EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/596513/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Solumarv

International non-proprietary name: insulin human

Procedure No. EMEA/H/C/003858/0000

Note

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

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Table of contents

List of abbreviations

3T3-L1	adipocyte cell line
A(D)Rs	Adverse (drug) reactions
A660	absorbance at 660 nm
AAS	atomic absorption spectrometry
ab, AB	Antibody
AEs	Adverse events
AEX	Anion Exchange Chromatography
Akt	proteinkinase B/PKB
ALT	Alanine aminotransferase
approx	Approximately
AR	Adverse reaction
AST	Aspartate aminotransferase
AUFS	Absorbance Units Full Scale
BHT	ButylhydroxytoluolButylhydroxytoluol
BHT-OH	2,6-Di-tert-butyl-4-hydroxy-4-methyl-2,5-cyclohexadien-1-one
BK-03, BK-03(o)	411-BK-03-01-0000 (db) and 411-BK-03-01-0001 (open, extension)
BLQ	Below the Limit of Quantitation
bp	base pairs
BPV	Bovine Parvovirus
BUN	blood urea nitrogen
BVDV	Bovine Viral Diarrhea Virus
bw	body weight
Ca	Calcium
CCDRD	Cooperative Clinical Drug Research and Development
CD	Circular Dichroism
CDSSTR	Algorithm for determination of protein secondary structure
CFA	Complete Freud's Adjuvant
CFU	Colony Forming Unit
CHMP	Committee for Human Medicinal Products
CHO	Chinese Hamster Ovary
CHO.T cells	Chinese Hamster Ovary cell line
CI	Confidence interval
Clamp	Hyperinsulinaemic euglycaemic clamp
Combimarv	Marvel rh-insulin intermediate biphasic pharmaceutical form
CPB	Carboxypeptidase B
CPE	Cytopathic Effect
CPP	Critical Process Parameter
CPV	Canine Parvovirus
CRO	Clinical Research Organisation
CRP	C-reactive protein
CRS	Chemical Reference Substance
CSR	Clinical study report
CTD	Common Technical Document
Curr. Ed	Current Edition
D	Dalton
Da	Dalton

Db	Double blind (study)
DF	Diafiltration
DLS	Dynamic light scattering
DP	Drug Product (referred to as finished product)
DS	Drug Substance (referred to active substance)
DSC	Differential Scanning Calorimetry
DSP	Downstream Process
DTT	Dithiotreitol
ECG	Electrocardiogram
EMCV	Encephalomyocarditis Virus
EMEA / EMA	European Medicines Agency
EoP	End of Production
EP	European Pharmacopoeia
EU	Endotoxin units
F	female
FARMOVS	FARMOVS-PAREXEL, PAREXEL-FARMOVS CRO
FDA	Food and Drug Administration
FT-IR	Fourier Transformation Infrared Spectrometry
GCP	Good Clinical Practice
GIR	Glucose infusion rate
GIRmax	Maximum glucose infusion rate
Gmean	Geometric mean
GS	glycogen synthase
GSK-3	glycogen synthase kinase
H, h	Hour(s)
HAd	Haemadsorption
Hb	haemoglobin
HbA1c	Glycosylated haemoglobin in blood
HCl	Hydrochloric Acid
HCP	Host Cell Proteins
HCT	haematocrit
HMW	Higher Molecular Weight
HMWP	High Molecular Weight Protein
HPLC	High Performance Liquid Chromatography
HPSEC	High pressure size exclusion chromatography
hrs	Hours
HV	Healthy Volunteers
i.p.	intraperitoneal
ICH	International Conference on Harmonisation
IEF	Isoelectric Focussing
IEP	Isoelectric point
IFA	Incomplete Freud’s Adjuvant
IGF-1	insulin-like growth factor-1
IgG	Immunoglobulin G, antibody
IPC	In-Process Tests
IR	Infrared
Isomarv	Marvel rh-insulin intermediate pharmaceutical form
ITT	Intent-to-treat
IU	International Unit
K	Potassium

kDa	Kilodalton
kg	Kilogram
LAL	Limulus Amoebocyte Lysate
LC-MS	Liquid Chromatography – Mass Spectrometry
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
Lys	Lysine
M	male
MA-08	411-MA-08-01-0000 immunogenicity study db and open extension
MAA	Marketing Authorisation Application
MAA	Marketing authorisation application
MAP-kinase	mitogen-activated protein-kinase
MCB	Master Cell Bank
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDL	Method Detection Limit
MedDRA	Medical Dictionary for Drug Regulatory Activities
Mg	Magnesium
mL	Millilitre
MLV	Murine Leukemia Virus
mM	Millimolar
MNC	mononuclear cells
MS	Mass spectrometry
Mw	Molecular Weight
Na	Sodium
NAB	Neutralising antibody
NIH-3T3	fibroblast cell line
NIR	Near-Infrared Analysis
nm	Nanometer
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOAEL	no observed adverse effect level
NOR	Normal Operating Range
NPH	neutral protamine Hagedorn
OD	Optical Density
OOS	Out of Specification
PAR	Proven Acceptable Range
Para-3	Parainfluenza Virus-3
PC-HPLC	perchlorate HPLC
PD	pharmacodynamics
PD	Pharmacodynamics
Ph. Eur.	European Pharmacopoeia
pI	Isoelectric Point
PK	Pharmacokinetics
PNC	polymorphonuclear cells
ppm	Parts per million

PPS	Per-protocol set
PRAC	Pharmacovigilance risk assessment committee
PROFIL	Profil Institut für Stoffwechselforschung GmbH
PROFIL study	PROFIL001SoluMarvHV, Solumarv study
PRV	Pseudorabies Virus
PST	Process Simulation Test
Pts	Patients
Q-TOF	Quadrupole Time-of-Flight
R	reference substance
recH insulin	recombinant human insulin
rh-insulin	recombinant human insulin
RMaP	Risk Management Plan (normally abbreviated RMP, but clashes here)
RMP	Reference Medicinal Product
RP-HPLC	Reverse Phase HPLC
RS	Reference Standard
RSD	Relative Standard Deviation
RT	Room Temperature
S, I and M3	Humulin soluble, Isophane and Mix pharmaceutical forms
s.c.	Subcutaneous
SAE	Serious adverse event
SAR	Serious adverse reaction
SC, s.c.	Subcutaneous (ly)
SD	Standard Deviation
SDS-PAGE	sodium dodecyl sulfate – poly-acrylamide gel electrophoresis
SDS-PAGE	Sodium Dodecyl Sulphate - Polyacrylamide Gel Electrophoresis
SE(C)-HPLC	Size Exclusion HPLC
SEM	standard error of the Mean
SmPC	Summary of Product Characteristics
SIHR/SIHRR	Batch-coding system
SMQs	Standardised MedDRA Queries (SMQs) (MedDRA version 15.0),
SOD	Superoxiddismutase
Solumarv	Marvel rh-insulin soluble/fast pharmaceutical form
Spec(s)	Specification(s)
SST	System Suitability Test
T	test substance
T1/2	Apparent terminal elimination half-life
T1DM	Type-1 diabetes mellitus
T2DM	Type-2 diabetes mellitus
TK	toxicokinetics
TMP	Test medicinal product
TTC	Threshold of Toxicological Concern
UF	Ultrafiltration
USP	United States Pharmacopoeia
USP	Upstream Process
UV	Ultraviolet
WCB	Working Cell Bank
WFI	Water for Injections
X-MuLV	Xenotropic Murine Leukemia Virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Marvel Lifesciences Ltd submitted on 5 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Solumarv, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004 . The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2013.

The applicant applied for the following indication: “treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis”

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products.

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

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice/Protocol Assistance

The applicant received Scientific Advice from the CHMP on 24 July 2008, 18 December 2008, 17 February 2011 and 23 April 2013. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 5 June 2014.
- The procedure started on 25 June 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 September 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 September 2014.

- PRAC RMP Advice and assessment overview, adopted on 9 October 2014.

- During the meeting on 23 October 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 October 2014.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 April 2015.

- The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:

A GMP inspection took place at one active substance manufacturer in France between 19th and 22nd January 2015.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 June 2015.

- PRAC RMP Advice and assessment overview, adopted on 11 June 2015.

- During the CHMP meeting on 25 June 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 September 2015.

- PRAC RMP Advice and assessment overview, adopted on 8 October 2015.

- During the CHMP meeting on 20 October 2015, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.

- During the meeting on 19 November 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Solumarv.

2. Scientific discussion

2.1. Introduction

Solumarv, by Marvel LifeSciences Ltd., contains the active substance human insulin in a soluble form produced by recombinant DNA technology in transformed Escherichia (E.) coli bacteria.

Solumarv is formulated as 100 IU/ ml, solution for injection in a cartridge, filled in 3 ml cartridges made of Ph Eur Type 1 glass closed with aluminium capped bromobutyl rubber disks (Ph Eur) and equipped with moveable rubber plungers (Ph Eur).

Solumarv is presented as a biosimilar to the EU reference product Humulin S from Eli Lilly and Company Ltd (UK). Humulin S has been licensed and placed on the European market since 1987.

The applicant applied for the indication “For the treatment of patients with diabetes mellitus who require maintenance of glucose homeostasis” in line with the indication of the reference product.

Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycaemia due to defective insulin secretion, insulin action or both. Use of insulin is well established for the treatment of type 1 and type 2 diabetes mellitus. The route of insulin administration for most patients with diabetes is subcutaneous.

The applicant has submitted previously two marketing authorisation applications for this recombinant insulin which were both withdrawn during the evaluation of the applications. Details on the two previous submissions at the time of withdrawal can be found in the withdrawal assessment reports, respectively for Insulin Human Rapid Marvel (EMEA/H/C/000845) and Solumarv (EMEA/H/C/002506).

The development program included the following clinical trials which were submitted by the applicant for the purpose of this application:

- One pivotal comparative PK-PD clamp study in healthy volunteers (PROFIL001SoluMarvHV)
- One supportive comparative PK-PD clamp study in healthy volunteers (FARMOVS 232/2002)
- A 6-month safety and efficacy 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, respectively.
- A 6-month 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

Hence, this submission contained two sets of BE studies (one manual clamp performed in 2002 (considered supportive) and one automated clamp performed in 2014 (considered pivotal), both in healthy volunteers), and two clinical phase 3 efficacy and safety studies, both in T1DM and T2DM (performed in 2005-2008 and 2009-2013).

The following Guidelines are relevant for this application:

1) Guidance on Similar Medicinal Products Containing Recombinant Human Soluble Insulin (EMEA/CHMP/BMWP/32775/2005) and its draft revision “Guidance on Similar Medicinal Products Containing Recombinant Human Insulin and insulin analogues” (EMEA/CHMP/BMWP/32775/2005 Rev. 2).

2) Guideline on similar biological medicinal products (EMEA/CHMP/437/04)

3) EMEA/CHMP/42832/2005 Guideline on similar biological medicinal products containing biotechnology derived medicinal products as active substances: non-clinical and clinical issues) and annexes and EMEA/CHMP/BWP/49348/05

4) Guideline on similar biological medicinal products containing Biotechnology-derived Proteins as Active Substance - Quality Issues (EMEA/ CHMP/BWP/49348/05).

5) Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, 2010)

2.2. Quality aspects

2.2.1. Introduction

Solumarv is presented as a Biosimilar medicinal product to the reference product Humulin S from Eli Lilly, which is produced in E. coli by recombinant DNA technology.

The finished product is presented as a solution for injection containing 100 IU/ ml of human insulin as active substance.

Other ingredients are meta-cresol, glycerol, water for injections and hydrochloric acid and sodium hydroxide (to adjust the pH).

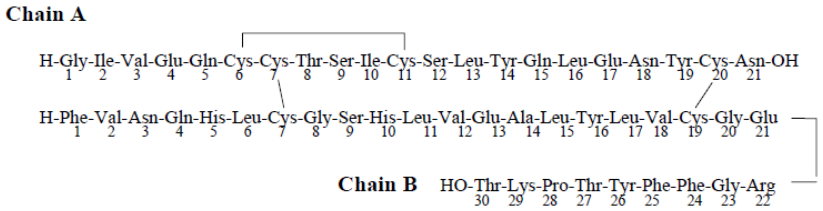
The product is available in a cartridge (Type I glass) equipped with a moveable bromobutyl rubber plunger head and closed with an aluminium rubber disc. Each cartridge contains 3 ml of solution and comes in a pack size of 5 cartridges. The cartridge is intended to be used with a re-usable pen device (AdvaPen).

Solumarv has the same qualitative composition and pharmaceutical form as the reference product Humulin S.

2.2.2. Active Substance

General information

The active substance, human insulin, is a human protein consisting of two polypeptide chains (A and B chain). The A-chain has 21-amino acids, and the B-chain has 30 amino acids. The chains are linked together through the sulphur atoms of cysteine (Cys) and are not glycosilated. The molecular formula is $C_{257}H_{383}N_{65}O_{77}S_6$ and the molecular weight is 5808 Da (based on the amino acid sequence).



The physical appearance of human insulin is a white to practically white powder or crystals. Human insulin is practically insoluble in water and in ethanol but soluble in solutions with pH <5 such as dilute mineral acids and in solutions with pH >7 such as dilute solutions of alkali hydroxides.

Manufacture, characterisation and process controls

The active substance, recombinant human insulin, is manufactured at two EU contract manufacturers by means of an upstream and a downstream process.

Description of the manufacturing process and process controls

The manufacturing process for the active substance has not been clearly identified and documented in the description of the manufacturing process and in the flow chart as presented in Module 3.2.S.2.2. This has been raised as a major objection at day 120 of the procedure and remains an outstanding major concern at the time of the CHMP opinion.

Main steps of the manufacturing process are fermentation, harvest, recovery from inclusion bodies and purification.

The upstream process is a conventional fermentation process. Starting from one WCB vial of E. coli) an inoculum is built up via several steps. A seed fermenter is used as inoculum for the production fermenter. The cells including the protein in the form of inclusion bodies are harvested by either centrifugation or ultrafiltration. The inclusion bodies are isolated and the inclusion body slurry is heat treated, stored and shipped for further purification.

Following shipment the heat inactivated inclusion bodies are dissolved and refolded. The precursor protein is then digested and the obtained protein complex is purified and stored for formulation into the finished product.

At the time of the CHMP opinion, information on the manufacturing process was still unclear and inconsistent throughout the dossier. With regards to the intended fermentation process it appears that the fermentation process performed results in two independent batches but this is not reflected in the flow chart and in the manufacturing process description contained in the revised Module S.2.2., Description of the Manufacturing Process. An Inspection Report of a GMP inspections performed on the active substance manufacturing site and issued during the procedure, revealed that a pooling procedure for one of the chromatographic step, which is not reflected in Module 3.S.2.2 has not been appropriately controlled. In addition assurance that the Applicant has full access to manufacturing records held at the active substance manufacturing site and that the Applicant will be informed of manufacturing process changes have not been obtained.

In addition, the Company's practice to enlarge the batch size remains to be clarified (considered obsolete since 1/22/2015 following the preapproval inspection by the ANSM inspectorate).

At time of the CHMP opinion, it also remains unclear whether purification side fractions that do not meet the pooling criteria are routinely being reprocessed and thus treated by a modified process. The routine introduction of originally unspecified and non-conforming material into the standard process is not considered appropriate by the CHMP. It has been agreed by the Applicant to remove this reprocessing from the process, but the option is still documented in the dossier.

Manufacturing process parameters, controls, respective set points and acceptance ranges as well as quantities/mass ranges of materials used have been indicated, however, with wide ranges.

At the time of the opinion, the batch size definition remains inconsistent and not conclusive. This has implications on the traceability of the manufacturing process and the active substance, respectively. The question how traceability is ensured between both active substance manufacturing sites in different EU countries can presently not be answered.

A clear batch definition was requested that includes the active substance and ensures traceability from the active substance back to one vial of WCB. The final commercial batch size can vary in quantity of recombinant insulin crystals depending on the number of inclusion body batches that may be combined. According to provided data, 95.1% of historical active substance batches have been produced from fewer inclusion body batches than applied for. Consequently, a limitation in the batch size range appears appropriate and remains an outstanding issue.

Control of Materials

Information on control and compositions of media, buffers, solvents, reagents and auxiliary substances used in the manufacturing process of human insulin has been provided.

Regarding the use of materials in the process the Applicant initially suggested using the “historical” process and a second process in parallel. Parallel use of two different active substance manufacturing processes is not considered acceptable.

The description of the construction of the insulin expression plasmid is considered satisfactory.

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 Applicant has adequately described the preparation of a future WCB.

Stability of the cell substrate was not considered adequately analysed in accordance with ICH Q5D. This remains an outstanding issue.

Control of critical steps and intermediates

Critical process parameters of the manufacturing process and the investigational results from which the respective acceptable ranges were derived have been presented. The rationale used for identification of critical steps and critical process parameters covering the manufacturing process is “risk based driven” and based on prior knowledge, which is considered acceptable based on the long manufacturing history of Solumarv active substance.

For the intermediate inclusion bodies, the specification has been amended to include acceptance criteria for all methods. However this information remains to be consistently updated throughout the dossier. Stability of the inclusion bodies has been studied to support the proposed stability of 24 months. However, it was agreed to remove the option to store inclusion bodies for a different time at different temperatures from the dossier. Several hold times are proposed both for upstream and downstream process. However, details on hold conditions have not been provided and remain an outstanding issue.

Process validation

The provided prospective process validation data is considered too limited because they cover the upstream process only and do not include the operational parameters for fermentation, harvest and recovery. This remains an outstanding major objection.

Process validation has also been presented as a retrospective review conducted in 2013 of the processes as performed in earlier years and covering the upstream and downstream process.

The basis of this validation is a total of more than 60 batches, of which 7 batches have been discarded due to technical problems. About 55% of the remaining batches are representative for the process as established since 2004 and the others are representative for a later process.

The available process validation data are considered insufficient to transparently reflect the intended commercial manufacturing process with regards to several manufacturing steps. Thus the reproducibility and robustness of the intended manufacturing process have not been demonstrated. It was further noted that differences in protein content and potency were seen when comparing the different manufacturing processes, a finding that has not be explained by the Applicant and remains unresolved. Differences are also seen in the downstream process when comparing two different processes, e.g., purity of a certain fraction and content of an impurity. However, no information on differences between the two processes has been disclosed.

Concerning the proposed reprocessing step in case of mechanical failure of a purification step acceptable validation data has been provided in support of the manufacturing step. The Applicant

agreed to discontinue another particular manufacturing step performed, however this revision is not consistently reflected in the dossier (i.e. Module S.2.5).

Following identification of the manufacturing process to be commercialised, comprehensive up-to date process validation data covering the entire manufacturing process remains to be provided in order to demonstrate reproducibility and robustness of the intended manufacturing process.

Manufacturing process development
Information on process development is very limited. The rights for the manufacturing process of recombinant human insulin were obtained from a third party following technology transfer.

Evolution of the fermentation process has been briefly described but development of the process scale has not been mentioned. Likewise, development of an alternative process using different reagents is not addressed.

The Applicant has failed to identify and document process history in detail. Distinct differences between the manufacturing processes used to generate all batches to support this MAA have not been evaluated by the Applicant taking into consideration ICH Q5E requirements. This pertains in particular to batches used during pre-clinical and clinical development and the final commercial manufacturing process. Details on changes and modifications that have been specifically introduced into the proposed commercial active substance manufacturing process have not been adequately documented. A science based risk assessment on the changes implemented during the manufacturing process history has not been provided. The impact of the process changes on the entire impurity pattern including specifically two Solumarv specific variants of insulin human has not been studied.
Thus, comparability of the different manufacturing processes preceding the final commercial manufacturing process has not been substantiated. Likewise, representativeness of materials used for characterisation, justification of specification and stability for the commercial material has not been verified.

In 2015, comparability of one retain batch each of the different batch sizes for the processes in terms of primary and secondary structure has been demonstrated in the Protagen study. However, the material as used for the immunogenicity study was not included and the Solumarv specific impurity profiles were not subject of this study.
In summary, the data for manufacturing process development presented in Module S.2.6 is insufficient to confirm comparability of the different manufacturing processes. This limits the assessment of the data used to establish the control strategy and to demonstrate biosimilarity.
In addition the representativeness of the batches used for clinical studies with the commercial product has not been demonstrated.

Characterisation
A first characterisation study was executed with one active substance batch in comparison to the Ph.Eur. insulin reference standard (CRS), the USP reference material and an in-house standard. An identical amino acid composition and sequence of both chains (percentage of sequence coverage was 95% for the A chain and 97% for the B-chain), a similar distribution of the secondary structures, an accurate molecular mass for the intact protein and A and B chains and a comparable 3D structure were confirmed for all insulin samples tested.

An additional comparability study on structural characteristics of insulin was conducted using retained samples of different manufacturing process development stages (Protagen study). The results confirm similarity of the primary, secondary and tertiary structure of the insulin.

The impurity profile of insulin was studied using four active substance batches and by applying three different methods. Apart from known impurities, a number of insulin variants could be

separated. Among these, two variants could only be detected in the Applicant's active substance batches. They result from an incomplete cleavage of the artificial insulin precursor sequence used for insulin expression. These variants showed similar results as insulin in the insulin binding assay and were categorised as product-related substances. The identity of all product-related substances was confirmed by sequence analysis using MS analysis.

The impact of specific degradation pathways on the impurity pattern of the Applicant's active substance was studied using different stress studies (e.g. elevated temperature, light, agitation, oxidation, acidic and basic conditions). Total amount of related proteins, variants of insulin, were monitored. Stressing the samples did not lead to a change in certain variants but to an increase of insulin degradation products.

Uncertainty remains on the quantity of two Solumarv-specific insulin variants in commercial active substance batches. Different methods for determination have been used during development. As equivalence of the previously used method and the method intended to be used for batch release has not been demonstrated no reliable data on the actual level of these variants in insulin is available.

