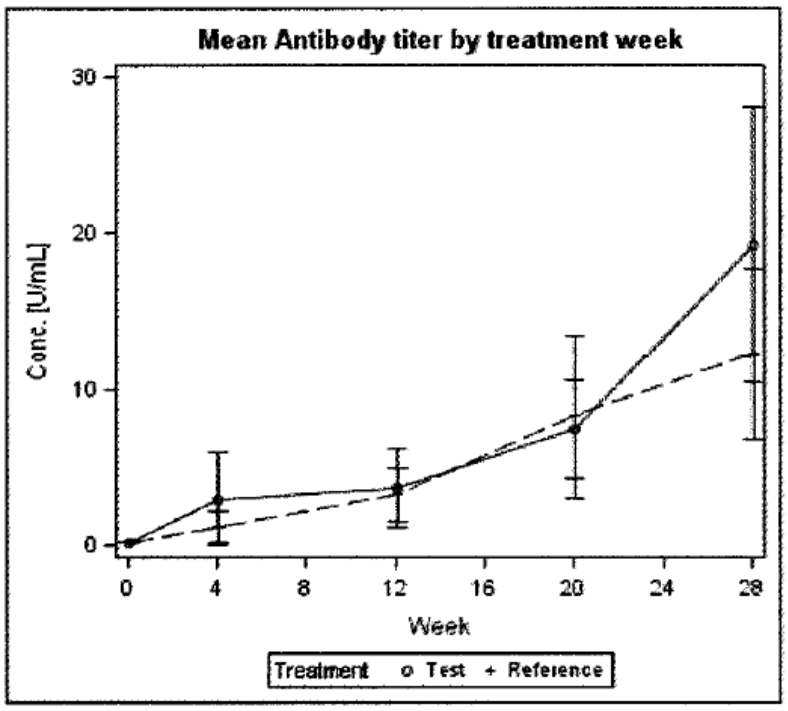


Figure TF 4: Mean titre (:t95% confidence intervals) of anti-insulin antibodies for the duration of double-blind treatment in patients positive for antibodies in the per protocol set

Safety in special populations

Special populations were not studied. This is not required for demonstrating biosimilarity.

Immunological events

There were several potentially immunological events, in most cases in patients receiving Marvel insulin. Potential immunogenicity is already widely discussed above.

Furthermore, in the CHMP Scientific Advice the Applicant was advised to also test for immunogenicity against host cell proteins. These data have not been presented. The quality data (protein purity data) indicates that the Marvel product is somewhat less pure than the originator. To justify that this has no impact on the clinical efficacy and safety of the product, the Applicant should submit immunogenicity data against host cell proteins. LoQ

Safety related to drug-drug interactions and other interactions

No special studies were performed according to the biosimilarity approach taken. Potential drug-drug interactions of insulin are well known.

Discontinuation due to AES

In study MA-08 and in the Type 2 diabetics of study BK-03 more patients in the Marvel than in the reference group discontinued due to AEs. The imbalance was mainly caused by potential hypersensitivity reactions which were in most cases considered related to study medication by the investigator. Potential immunogenicity is in detail discussed above.

One patient discontinued the study due to deterioration of diabetes in association with the development of anti-insulin antibodies (IgG levels increased and HbA1C increased). This case should be presented. LoQ

Discussion on clinical safety

Overall, the presentation of data is limited and many tables included in this assessment report have been found in appendices to the study protocols. Furthermore, in several instances there are discrepancies between the data presented in the text and in the different tables. Also, safety data from the Phase 3 studies are presented separately for each study, whereas a pooled analysis, accounting for patient exposure (number and duration), would have been preferable. This makes the safety assessment difficult.

There were some rather unusual events in the Marvel group of both trials, MA-08 and BK-03, which were considered related by the investigator and led to discontinuation of study drug. In consequence, there were more discontinuations due to AE in trial MA-08 and in the T2DM subpopulation of trial BK-03. These unusual events were suspicious of hypersensitivity reaction (3 cases of face oedema, in part combined with other signs such as skin reaction and tongue oedema and one further case of skin oedema); one case of eyelid oedema was reported in the reference group, considered not related by the investigator and not leading to discontinuation. No clear cause for these reactions could be established. The Applicant compiled all AEs that could theoretically represent a hypersensitivity reaction. This listing included rather unspecific events such as cough or dyspnoea for which could also be due to other conditions. Detailed reports of these cases are needed to decide whether or not hypersensitivity is the likely cause and, in consequence, there is an imbalance in hypersensitivity reactions between the Marvel and reference group.