Based on the results of the characterisation studies it can be concluded that the Applicant's recombinant insulin has the expected primary, secondary and tertiary structure of human insulin. In addition to the known insulin product related species and degradation products there are two insulin variants present only in Solumarv. The exact amount of these variants in a commercial batch is uncertain.

Specification

For the active substance a set of specifications has been provided which includes testing of identity by RP-HPLC and peptide map, solubility characteristics, purity by determination of high molecular mass proteins (SE-HPLC) and related substances (A21-desamido, others total by RP-HPLC), single chain precursor content, determination of sulphated ash, loss on drying, Zinc, host cell proteins and endotoxins. This set of specifications is in compliance with the Ph. Eur. monograph.

Additionally, appearance and colour, visible impurities, assay RP-HPLC (as such) and assay RP-HPLC (on dried substance), related substance including, microbial quality (TAMC) and content of residual solvent are specified. The test methods comply with the methods described in the Ph. Eur. monograph for insulin human, except for determination of certain impurities and related substances.

Determination of a particular process-related impurity is not included in the active substance specification. This has been sufficiently justified by data. The active substance specifications still need some amendment in particular with regards to the implementation of acceptance criteria for purity determination performed by SE-HPLC and all applied HPLCs.

Analytical methods

Most of the analytical procedures mentioned in the specification are compliant with the methods indicated in the Ph.Eur. monograph for Insulin human. Two analytical RP-HPLC methods have been established and validated as release methods to determine the specific impurity profile of Solumarv active substance. Different analytical methods have been used during development. However, a side-by-side comparison of the methods has not been performed. Thus, equivalence among the previously used and the intended release methods has not been demonstrated, which remains an outstanding major objection. This lack of data precludes a comparison of the batch results reported for the clinical active substance lots with those of the commercial ones and a final assessment on the actual amounts of these Solumarv-specific insulin variants in the active substance batches. Thus, the proposed specification limits for two Solumarv-specific insulin variants are not justified.

Moreover, most of the acceptance limits included in the active substance specification have been set based on a certain data set, for which statistical key data is provided. However, the historical data base is given for a particular manufacturing period and it remains to be confirmed whether the underlying data base is representative for the commercial manufacturing process.

The Applicant proposes to use only the Ph.Eur. and USP internal standards as reference standards.

Stability

The container for storage of the active substance is defined. Depending on the amount of active substance to be packed, containers of a certain size are used. The proposed and approvable storage conditions for the active substance have been provided.

Real time, real condition stability data has been presented for batches representing different active substance manufacturing processes. However only a fraction of those batches conform to the manufacturing process intended to be commercialised hence the CHMP considered that only those conforming batches should be taken as the base for claiming active substance stability.

The results for batches stored at the proposed storage conditions were found complying with the defined specification limits. Accelerated studies could support the assumption of a stable active substance under the indicated storage conditions. In accordance with the requirements of the Ph. Eur. monograph light sensitivity of the active substance should be considered when storing the active substance. The Applicant has provided a respective commitment.

The provided stability study design is considered acceptable. The respective test parameter and methods as proposed for stability testing have been reconsidered and Module S.7 has been revised to include the proposed and requested changes for stability testing.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product (Solumarv) is a multi-dose preparation. It is a clear, colourless sterile solution for injection containing 100 IU human insulin/mL (equivalent to 27.60 IU/mg). It contains meta-cresol (3.0 mg/mL), glycerol (16 mg/mL), water for injections, hydrochloric acid and sodium hydroxide as excipients. Glycerol is added as a tonicity modifier and meta-cresol as preservative. Hydrochloric acid and sodium hydroxide are added as solvent and to adjust the pH. All excipients are compendial and well known for parenterals.

The finished product is presented in 3 mL glass cartridges closed with rubber disks and equipped with a moveable rubber plunger. Each cartridge is filled with 3.2 mL to ensure a delivery volume of 3 mL. The finished product is administered after incorporating the cartridge into a re-usable pen. The brand name of the device is AdvaPen; the use of Solumarv cartridge with AdvaPen is indicated in SmPC section 6.5.

The composition of Solumarv is presented in Table 3.

Table 3. Composition of Solumarv finished product

Ingredient	Reference	Amount/1 mL	Function
Recombinant Human Insulin	Ph. Eur.	100 IU	Active substance
Meta-cresol	Ph. Eur.	3 mg	Preservative
Glycerol	Ph. Eur.	16 mg	Isotonic modifier

Ingredient	Reference	Amount/1 mL	Function
Hydrochloric acid 0.01 M	Ph. Eur.	0.4 mL	Solvent
Sodium Hydroxide 0.2 M	Ph. Eur.	q.s (~0.025 ml)	pH adjuster
Water for injections	Ph. Eur.	q.s. to 1 mL	Solvent

The formulation consists of the same excipients as the comparator Humulin S. The efficacy of the preservative meta-cresol has been demonstrated also under simulated in-use conditions fulfilled the criteria of Ph. Eur. 5.1.3.

The ability of the selected container closure system to maintain integrity under repeated use has been demonstrated. The compatibility of the container closure system with the finished product has been confirmed with real time stability studies and with supportive data of extractables and leachables studies.

The pen-injector, CE-marked Advapen, is intended for use with 3 mL insulin cartridges along with CE-marked Type A pen needles. The pen is designed to administer insulin doses in the range of 1 to 60 units, in increments of one unit. Dose accuracy test results are in compliance with the dose accuracy acceptance criteria according to ISO 11608 -1:2012.

Manufacture of the product and process controls

The manufacturing process is a traditional aseptic filling process. Insulin is dissolved in 0.01 M hydrochloride acid. After pH adjustment, water for injections is added to achieve the final volume of the active substance solution. A second solution is prepared by mixing the preservative, the isotonic agent and water for injections. The two solutions are separately sterile filtered (0.22 µm) into a common vessel to prepare the bulk solution. The solution is mixed and filled in sealed cartridges. The filled cartridges are automatically blistered and packaged.

A maximum holding time of not more than 3 hours from the end of filtration and start of the filling process was established for the sterile bulk solution. A filling time of not more than 5 hours is specified. The storage temperature of the bulk sterile product is between 15°C and 25°.

Process validation has been confirmed based on data of three commercial validation batches. The three consecutive validation batches comply with the predefined in-process control acceptance criteria and the proposed release specification.

Product specification

The finished product specification include tests for appearance, identity of the active substance and preservative (meta-cresol), High Molecular Weight Proteins (HMWP), related proteins, pH, extractable volume, total zinc, assay, meta-cresol content, sterility, bacterial endotoxins, and sub-visible particles.

The proposed release and shelf life specifications are mainly based on the Ph. Eur. monograph (0854) but have tightened limits with respect to determination of HMWP, related proteins (desamido insulin, total proteins (without desamido insulin)), human insulin content and content of zinc. In addition, Ph. Eur. procedures and specifications are included for fill volume, sub-visible particles, sterility and bacterial endotoxins.

Upon request the Applicant confirmed to further tighten the limits for A21 desamido insulin, total related proteins without A21desamido, impurities with molecular masses greater than insulin and

the assay in the shelf life specification. Furthermore, it was confirmed to establish an upper limit for the Extractable volume.

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

Batch analysis

Batch analytical data have been provided for a number of full scale production scale batches manufactured from 2003 until 2013. All batch analysis results met the finished product specification which was in force at the time of release of the batch.

Reference materials

The procedure for establishing the current and future working standard is sufficiently described.

Stability of the product

Seven commercial scale batches and three validation batches were tested for storage at 5 °C for 36 months packaged in 3 mL cartridges proposed for marketing. Stability data from six batches stored at accelerated conditions (25°C) for 6 months is also available. All stability results obtained during 36 months of storage under long term conditions comply with the proposed finished product shelf life specification. The conditions used in the stability studies were in line with ICH requirements.

In-use stability of Solumarv at 30 °C for 28 days was demonstrated with two batches, one tested at the end of the shelf-life and one tested 6 months after production.

Furthermore, it was demonstrated that the proposed packaging material (glass cartridge packed into a carton box) is suitable to protect the finished product from light.

Provided that the active substance material introduced into the finished product stability lots is confirmed to be representative for the commercial active substance quality, a finished product shelf life of 3 years when stored at 2-8 °C and four weeks after first opening when stored outside of the refrigerator and not above 30°C is approvable.

Adventitious agents

Specific raw materials are routinely used for production of the active substance. During the marketing authorisation application procedure a major objection was raised regarding the Applicants proposal to use simultaneously particular raw materials of recombinant and of animal-derived origin. During the procedure it could be clarified that the Applicant intends to use raw materials of a particular origin for the commercial process; however the concerns could only be partially resolved. The applicant intends to use raw materials of a particular origin for which viral safety has not been adequately demonstrated. For a particular raw material used no report of the virus validation study performed by the supplier has been provided. With regard to another raw material, the report of the virus validation study demonstrated that the manufacturing process of that raw material is incapable of removing / inactivating small, non-enveloped viruses. In vitro virus testing is not considered adequate to compensate for this lack of virus removal capacity of the manufacturing process or the lack of knowledge regarding the virus clearance capacity.
The confirmation of the recombinant origin of another raw material remains to be provided.

Comparability exercise versus the reference medicinal product

An analytical comparability study was performed in 2008, testing the following samples of insulin: four Solumarv active substance batches, active substance extracted from one Solumarv finished product batch and insulin extracted from three Humulin S lots. All active substance samples extracted from the Solumarv batch contained insulin material produced between 2003 and 2007.

No evidence has been provided that these batches are representative for the commercial active substance manufacturing process taking into account the different changes implemented in the manufacturing process since that time. In this study, the structural comparability of insulin samples from the active substance batches and from Eli Lilly was evaluated using numerous analytical state-of-the-art methods. Similarity in terms of primary, secondary, tertiary structure, molecular mass and size distribution was shown. A similar pI was confirmed. Comparable results by another method described in the Ph. Eur. were demonstrated. One Solumarv active substance sample and three Eli Lilly insulin samples resulted in comparable peptide maps also when peptide mapping was performed under reducing conditions.

The same insulin samples were also used to evaluate the differences in the impurity profiles. Similar levels of hydrophilic and hydrophobic impurities were found in Humulin S and Solumarv batches. Likewise comparable amounts were determined for the insulin variants B3 desamido, B4and/or A5 desamido and A21 desamido insulin. However two specific variants could only be detected in Solumarv insulin.

Stress studies by applying different stress conditions (heat, acidic pH, basic pH, oxidation, agitation and light exposure) confirmed similar degradation curves for high molecular weight proteins, desamido variants, DesThreB30 insulin and total related proteins between the test and reference product. It was further demonstrated that stress conditions do not have an effect on the amount of Solumarv specific insulin in the finished product batch.

Comparability between the test and the reference medicinal product was further studied at finished product level. Three Solumarv batches produced with certain active substance material were tested in comparison to five Humulin S batches. Analyses were conducted based on the release specification only. The panel of test parameters chosen and the methods applied were far below the requirement for an extensive analytical characterisation of the test and reference medicinal product in parallel to support a biosimilar approach. The related proteins were not tested in detail. Only results for A21 desamido insulin and total amount of impurities (without A21 desamido) have been presented. The same test program has been applied in a recent comparability study with one Solumarv finished product lot against two Humulin S batches.

The difference in the Zn content in Solumarv finished product solution versus Humulin S has been discussed by the Applicant and is considered justified from the quality point of view. In addition, comparable biological activity of Humulin S and Solumarv was confirmed by applying different biological assays.

Furthermore, a structural and physiochemical comparison study between the test and the reference product was conducted in 2015 (Protagen study). Retained samples from previous active substance manufacturing processes stated to represent the commercial process were compared versus insulin from Humulin S. The results confirmed the expected primary, secondary and tertiary structure of human insulin for insulin generated from different stages of process development and similarity to the insulin structure of Humulin S. A comparison of the impurity profiles was not performed as it would not be meaningful considering the age of retained samples.

A final conclusion on analytical comparability between Solumarv and Humulin S from Eli Lilly, however, cannot be drawn on the basis of the data provided. While overall the number of batches of the test and the reference product introduced into the comparability exercises is deemed sufficient, the representativeness of the test product batches for the commercial process and product has been questioned. As the commercial active substance manufacturing process has not been clearly identified and comparability between the process development stages has not been confirmed, the analytical comparability study performed in 2008 to support biosimilarity of Solumarv and Humulin S cannot be considered representative for the commercial product. Further

analytical comparative studies conducted so far did not cover the complete quality profile of Solumarv active substance and can only be considered supportive.

Furthermore, different analytical methods were used to determine the two Solumarv specific variants and equivalence among these methods was not demonstrated. The reported amounts of the two Solumarv specific variants in Solumarv active substance development lots cannot be directly compared with those of the commercial lots. Thus, evidence has not been provided that the quality profile of commercial Solumarv represents the profile of active substance lots used in the analytical, preclinical and clinical studies with regard to the specific insulin variants**.**

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

At Day 120 of the procedure seven major objections on quality aspects have been raised by the CHMP. After the responses to the Day 180 List of Outstanding issues, five of the seven major objections and a number of other concerns remained unresolved. Two of the initial major objections were combined and one major objection has been proposed to be addressed in the context of the GMP framework. The Applicant gave an oral explanation in front of CHMP in relation to the five outstanding major objections on quality.

The first unresolved major objection relates to the description of the manufacturing process, which contains contradictory information on the fermentation process, pooling procedure, reprocessing of non-complying RP-HPLC side-fractions and blending of batches. The batch numbering system for the two manufacturing sites is not consistent impeding traceability of materials throughout the process from the working cell bank to the final active substance. During the oral explanation at CHMP it became evident that the Applicant does not yet have full access to all process data on the active substance manufacturing process from the cell banks, through upstream processing and downstream processing. In addition, assurance that the Applicant will immediately be informed of all changes at both EU manufacturing sites affecting the active substance manufacturing process remains outstanding. Full access to all manufacturing data affecting the active substance and finished product is a basic requirement for all biological medicinal products in the EU.

The active substance manufacturing process which is intended to be commercialised remains to be clearly identified and documented in the description of the manufacturing process and the flow chart as presented in Module 3.2.S.2.2. In particular, current manufacturing processes and certain manufacturing steps are not reflected by the flow chart and the manufacturing process description.

Reprocessing of undefined, not-complying RP-HPLC side-fractions and blending and homogenisation of batches are not acceptable and need to be removed from the process and the dossier.

The second unresolved major objection is in relation to process validation. Process validation data have been provided from a manufacturing process, which has not been clearly identified and documented. Prospective process validation data only cover the upstream process but do not include operational parameters for fermentation, harvest and recovery. Retrospective process validation data for the processes are considered insufficient to reflect splitting, pooling and blending of the maximum defined batches and batch traceability as proposed for the commercial process. Thus, adequate process validation data covering the intended commercial manufacturing process remain to be generated to demonstrate reproducibility and robustness of the intended commercial active substance manufacturing process.

The third unresolved major objection relates to the comparability of Solumarv product used for nonclinical and clinical studies with the commercial product that has not been established. The applicant has failed to identify and document process history. The manufacturing processes differ with regards to fermentation scale, origin of enzymes, pooling and blending procedures, for

example. Information on the distinct differences between the manufacturing processes used to generate material for nonclinical and clinical studies and the proposed commercial active substance manufacturing process have not been provided and the applicant has not evaluate process changes in line with ICH Q5E requirements. A science based risk assessment on the changes implemented during the manufacturing process history has not been presented. In addition, the impact of the process changes on the impurity pattern including the Solumarv specific insulin variants has not been demonstrated. Representativeness of materials used for characterisation, justification of specification and stability for the commercial material is also questioned. Hence the commercial active substance material cannot be confirmed to be representative for the active substance material used in nonclinical and clinical studies.

The fourth unresolved major objection relates to the reliability of analytical results for Solumarv specific insulin variants. Two analytical in house-methods have been established and validated in 2015 as active substance release methods for the Solumarv specific impurities. Different analytical methods have been used during development. However, a side-by-side comparison of the methods has not been performed. Thus, equivalence of the previously used methods with the intended active substance release methods has not been demonstrated. This shortcoming precludes a comparison of the batch results for active substance batches used in the clinical studies with those derived from the intended commercial process. A final conclusion on the actual amounts of Solumarv specific insulin variants in Solumarv active substance batches is hampered.

Following from the major objections above, the fifth major objection relates to the demonstration of biosimilarity based on the analytical comparability between Solumarv and the reference product Humulin S. The data provided by the Applicant to support the biosimilarity of Solumarv and the reference product Humulin S are not sufficient to allow a final conclusion on analytical comparability.

At day 120, a major objection was also raised in relation to the use of internal reference materials and their qualification. Insufficient and inconsistent information on the use of in-house reference materials was provided, which questions the reliability of any analytical result and conclusion drawn from it. Based on the D180 response it was concluded by the CHMP that the handling of reference materials, primary and secondary standards as used at the manufacturing sites for manufacture and release of the active substance cannot be conclusively resolved in the context of this assessment. Instead the issue should be kept under GMP surveillance and considered for the next regular GMP inspection.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the CHMP considers that the marketing authorisation application for Solumarv is currently not approvable from the quality point of view since major objections still remain that preclude a recommendation for a positive opinion.

The outstanding Major Quality Objections are as following:

- The commercial manufacturing process for the active substance has not been clearly identified and documented. In particular, the intended commercial fermentation process and pooling procedures are not reflected by the flow chart and the manufacturing process description. Reprocessing of undefined, non-complying RP-HPLC side-fractions and blending and homogenisation of batches are not acceptable and need to be removed from the dossier. Assurance that the Applicant has full access to manufacturing records held at the two active substance EU manufacturing sites and that he will be informed of manufacturing process changes have not been obtained.

- Process validation data supporting the intended manufacturing process for the commercial product have not been provided. Retrospective process validation data for the process as performed in 2008/2009 are considered insufficient to demonstrate validation of the intended commercial manufacturing process as performed in 2015. The data are insufficient to reflect splitting, pooling, blending of the maximum defined batches and batch traceability as proposed for the commercial process. Thus the reproducibility and robustness of the intended manufacturing process have not been demonstrated.

- Comparability of Solumarv product used for pre-clinical and clinical studies with the commercial product has not been established; therefore the relevance of the non-clinical and clinical data for the product intended for marketing is not demonstrated. Process history has not been documented and information on the differences between the intended commercial active substance manufacturing process and the active substance manufacturing processes used to generate material for nonclinical and clinical studies has not been provided. Process changes have not been evaluated in line with ICH Q5E requirements and a science based risk assessment on the changes implemented during the manufacturing process history is not available. The presented data are insufficient to confirm comparability of the different manufacturing processes.

- Reliability of analytical results for the specific variants of recombinant insulin in Solumarv has not been assured. Two analytical in house-methods have been established and validated in 2015 as active substance release methods. However, equivalence of the previously used methods with these new active substance release methods has not been fully demonstrated. This precludes a comparison of the batch results for clinical lots with the commercial batches and a final conclusion on the actual amounts of Solumarv specific insulin variants in the active substance batches.

- Following from the above grounds, analytical comparability between Solumarv and the reference product Humulin S has not been established. The data provided by the Applicant to support the biosimilarity of Solumarv and Humulin S are not sufficient to allow a final conclusion on analytical comparability.

2.3. Non-clinical aspects

The non-clinical programme was based on the requirements for a biosimilar application. There are three major process-related stable impurities, which derive from the insulin molecule. Two of these impurities are a unique feature of Marvel insulin which can be explained by a different production process. The possibility exists that these impurities might lead to increased immunogenicity. To address this, the Applicant performed an additional antigenicity study with Balb/C mice comparing Recombinant Human Insulin (Marvel soluble insulin) with the three purified impurities.

Different Marvel insulin preparations (i.e. soluble, isophane and mixed insulin preparations) have been developed and were used in the non-clinical studies. In the current MAA, only the soluble form is applied for. The soluble Lilly insulin Humulin S will also be referred to as Humulin R (for regular insulin) in the following. Marvel insulin preparations are also referred to as Biosulin R, Biosulin S or Recombinant Human Insulin (soluble insulin), Biosulin 30:70 (mixed insulin) and Biosulin N (isophane insulin) in some reports of the dossier.

2.3.1. Pharmacology

Insulin acts by binding to its receptor and cross-linking two extracellular subunits, causing a conformational change in the receptor which triggers intracellular tyrosine kinase signalling. This

leads to a number of effects, including stimulation of glucose transport, inhibition of lipolysis, protein and glycogen synthesis, influence on gene transcription and cell proliferation.

Seven comparative primary pharmacodynamic (PD) studies were provided which are considered of limited usefulness because of the small number of replicates. These experiments included concentration-response curves for insulin receptor binding, phosphorylation of the insulin receptor, AKT, GSK3 and MAP kinase, and for insulin-stimulated glucose uptake in 3T3-L1 adipocytes. The Applicant has also provided insulin receptor binding assays and lipogenesis assays with a sufficient number of replicates to allow meaningful conclusions. The table below gives an overview of all *in vitro* studies performed:

Table 1. Overview of performed in vitro PD 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 adipocytes	Dose dependency from 0.01 to 10 nM IC_{50} = 0.1~1 nM	Insulin-stimulated glucose uptake
Marvelreport2008v2	Competitive binding study	NIH-3T3	Similar between T and R when tested from 10^{-11} to 10^{-5} M	Binding affinity
Marvelreport2008v2	Receptor auto-phosphorylation	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
SGS Cephac CP135336 (2014)	Insulin receptor binding assays	*In vitro* incubation of	Relative potencies between 80 –	Receptor binding affinity

		human recombinant soluble insulin receptor with ^{125}I-insulin and competitors	120% with precision within acceptance criteria (<30%) for DS and drug product (DP, Insulin Solumarv) as compared to Humulin S.	
SGS Cephac CP145291 (2014/15)	Lipogenesis/Red Oil staining	3T3-L1 adipocytes	Similar T DS DIHR and T DIHRR to R	Insulin-stimulated adipogenesis, lipid accumulation
SGS002SolumarvBind - CP145316 (2015)	Receptor binding study	*In vitro* incubation of human recombinant soluble insulin receptor with ^{125}I-insulin and competitors	Similar between historical (2) and current DS (1) and R. All 3 DS comparable.	Receptor binding affinity
SGS003SolumarvBind - CP145384 (2015)	Receptor binding study	*In vitro* incubation of human recombinant soluble insulin receptor with ^{125}I-insulin and competitors	All 3 variants and DS comparable	Receptor binding affinity

Abbreviations: DP, drug product; DS, drug substance; R, reference product; T, test product.