The number of patients with newly developing antibodies against insulin in study MA-08 was not different between test and reference. On the other hand, among patients receiving Marvel insulin the mean insulin antibody titres were higher at the last measurement point (week 28), although with a wide and overlapping SD, and the maximal titres reached were higher than among patients receiving Humulin. More patients on test vs. reference insulin developed AEs suggestive of hypersensitivity reactions, although insulin antibodies, so far, have not been implicated in the development of such reactions. To further clarify the issue, additional safety and immunogenicity data from the extension phase of study MA-08 are requested pre-licensing.

In the CHMP Scientific Advice, the Applicant was encouraged to include a sufficient number of subjects with T1DM in the immunogenicity study. The Applicant should therefore explain the reasons for why more T1DM patients were not included. Also, any measures that could be taken to gain more information regarding the comparative immunogenicity in type 1 diabetics should be discussed.

Increased immunogenicity, if real, could be due to some alterations in active substance itself but could also be due to aggregates, accompanying impurities such as modified insulin molecules, excipients (in particular protamine) or host cell proteins (HCP). In the CHMP Scientific Advice the Applicant was advised to also test for immunogenicity against host cell proteins. Thus,the Applicant should submit immunogenicity data against host cell proteins.

Furthermore, the hypersensitivity reactions observed could hint to the formation of antibodies of the IgE class. The assay used for detection of insulin antibodies is designed to detect IgG type. An assay for detection of HCP antibodies in serum was validated but was obviously not used. Thus, no information is available on the presence of HCP antibodies of either class.

The most salient difference between Marvel insulin and Humulin in respect to pharmaceutical quality is the presence of the impurity (see pharmaceutical part of the AR for details).. Therefore, it should be made clear whether or not the impuritycould contribute to the immunogenicity of Marvel insulin. It should also be looked for antibodies of other classes than IgG because hypersensitivity reaction could also be caused by IgE.

More information is needed to allow full assessment of the reliability of the antibody assay, e.g. method transfer, appropriate use of tracer and reactivity of antibodies towards Marvel insulin and Humulin, see LoQ.

Marvel insulins were obviously already marketed in Russia and other countries for some time. More detailed information is not available to date. This post-marketing experience could contribute to the safety database but the Applicant did not comment whether or not post-marketing data are available. This should be clarified, see LoQ.

Conclusions on clinical safety

Isomarv yielded overall a similar incidence of adverse events and serious adverse events as the comparator Humulin. However, potential hypersensitivity reactions, regarded as related and leading to discontinuation of study drug, were more frequent in the Marvel than in the Humulin group in both trials, MA-08 and BK-03. Therefore, all cases of potential hypersensitivity should be presented in detail to confirm or rule out other causes for these AEs. Furthermore, a careful comparison of the impurity profile of Marvel insulin and Humulin should be provided in order to identify potentially immunogenic by-products. The immunogenicity should be further evaluated and additional safety and immunogenicity data from the extension phase of study MA-08 should be provided pre-licensing.

As long as it cannot be ruled out that the Marvel insulin preparation has a higher risk for serious hypersensitivity reactions the product appears not approvable.

Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the Marvel LifeSciences system of pharmacovigilance (Version 2.0 dated 30 June 2011). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considers that the Pharmacovigilance system as described by the applicant has the following deficiencies:

- The description of the organisation should also include an organisation chart for Marvel Sciences Ltd. showing the external pharmacovigilance department and the reporting lines of the QPPV.
- Interfaces with other departments involved with pharmacovigilance activities (e.g. regulatory affairs, marketing, quality assurance) should be identified and a brief summary of pharmacovigilance activities undertaken by each unit should be provided.
- The flow chart illustrating the flow of safety reports or the description of the major processing steps should be expanded to include internal and external timelines.
- From the description of written procedures it is unclear if the applicant or his service provider has SOPs covering the following activities: activities and back-up procedure for the QPPV, meeting commitments to competent authorities in relation to a marketing authorisation, and archiving. For those activities covered by SOPs the description in the section on procedures should be updated

accordingly, for those activities not covered a time plan should be provided by when the SOPs are expected to have been implemented. This should be before the product is placed on the market.

- The location of training records, CVs and job descriptions (e.g. pharmacovigilance or human resources department) should be provided.
- The archiving location of pharmacovigilance source documents should be briefly described (Access control? Fire safety?).
- The characterisation of the quality management system should include information on organisational roles and responsibilities for the activities and documentation, and for insuring corrective and preventive action. Special emphasis should be placed on the aspects quality assurance (frequency and documentation of the internal audits of the pharmacovigilance system, responsibility for ensuring resulting corrective and preventive action) and quality control (e.g. control of compliance with 15-day-report and PSUR-submission dates).
- Audit frequencies should be providedThe applicant is requested to provide a revised description of the pharmacovigilance system answering the above-mentioned questions. The revised description should be submitted in a tracked and in a clean version to facilitate assessment. Future versions of the detailed
- description of the pharmacovigilance system should adhere to the content and structure specified in Volume 9A.