Comparative receptor binding

The *in vitro* receptor binding study was performed by the CRO SGS Cephac Europe (non-GLP). The assay has previously been validated (under GLP) and was qualified by the CRO. The following table summarises the key features of the study.

Table 2. Analysis of the Properties of Solumarv in Relation to Insulin Receptor Binding (SGS Cephac CP135336; 2014).

Test System:	*In vitro* incubation of human recombinant soluble insulin receptor (purchased from R&D Systems) with ^{125}I-insulin (tracer) and various concentrations of unlabelled insulin competitor to be tested (Humulin S, drug substance (DS), drug product (DP, Solumarv), or insulin EDQM): bound tracer is competitively displaced by unlabelled competitor.
Method of Administration:	*In vitro* incubation
Administration Dose and Compound:	1.000, 6.000, 25.00, 50.00, 100.0, 150.0, 400.0, 1000, 2000, 4000, 10000, 30000 and 100000 pmol/L rh-insulin
Examination Items:	Measurement of radioactivity (bound tracer, in cpm) which is correlated to binding affinity of unlabelled Insulin competitor

The experiments included an assessment of the binding properties of insulin Solumarv drug substance (DS; formulated with the placebo of Solumarv) and drug product (DP) and the reference product Humulin S towards the insulin receptor by a dose-response analysis according to the following protocol: incubating insulin receptor with ^{125}I-insulin (tracer) and various concentrations (see Table 2.1.9.) of unlabelled insulin competitor to be tested (Humulin S, DS, DP or Insulin EDQM). Bound tracer was competitively displaced by unlabelled competitor. Precipitation and measurement: at equilibrium, any bound tracer was isolated by precipitation using a PEG solution, washed and centrifuged. The supernatant was discarded and the radioactivity in the pellet was measured in a gamma counter.

In the final assay step, the relative potency of DS and DP against Humulin S were compared side-by-side (Figure 1).

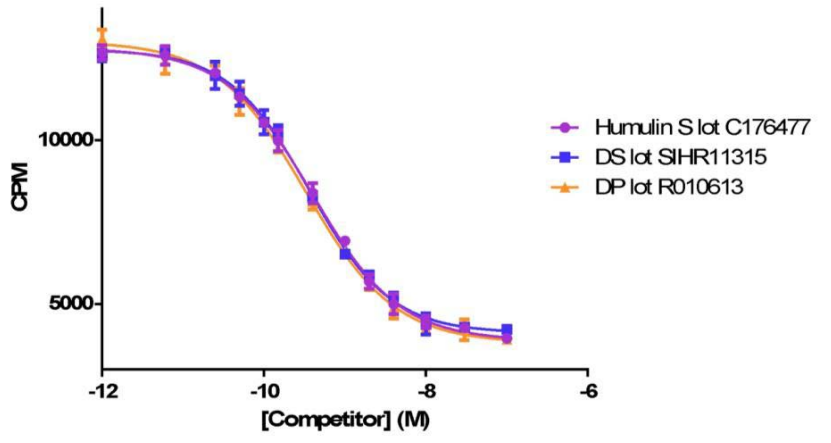


Figure 1. Insulin receptor binding three way comparison of selected Humulin S and Solumarv batches, dose-response curves obtained during run No. 11 (taken from study report).

In this experiment, the relative potencies were between 80 – 120% with precision within acceptance criteria (<30%) for Solumarv drug substance and drug product as compared to Humulin S.

The assay convincingly shows *in vitro* comparability of insulin Solumarv drug product and drug substance with the comparator insulin Humulin S.

Receptor binding of the impurities (i.e. the modified insulins)

Study CP145384 (2015): Three batches of variants of drug substance, derived from the upstream manufacturing process, as by-products, provided by the Sponsor were tested in this study:

- Modified-Lys-InsulinB31 (predominantly acetyl-derivative, -COCH3) - Lot 02Dec2014M
- Lys-Insulin – Lot 11Dec2014L
- Des ThrB30 Insulin (Des Thr) – Lot 11Dec2014D a well-known related substance present significantly in all marketed rHu-insulins.

The results are shown below:

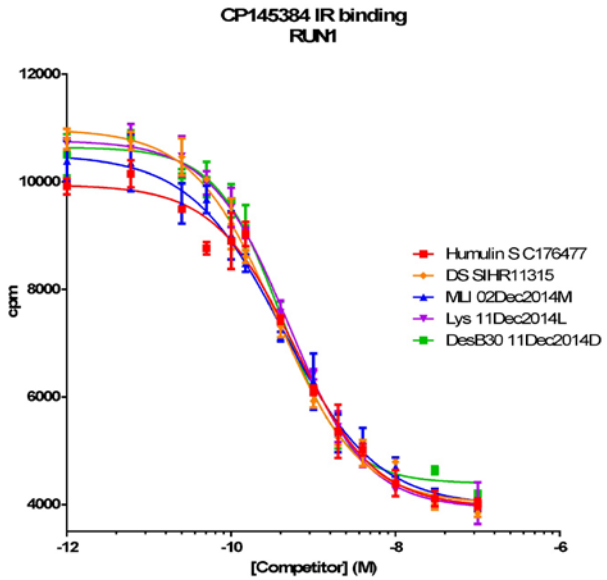


Figure 2. Comparability of insulin variants to insulin parent at the level of DS)

The inter-run precision of relative potency for one batch of DS parent and three batches of insulin variants compared to Humulin S batch C176477 was below 30% for all compounds except for DesB30 (CV% = 40.86%).

The inter-run precision of relative potency of three batches of insulin variants compared to DS parent (at the level of DS) was below 25%.

Relative potencies of DS and insulin variants compared to Humulin S were between 88.45% and 109.37%.

Relative potencies of insulin variants compared to DS were between 83.39% and 104.76%.

Study CP145316 (2015):

In this study drug substance batches from SIHR processes representing production from 2002-2014 were investigated. The procedure served to

- requalify the receptor binding assay previously validated as new batches of reagents were used,

- assess and compare relative potency and binding capacity of three batches of Solumarv DS derived from comparable processes
- assess biosimilarity to Humulin S batch No. C176477,
- provide bridging data to previous study (No. CP135336) in which SIHR11315 and Humulin S C176477 (chosen from 3 batches in that prior study as the batch giving the best inter-run precision on relative potency) were tested against Solumarv biosimilar DS representing another DS process (defined as SIHRR), also Solumarv biosimilar DP; therefore investigation of those 4 batches was not repeated.

The results are shown in Figure 3:

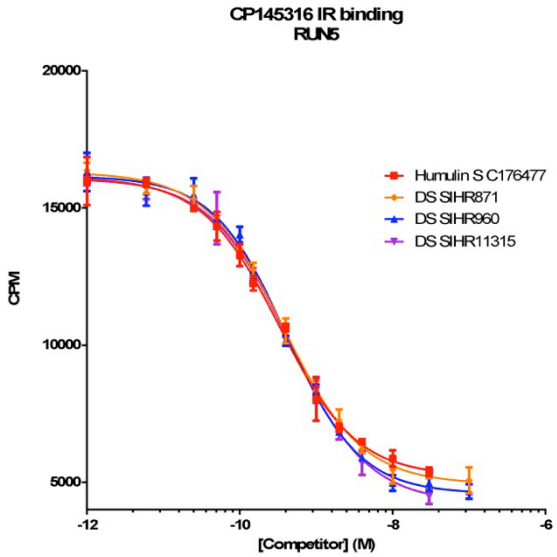


Figure 3. Comparability of DS batches over 2004-2012 to Humulin S (taken from study report).

Lipogenesis Assay

Originally, the Applicant had planned a glucose-uptake assay to investigate receptor activation by Solumarv and comparator. However, no reliable assay could be developed so that Marvel turned to lipogenesis as a functional parameter. A lipogenesis assay measuring lipid accumulation by Oil Red O staining in 3T3-L1 adipocytes as an endpoint was established and qualified and final study data were provided. Key features of the assay are summarised in the table below.

Table 3. Lipogenesis study CP145291

Test System:	differentiated 3T3-L1 adipocytes
Method of Administration:	*In vitro* incubation
Administration Dose and Compound:	The optimised range of human insulin (or reference or test compound) is from 0 to 1000 nM
Examination Items:	Red Oil staining of differentiated adipocytes

Results were provided comparing Humulin S with several batches of Solumarv drug substance. Selected dose-response curves are shown in the following figures.

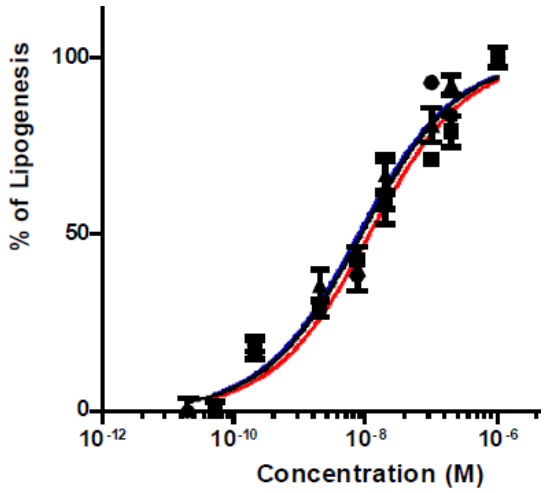


Figure 4. In-vitro comparability at the level of receptor function (lipogenesis assay): Side-by-side comparison of two Solumarv drug substance (red and blue line) batches versus Humulin S lot No. C176477 (black line), part 1.

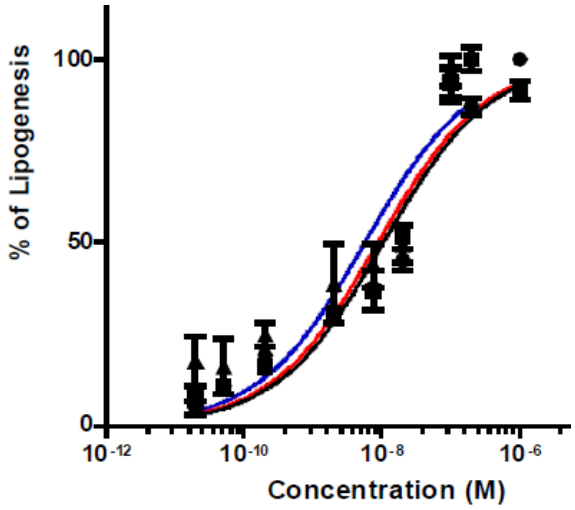


Figure 5. In-vitro comparability at the level of receptor function (lipogenesis assay): Side-by-side comparison of two Solumarv drug substance batches (re and blue line) versus Humulin S lot No. C176477 (black line), part 2.

From these data it can be concluded that Solumarv drug substance, irrespective of enzyme source, and Humulin S are comparable, were similar to Humulin S, and all four batches comparable to each other. However, when Solumarv DP was compared to RMP Humulin S no final conclusion on comparability could be drawn as stated in the study report due to high variations between sets of experiments with drug product. This however is not a concern as DP contains many excipients which might interfere with the assay. In general for biosimilar exercises comparability of DS is considered sufficient.

***In vivo* PD study**

A pilot study in male Wistar rats compared the glucose suppressive activity of the isolated impurity of with Marvel recombinant human insulin DS itself. No relevant differences between and native insulin were observed. A follow up study comparing glucose suppressive activity with recombinant human insulin in male Sprague Dawley rats has been performed. The test substances were administered as a single subcutaneous injection to fasted male Sprague Dawley rats at dose levels of 6 and 18 nmol/kg /day. In total 9 groups were used, each consisting of 4 male animals/group. .Results are displayed in the following figure.

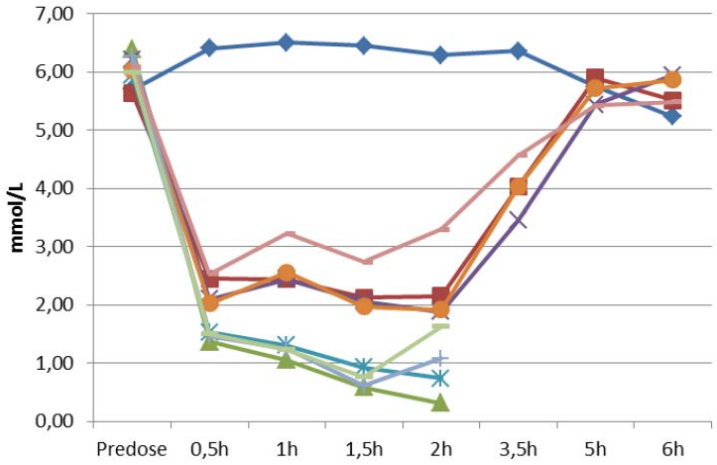


Figure 6. Comparison of blood glucose lowering capacity of recombinant human insulin (6 nmol/kg —■—, and 18 nmol/kg, —▲—), at 6(orange and redish lines) and 18 nmol/kg (light blue and green lines). —◆—: negative control.

The results indicate that recombinant human insulin, insulin are all equally capable of lowering the blood glucose levels. There was a dose response relationship between the 6 and 18 nmol/kg treated groups. However, the sensitivity of an in-vivo assay for detecting small differences is questionable.

2.3.2. Pharmacokinetics

No data was provided. Insulin is a well-established substance. Hence, in line with the EU guideline on comparability testing for recombinant human insulin (CHMP/BMWP/32775/2005), no ADME studies are required. Toxicokinetic data are available from a 7-day rat study comparing Marvel insulin with the respective Humulin preparations (see Toxicology section).

2.3.3. Toxicology

Three single dose toxicity studies and three local tolerance studies have been provided by the Applicant. These studies compared Marvel with reference for all three preparations, soluble (Biosulin R vs. Humulin S), isophane (Biosulin N vs. Humulin I) and biphasic (Biosulin 30:70 vs. Humulin M3). Taken together, it can be concluded that acute toxicity and local tolerance of the two brands of insulins are comparable.

Two 28-day repeat-dose toxicity studies (JRF 6207 and JRF 7410) were performed comparing soluble Marvel insulin with Eli Lilly insulin (Humulin R/S). In study JRF 6207 non-EU-sourced Humulin R was used as a comparator. Therefore, a new study (JRF 7410) was submitted were EU-sourced Humulin S was used as a comparator. In conclusion, both studies yielded similar results; the NOAEL was 270 IU/Kg/day. No unexpected toxicities were observed. Doses were reduced compared to the acute toxicity studies in order to avoid exaggerated PD effects; in fact, no signs of hypoglycaemia were observed in the repeat-dose study. This limits the sensitivity to detect toxic effects, but it is acknowledged that it is difficult to find an appropriate dosing for insulin.

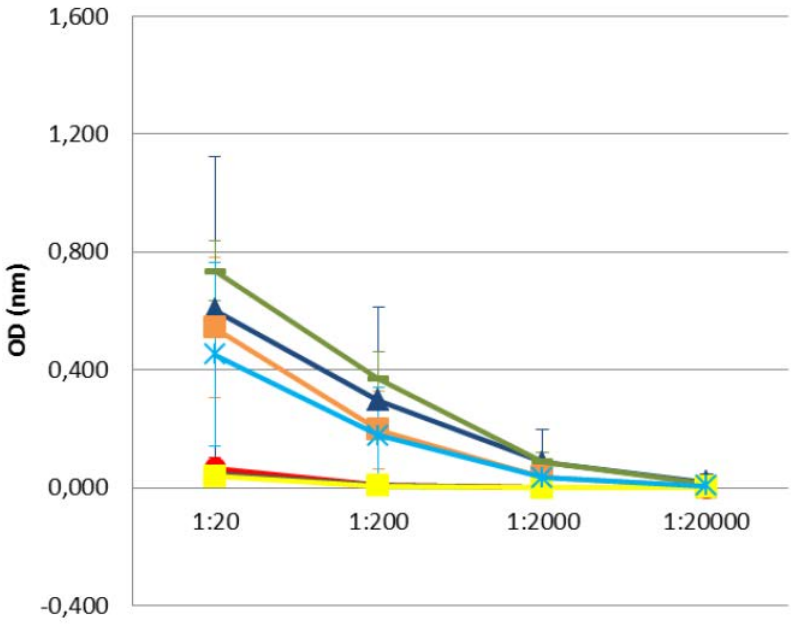
In addition to the 28-day repeat-dose toxicity study (JRF 7410) a 7-day TK study in rats was conducted separately by the same laboratory (JRF) comparing soluble Marvel insulins with Eli Lilly insulins (Humulin S, EU-sourced). This is in accordance with a scientific advice given by the EMA in 2008 (EMEA/CHMP/SAWP/368924/2008), where it was concluded that TK can be assessed in a separate study. 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.

The occurrence of antibodies against human insulin or host cell proteins were not determined in these studies although recommended by the guideline on comparability testing for recombinant human insulin (CHMP/BMWP/32775/2005). In the clinical programme some adverse events suspicious for hypersensitivity reactions were observed, predominantly in the Marvel insulin groups (see Clinical AR for details). There are three major process-related stable impurities, which derive from the insulin molecule. One of them was DesThrB30-insulin, a truncated form of insulin due to enzymatic cleavage and removal of threonine from the B-chain, which is common to Marvel, Lilly and other insulins. The theoretical possibility exists that these impurities might lead to increased immunogenicity. To address this, the Applicant performed an antigenicity study with Balb/C mice comparing Recombinant Human Insulin (Marvel soluble insulin) with the three purified impurities.

For the detection of antibodies in the sera of mice directed against Recombinant Human Insulin and the three impurities a Sandwich ELISA was established and qualified. Therefore, ELISA plates were coated with Recombinant Human Insulin and the variants, . The coated plates were incubated with the sera in stepwise dilution from 1:20 to 1:20.000. Antibodies bound to the coated plates were detected with a horseradish peroxidase antibody detection system and absorbance was read at 450 and 630 nm.

No clear difference in immune response was observed when the sera were tested on the coatings with the variants when compared to the coating with Recombinant Human Insulin. In the absence of adjuvant, all three product-related substances showed comparable antibody responses after two (upper panel of Fig. 7) or three (lower panel of Fig. 7) immunizations when compared to Recombinant Human Insulin. This antibody response was considered to be very low and similar to the antibody response observed in the PBS-treated control group. Therefore, the Recombinant Human Insulin and the three product-related substances are considered to be non-immunogenic in the absence of an activated immune system.



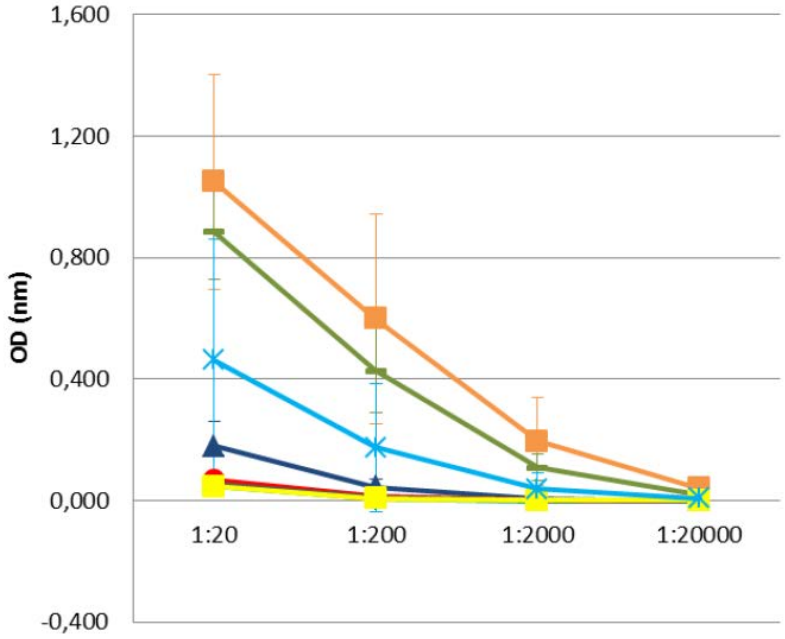


Figure 7. ELISA results of immunogenicity with Recombinant Human Insulin and related substances when tested on day 32 (upper panel) and days 42 (lower panel). , rec. human insulin with adjuvant; , variant 1 with adjuvant; , variant 2 with adjuvant; , DesThrB30 with adjuvant. The remaining lines represent the samples without adjuvant and the negative control (not all of these lines are visible because of overlay).

In the presence of adjuvant, after two immunizations (day 32 in the left upper graph, Figure 7), the antibody responses against Recombinant Human Insulin and the variants were comparable. However, after three immunizations (day 42 in the lower graph, Figure 7) differences in antibody responses were observed. The antibody response against Recombinant Human Insulin had declined, whereas the antibody response against the three impurities remained similar or further increased as compare to day 32 (upper graph). The reason of these findings remained unclear.

2.3.4. Ecotoxicity / environmental risk assessment

The active ingredient of the medicinal product “Solumarv” is human insulin (100 IU/mL). It is a naturally occurring protein and therefore, no detailed Environmental Risk Assessment is necessary. According to the EMA guideline (EMEA/CHMP/SWP/4447/00 corr 1, 2006) proteins are unlikely to result in significant risk to the environment.