Provided that the deficiency is rectified prior to the applicant placing the medicinal product on the market, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of Pharmacovigilance is in place and functioning before the product is placed on the market. (other concerns)

Risk management plan

The applicant provided the following pharmacovigilance plan:

SAFETY CONCERN	PLANNED ACTIONS
Important Identified Risks:	
1) Hypoglycaemia	Routine pharmacovigilance including: Continued monitoring of event frequency
2) Injection Site Reactions	Routine pharmacovigilance including: continued monitoring of frequency
3) Hypersensitivity	Routine pharmacovigilance including: continued monitoring of frequency
4) Interchangeability or substitution	All adverse events received concerning patients who change from other insulins to Marvel insulins should be monitored and considered cases of interest. Frequencies of events from the patients should be monitored using routine Pharmacovigilance including changes in frequency.
Important Potential Risks:	
1) Antibody-Mediated Insulin Resistance	Routine pharmacovigilance including: Continued monitoring of event frequency
2) Hyperglycemias	Hyperglycaemias will be monitored as a case of interest and following review, an update will be made to the reference safety information if warranted.
Important Missing Information:	
1) Use in Paediatrics Under 18 Years Old	Events resulting from use in children will be monitored as cases of interest and routine Pharmacovigilance will be carried out including signal detection.
2) Use in pregnant and lactating women	Routine pharmacovigilance including: Continued monitoring of event frequency
3) Use in a variety of ethnicities (non-Caucasian)	Plan is to market Marvel insulins throughout Europe in cosmopolitan areas where all races will be exposed. Adverse events from these groups will be monitored using routine pharmacovigilance.

The inclusion of *hypoglycaemia* and *hypersensitivity* as important identified risks in the RMP is endorsed, as is the inclusion of *antibody-mediated insulin resistance* as an important potential risk. *Lipodystrophy* also described as *injection side reactions* does not need to be included in the RMP as the health impact is considered low and the risk should be easy manageable. *Transferring patients to another brand of insulin* (=*interchangeability or substitution*) can be associated with hypoglycaemia and/or hyperglycaemia. However, *hypoglycaemia* is already included as an important identified risk. Furthermore, *hyperglycaemia* is normally managed by the patient, who will monitor glucose levels and increase the insulin dose when needed. Thus, *hyperglycaemia* and *interchangeability* do not need to be included in the RMP. On the other hand, the applicant should consider including patients with important renal, hepatic or cardiac co-morbidities or patients with cancer in their medicinal history those were excluded from the studies as important missing information.

Formal aspects:

The classification of risks as identified or potential in the *summary of ongoing safety concerns*, is different from the classifications provided in the details of identified and potential risks in the safety specification. The wording should be harmonised by the applicant.

The Applicant states in section 1.3.5 and section 1.3.2 respectively that *use in different disease severities* like in patients with severe insulin resistance and *use in elderly subjects with T1DM* have been included as missing information, however, it cannot be found in the summary of safety concerns (section 1.10 or section 2). So, it should be added.

The applicant should classify studies as additional pharmacovigilance activities and labelling as routine risk minimisation activity according to the RMP template.

The open-label extension phase of the immunogenicity study 411-MA-08-01-000 is still ongoing. The study protocol should be annexed to the RMP.

Evaluation of the need for risk minimisation measures/Risk minimisation plan

The Applicant considers additional risk minimisation measures necessary for the potential risk of antibody-mediated insulin resistance (section 3.1). The Applicant should clarify what additional risk minimisation activities are being proposed and should include them in the risk minimisation plan as appropriate.

However, to be in line with the RMP template the applicant should include in the RMP (section 5) a summary of all routine and additional pharmacovigilance activities as well as all routine and additional risk minimisation activities within a table as outlined in the template.

4. ORPHAN MEDICINAL PRODUCTS

N/A

5. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

The current application is for a biological medicinal product, claimed to be similar to a reference product already licensed. For a biosimilar medicinal product, it is important to show similarity with the reference product, not patient benefit *per se*. Based on demonstrated similarity, the biosimilar can refer, at least partly, to the efficacy and safety experience gained with the reference product.

The previously submitted study FARMOVS 21/2003 in healthy volunteers and the new study BBRC/CLN/08/001 in T1DM patients could support the assumption of similar time-concentration and time-action profiles of Isomarv and Humulin I but several major issues would need to be resolved (see below). PK and PD studies are pivotal for the demonstration of similar efficacy of two insulins because they are more sensitive to detect product-related differences than efficacy studies using HbA1c as endpoint.