2.3.5. Discussion on non-clinical aspects

In order to demonstrate biosimilarity between Marvel insulin and the comparator Humulin, the Applicant submitted in-vitro assays for insulin receptor autophosphorylation and for activation (phosphorylation) of downstream signalling proteins. However, the reliability of these assays is limited due to the low number of replicates and open methodological questions. Subsequently, results of an insulin receptor binding assay involving a sufficiently high number of replicates, and a lipogenesis assays were provided. The insulin receptor binding assay convincingly shows *in vitro* comparability of Solumarv with the reference product Humulin S. In the lipogenesis assay Solumarv (irrespective of the enzyme source) and reference product were comparable. The conducted pharmacology studies are considered sufficient to claim comparability between the tested batches of Marvel soluble insulin Solumarv and the reference insulin Humulin S from a non-clinical point of view.

A pilot study in male Wistar rats compared the glucose suppressive activity of one of the isolated product related substances with Marvel recombinant human insulin drug substance itself. A follow up study could confirm the previous findings additionally showing that all three product-related impurities are equally capable of lowering blood glucose levels. Furthermore, an in-vitro receptor binding study with the modified insulin impurities as compared to native insulin was performed. This study showed binding activity of the modified forms which was very similar to native insulin.

In order to investigate the effects of the three product-related impurities on the immune system of rodents, the Applicant performed an antigenicity study with male Balb/C mice comparing Recombinant Human Insulin (Marvel soluble insulin) with the three purified impurities. All substances showed a similar antibody response on day 32. The picture on day 42 was more complex. Again, in the absence of adjuvant, antibody formation was hardly detected. In the presence of adjuvant, the Marvel-specific impurities Lys-insulin and modified Lys-insulin showed a more pronounced antibody response than DesThrB30-insulin and native insulin. However, at least part of this difference can be explained by the unexpectedly low (lower than on day 32) immune response to native insulin.

The results of day 32 indicate a comparable immunogenic potential of native insulin and the tested derivatives, although the findings of day 42 could indicate increased immunogenic potential of at least two of the product-related impurities. Therefore, the obtained results cannot provide a definite answer.

The active ingredient human insulin is a naturally occurring protein and therefore, no detailed Environmental Risk Assessment is necessary.

2.3.6. Conclusion on the non-clinical aspects

The biosimilarity programme consisting of insulin receptor binding studies and the lipogenesis assay is considered sufficient to conclude comparability of Solumarv and Humulin S at the non-clinical level.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- **Overview of clinical studies**

The applicant submitted final study reports on the following studies with Solumarv:

1. One pivotal comparative PK/PD (clamp) study (double-blind, randomised, cross-over) in healthy volunteers, Protocol code PROFILE001SoluMarv HV, (start of study 28 August 2013, date of report 26 May 2014)

2. One supportive comparative PK/PD (clamp) study (open-label, randomised, cross-over), FARMOVS 232/2002, (start of study: 18 September 2003 end of study: 28 October 2003)

3. A 6-month double-blind, randomized controlled safety and efficacy study (411-BK-03-001-0000) in patients with Type I or Type II diabetic patients with a further 6-month open-label extension (separate study), (study start March 2005) and

4. A 6-month double-blind, randomised immunogenicity study (411-MA-08-001-0000) in *both* Type I and Type II diabetes patients with a 6 month open-label extension. (start of study October 2009).

The safety and efficacy studies used three types of Marvel Insulins (tentative names: Insulin Human 30/ 70 Mix Marvel, Insulin Human Long Marvel (Isomarv) and Insulin Human Rapid Marvel (Solumarv), which were compared to the respective reference products, Humulin S, Humulin I and Humulin M3, from Eli Lilly. The PK/PD studies, including the pivotal trial PROFIL001SoluMarvHV, compared Solumarv with Humulin S. This application only concerns Solumarv, a soluble (regular) form of insulin.

The key features of the clinical pharmacology studies are tabulated below:

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** Solumarv vs. Humulin S	5.3.1.2.1	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 (25 safety)	Healthy male, adult volunteers	Single dose	Complete; Full
Profil	**PROFIL001SoluMarvHV** Solumarv vs Humulin S Neuss, Germany	5.3.1.2.2	To compare the PK and PD of the recombinant human insulin Solumarv® (Marvel Life-Sciences Ltd.) with Humulin® S (Eli Lilly), using the euglycaemic clamp technique	A single-centre, single-dose, randomi-sed, cross-over study	Dose: 0.3 IU/kg, Solumarv®: R010613	26/26 M: 22, F: 4	Mean age: 33.3 yrs.	1 day twice	Complete; Full
					Dose: 0.3 IU/kg, Humulin® S: C154831	24 subjects included in PK/PD analysis	Range: 22-50 yrs.		Complete; Full

The pivotal study for demonstration of equivalent PK and PD and thus efficacy in this MAA submission was the automated glucose clamp study in healthy volunteers (PROFIL001SoluMarvHV).

The previously submitted and assessed manual clamp study in healthy volunteers (FARMOVS 232/2002) was considered supportive for this application. The latter study was performed prior to the availability of the guidance on biosimilar insulin and did not follow the guideline in all aspects. Study FARMOVS 232/2002 did not conclusively prove similar PK and PD, as the CI for the key PK parameters (AUC and C_{max}) was prospectively set at 95% CI instead of 90%. Using 95% CIs to demonstrate BE for PK parameters was never an EU requirement, and the data in FARMOVS 232/2002 did not meet this threshold. In addition, the open label design of the FARMOVS trial was considered a potential and relevant drawback. For further details on this study see also introduction section references to previous assessment reports of this biosimilar insulin.

2.4.1. Pharmacokinetic and Pharmacodynamic Studies

Pivotal trial: PROFIL study (healthy subjects)

Protocol Code PROFIL001SoluMarvHV, Profil Studycode 125/0598-Solu, EudraCT-No. 2013-002128-18

Analytical methods:

1. Serum insulin

ECLIA Test Kit for Insulin, Roche Diagnostics, Mannheim, Germany; instrument: Roche/Hitachi/MODULAR E170 analyser

The test method is an automated heterogenous immunoassay. As a first step of the reaction the analyte (insulin) forms a sandwich complex with a biotinylated monoclonal insulin-specific antibody and a monoclonal insulin-specific antibody labelled with a ruthenium complex. After addition of streptavidin-coated magnetic microparticles the antibody-insulin complexes bind to these magnetic particles conjugated with streptavidin. These complexes are then separated from unbound components by magnetic separation and captured onto the surface of the electrode. Application of voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. The commercially available kit was successfully validated for its intended use.

2. Serum C-peptide

ECLIA Test Kit for human C-peptide from Roche Diagnostics; instrument: Modular EVO / E-Module, Roche

The assay works as described for serum insulin above. It was successfully validated for its intended use.

3. Serum glucose

Blood glucose was measured with the Super GL glucose analyser (Dr. Müller Gerätebau GmbH, Freital, Germany).

The super GL glucose analyser is an established CE certified device for the determination of glucose in human liquid samples.

Title: A randomised, single centre, double blind, two-period crossover, euglycaemic glucose clamp trial to compare the relative pharmacokinetic and pharmacodynamic properties of the two recombinant human insulins Solumarv and Humulin S in healthy subjects

Design: A randomised, double-blind, single centre, single dose, two-period crossover, two-treatment, euglycaemic glucose clamp trial in healthy male and female subjects

Test insulin: Solumarv (soluble insulin, test product, Marvel LifeSciences Ltd., UK), 100 IU/mL, in cartridges 3.0 mL, batch no.: R010613; expiry date: 06/2016.

Reference insulin: Humulin S (soluble insulin, reference product, Eli Lilly and Company Ltd., UK), 100 IU/mL, in cartridges 3.0 mL, batch no.: C154831; expiry date: 03/2015

Glucose: After test drug administration blood glucose was kept constant with a 20% intravenous glucose infusion. The glucose infusion rate represents a measure for the blood glucose lowering effect of the administered drug. An automated glucose clamp was performed using ClampArt, a CE-certified device. After a four-point calibration before the start of the clamp, ClampArt measures blood glucose continuously and adapts glucose infusion rates every minute. The blood glucose measurements were double-checked with a laboratory device at least every 30 min and adjusted, if necessary. The subjects' average fasting blood glucose was calculated from ClampArt blood glucose values from -15 to -1 min prior to dosing. The clamp level was set 0.5 mmol/L (9 mg/dL) below the individual average fasting blood glucose via automated administration of a 20% glucose solution. The glucose infusion rate necessary to keep constant blood glucose level during 12 hours after trial drug administration was recorded every minute.

Study period: 28 August 2013 to 30 October 2013, final report (1.0): 26 May 2014

Objectives:

Primary Objectives: The primary objective was to compare the relative pharmacokinetic (PK) and pharmacodynamic (PD) properties of the two recombinant human soluble insulins, Marvel's Solumarv (test) with the soluble Humulin S of Eli Lilly (reference), in healthy subjects.

Primary endpoints: PK: Mean AUCins.0-12h, Cins.max, PD: AUCGIR0-last, GIRmax

Bioequivalence between the trial insulins was accepted, if the 90% confidence interval for the AUCins.0-12h-ratio and Cins.max-ratio were within an acceptance interval of 0.8-1.25. Pharmacodynamic equivalence was accepted if the 95% confidence interval for AUCGIR0-last–ratio and GIRmax-ratio were within an acceptance interval of 0.8-1.25.

Secondary endpoints: PK: AUCins.0-4h, AUCins.0-6h, AUCins.6-12h, AUCins.0-inf, tmax, t50%-early, t50%-late, t½, terminal elimination rate constant (λz), MRT, CL/F, and V/F.

PD: To compare the PD time-effect profile in more detail: AUCGIR0-4h, AUCGIR0-6h, AUCGIR6-last, tGIRmax, tGIR50%-early, and tGIR50%-late.

Safety endpoints: Adverse events (AEs), haematology, biochemistry, urinalyses, physical examination, vital signs, electrocardiograms (ECG), and local tolerability at the injection site.

PK-Sampling: Insulin was determined at the following time points: -30, -20, -10, 0 min (trial drug administration), 5, 10, 15, 30, 45, 60 min, every 30 min up to 360 min (6h), every 60 min up to 720 min (12 h).

C peptide was determined for the following time points: -10 min, 0 min, 2h, 4h, 6h, 8h, 10h, and 12h.

PD-Sampling: Blood glucose was measured at time points relative to dosing: -60, -30, -20, -10 min and within 1 min prior dosing.

Human insulin and C-peptide were determined using the respective ECLIA Test Kits for Insulin and C-peptide from Roche Diagnostics, Mannheim, Germany

Study participants: Key inclusion criteria: Healthy male and female subjects, 18 – 50 years, BMI between 18.5 and 28.0 kg/m2, fasting plasma glucose ≤ 5.5 mmol/L (100 mg/dL), non-smokers (not >5 cigarettes per day) without evidence of disease.