The two clinical trials, study 411-BK-03-001-0000 and study 411-MA-08-001-0000 in patients with type 1 or type 2 diabetes are considered only supportive for the purpose of demonstrating similar efficacy of Isomarv and the reference product Humulin I. Although in both studies results of HbA1c at week 28 (change from baseline was not investigated) tended to favour reference treatment, the upper limit of the 95% CIs of the treatment differences for the overall study populations were contained within the non-inferiority margin of 0.4% considered acceptable by CHMP (see EMEA/ H/ SA/1118/1/ FU/ 2008/ SME/ II). HbA1c results of the extension study 411-BK-03-01-0001 showed no trend for deterioration of glycaemic control in the course of treatment with the study drug. Therefore, the data submitted provide reasonable support of comparable efficacy between Marvel insulin and Humulin.

Uncertainty in the knowledge about the beneficial effects

The old study FARMOVS 21/2003 was performed open-label, which could have introduced a bias in adjustments of glucose infusion rate in this manual clamp. This issue should be addressed by the Applicant.

Several issues have been identified in the study report of the new study BBRC/CLN/07/001 including statistical errors, unclear calculations (statistical analysis plan has not been provided) and inconsistent or missing information casting serious doubts on the validity and reliability of the data. Furthermore, the duration of the new clamp study is considered too short to appropriately capture the time-action profile of this intermediate-acting insulin. The original study protocol, the statistical analysis plan and the bioanalytical reports have not been submitted

Regarding the phase 3 studies, no analysis comparing the evolution of HbA1c from baseline to week 28 in study 411-08-01-0000 has been submitted, which is regarded to be the comparison of interest. In addition, data in this study should also be presented for the safety population as the objective of the study has been changed from a non-inferiority to a descriptive approach.

Risks

Unfavourable effects

Apart from the known undesired effects of insulin (e.g. hypoglycaemia, weight gain) which were similar between Marvel insulin and Humulin there were more adverse events that led to discontinuation in the latest phase 3 study MA-08 and there were more events that were considered probably or certainly related to treatment in the Marvel group. Notably, these events were not expected from the known pharmacological profile of insulin but instead were suggestive of hypersensitivity reaction (e.g. face oedema and skin reaction). In fact, Marvel insulin contains a major impuritythat is not present in Humulin. The immunogenicity of this impurity was not fully established.

Furthermore, although the incidence of anti-insulin antibodies was similar between treatment groups, the titre of anti-insulin antibodies was numerically higher in the Marvel group than in the comparator group at week 28. The significance of this finding is unknown

Uncertainty in the knowledge about the unfavourable effects

It is not known whether the adverse events that were suspicious of hypersensitivity were indeed due to immunological processes. Furthermore, it is not clear whether the numerical imbalance in the incidence of these events is true or if it is only due to random fluctuation. Therefore, the Applicant should provide detailed information on all cases of potential hypersensitivity to confirm or rule out an immunological event. Furthermore, the impurity profile of Marvel insulin should be re-evaluated in respect to potentially immunogenic compounds.

Balance

Importance of favourable and unfavourable effects

For a medicinal product claimed to be similar to another one already licensed, it is important to demonstrate similarity with the reference product, not patient benefit *per se*. Being a biosimilar drug, the favourable effects are limited to the established therapeutic effects of insulin. The advantage of a biosimilar insulin could improved access. On the other hand, hypersensitivity reactions, if true, that appear more frequent and more serious with Marvel insulin than with the comparator are considered

an important drawback. In fact, one case of tongue oedema was observed what could in principle be life-threatening.

Furthermore, due to open issues (including GCP) in the conduct of the PK and PD studies, biosimilarity could not be demonstrated yet.

Benefit-risk balance

The submitted data currently do not allow a conclusion of similar quality, efficacy and safety of Isomarv medium with the reference product Humulin I. A relevantly increased immunogenicity (if true) of Marvel insulin would not be acceptable. Demonstrating biosimilarity is essential for this type of application to allow safe use of the product.

Discussion on the benefit-risk assessment

The Applicant will need to solve major quality issues related to validation of the drug substance manufacturing process, specification of impurities specific for Marvel insulins and specifications to support consistent quality of the drug product.

On the clinical side, missing documents and information will need to be submitted for evaluation, major concerns regarding the validity and reliability of the data of study BBRC/CLN/08/001 and safety concerns regarding potential immune-mediated hypersensitivity reactions need to be resolved pre-licensing to ensure safe use of Isomarv medium.

In addition, further issues as described in the LoQ need to be resolved pre-licensing.

5.1. Conclusions

The overall B/R of Isomarv medium is negative.