Statistical analysis: The primary PK endpoints, AUCins.0-12h and Cins.max, were analysed using log-transformed data, and analyses were based on a linear mixed model analysis of variance (ANOVA) using treatment, sequence and period as fixed effects, and subject within sequence as a random effect. If the 90% CI of the ratio of responses for both AUCins.0-12h and Cins.max fell within the limits of 0.8 and 1.25, pharmacokinetic bioequivalence was demonstrated.

The secondary pharmacokinetic endpoints AUCins.0-4h, AUCins.0-6h, AUCins.6-12h, AUCins.0-∞, were to be compared for the two insulin formulations using the same statistical approach as for the primary PK endpoints. The ratios were to be presented with 90% CIs. The endpoints tmax, t50%-early, t50%-late, t1/2, λz, MRT, CL/F and V/F (=Vd) were to be analysed by means of descriptive statistics only.

The primary PD endpoints, AUCGIR0-last and GIRmax were analysed using the same linear mixed model as for the pharmacokinetic parameters. GIRmax was to be derived as the maximum of a smoothed GIR profile. AUCGIR0-last and GIRmax were to be analysed from untransformed data if normal distribution could be shown, and 95% confidence intervals of the ratios were to be calculated by Fieller's theorem in this case. However, if initial data evaluation revealed non-normal distribution, PD endpoints were to be log-transformed. Actually, log-transformed endpoints were used. If the 95% CI of the ratio of PD endpoints for both AUCGIR0-last and GIRmax fell within the limits of 0.8 and 1.25, pharmacodynamic equivalence was demonstrated. This two-stage procedure, assessing the type of distribution of AUCGIR0-last and GIRmax first to decide on the method to apply for analysis, is generally not appropriate as the type I error of this procedure is unknown. Details on the assessment of the type of distribution should be provided, and the 95% CIs based on Fieller's method using untransformed values should be calculated as sensitivity analysis.

Secondary pharmacodynamic endpoints AUCGIR0-6h and AUCGIR6-last were to be compared for the two insulin formulations using the same statistical approach as for the primary pharmacodynamic endpoints. The ratios were to be presented with 95% CIs. The endpoints tGIR50%-early, tGIR50%-late, and tGIRmax were to be analysed by means of descriptive statistics only.

Disposition of patients and numbers analysed

40 subjects were screened, 26 were randomized in a 1:1 fashion. Two subjects (nos. 116 and 117) were not treated as randomised and were therefore excluded from the PK and the PD analysis set, but not from the safety analysis set. No subject discontinued the study.

All study participants were Caucasian. Twenty-two (22) subjects (84.6%) were male and 4 subjects (15.4%) were female. Two subjects were excluded from the PK/PD analyses since they received by mistake Solumarv in both periods

Supportive study FARMOVS 232/2002 (short acting insulin; healthy subjects):

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

Design: Single centre, single-dose, randomised, open-label, cross-over study consisting of

4 trial periods: trial period 0 (screening visit), trial periods 1 and 2 (treatment visits), trial period 3 (follow-up visit).

Test insulin: Recombinant human insulin (RHI), Cartridge containing 100 IU/mL human insulin (Human insulin assay according to CoA: 100.5 IU/mL), Batch Number: R020703, Expiry Date July 2005Manufacturer and Supplier: BIOTON Sp. Z o.o., Poland

Reference insulin: Humulin S, Cartridge containing 100 IU/mL human insulin (Human insulin assay according to CoA: 104.2 IU/mL), Batch Number: FF3H24A, Expiry Date: May 2005, Manufacturer: Eli Lilly and Company Limited, UK

Study period: 18 September 2003 to 28 October 2003

Objectives: *Primary objective*:1. To compare the $AUC_{(0\text{-end of clamp})}$ of GIR of a recombinant insulin (Marvel LifeSciences Ltd) and Humulin S (Eli Lilly), using the euglycaemic clamp technique. *Secondary objective*:1. To compare the pharmacodynamics and pharmacokinetics of a recombinant human insulin (Marvel LifeSciences Ltd) and Humulin S (Eli Lilly). 2. To assess the safety profile after single doses of recombinant human insulin (Marvel LifeSciences Ltd), as evaluated by standard safety parameters.

Study Population: Healthy, non-smoking, male subjects, aged between 18 and 55 years with body mass index (BMI) within 10% of the ideal BMI (between 18 and 28 kg/m2), with a minimum body weight of 60 kg.

Patient disposition: 27 healthy subjects were screened, 24 initially randomised and administered study medication, and one subject was withdrawn from the study before completion and was replaced. Thus, 25 subjects were randomised in total, of whom 24 completed the study according to the protocol.

Endpoints

PK evaluation: Secondary endpoints: AUC0-end-of-clamp (AUC0-EoC) of insulin, AUC0-1, AUC0-1.5 , AUC0-2 of insulin, Cmax, tmax, t1/2, MRT, CL/F and VZ/F.

PD evaluation: Primary endpoints: AUC0-end-of-clamp (AUC0-EoC) of GIR. Secondary endpoints: AUC0-1, AUC0-1.5 AUC0-2 of GIR, GIRmax and its tmax, tonset, earlyt50, late t50, td.

A commercial insulin RIA Kit was used (Linco Research, Inc.), but with calibration standards and quality control samples prepared by FARMOVS-PAREXEL Bioanalytical Services Division (BSD). For the determination of human C-peptide of a commercial C-peptide RIA Kit (Cat No. HCP-20K supplied by Linco Research Inc., Missouri, USA) was used.

Statistical analysis: Pharmacokinetic analysis was performed using WinNonlin (Version 4.0.1, Professional). Graphs, listings and tables were created using SAS Software (Version 8.2, Release 8.02).

Treatments: Each subject received one dose of 0.2 IU/kg recombinant human insulin per treatment phase; either the reference product (Humulin S) or the test product.

Method of administration and sampling: In this manual euglycaemic clamp study one insulin delivery device (Autopen) was used per subject for both trial periods (TPs). Each TP was separated by a washout of 7 or 8 days. Each subject received one dose of 0.2 IU/kg insulin s.c. per TP after an overnight fast of 10 hours. 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 mean baseline level was calculated from the four blood glucose values recorded before study medication administration, in order to "clamp" it at the subject's individual baseline glucose level. 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.

Serum insulin and C-peptide: Venous blood was scheduled to be collected at -60, -30, -15 minutes before dosing, and at 30 min, 1 h, 1 h 15 min, 1 h 30 min, 1 h 40 min, 1 h 50 min, 2 h, 2 h 10 min, 2 h 20 min, 2 h 30 min, 2 h 45 min, 3 h, 3 h 15 min, 3 h 30 min, 3 h 45 min, 4, 5, 6, 7, 8, 10, 12, 14 and 16 h post-dosing. However, the last sample was drawn at the end of the clamp procedure regardless of the scheduled protocol time. No subject had a blood sample for serum insulin determination drawn after 10 hours post-dosing. A maximum of 96 mL of blood for serum insulin and 48 mL for serum C-peptide was collected per trial period.

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 four hours thereafter. From four 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 29 mL of blood was collected per trial period

2.4.2. Pharmacokinetics

Results

PROFIL001SoluMarvHV:

Figure 2 shows the overlaid mean concentration profiles of the two insulin preparations.

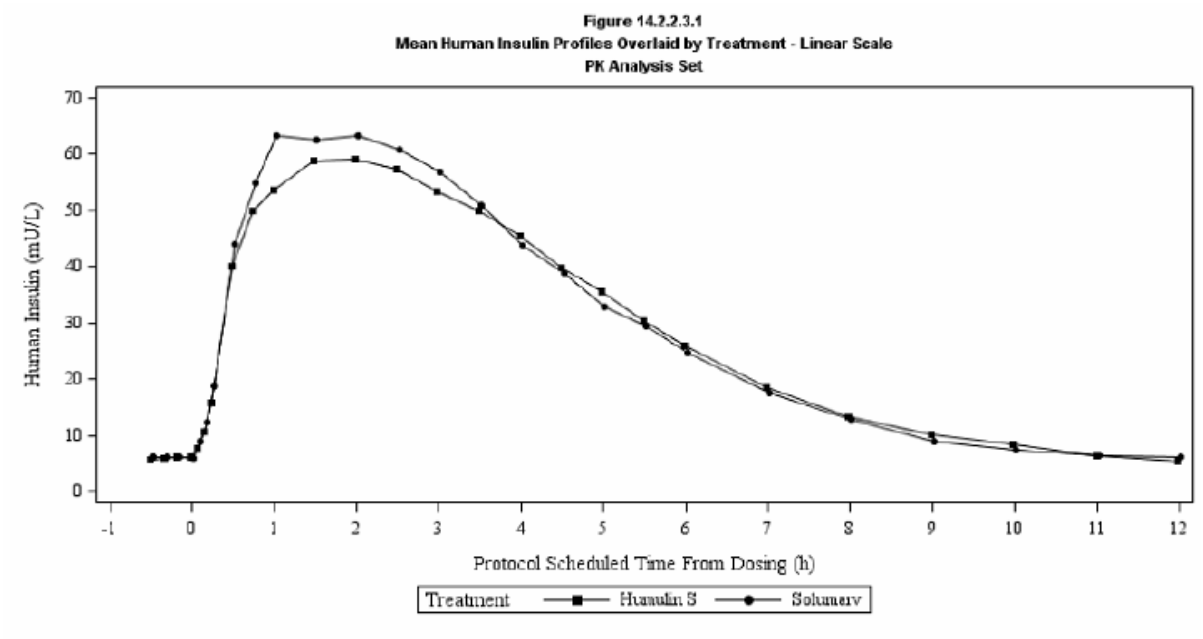


Figure 2 Mean serum insulin profiles after s.c. administration of 0.3 IU/kg Solumarv and Humulin S – linear scale (PK analysis set)

Cross-reference: Figure 14.2.2.3.1, Section 14

Treatment comparisons of the primary PK endpoints and summary statistics of the secondary PK endpoints are displayed in Table 6 and 9

Table 6 Treatment comparisons of primary PK endpoints (PK analysis set)

Parameter	N	Ratio test/reference [1]	90% CI	P-value [2]
$AUC_{ins.0\text{-}12h}$	24	1.015	(0.975; 1.056)	0.5276
$C_{ins.max}$	24	1.104	(0.991; 1.230)	0.1283

[1] Geometric LS-mean of ratio of treatments (Solumarv/Humulin S)
[2] Two-sided t-test from ANOVA
The log-transformed $AUC_{ins.0\text{-}12h}$ values were normally distributed.
The log-transformed and untransformed $C_{ins.max}$ values were not normally distributed (due to outlier in subject no. 125).
Cross-reference: Tables 14.2.1.2.1.1 and 14.2.1.2.2.1, Section 14

Table 9 Summary statistics of secondary PK endpoints (PK analysis set)

Parameter	Treatment	N	Mean (SD)	GeoMean	CV%	Median	Min-Max
$AUC_{ins.0-4h}$ [mU*h/L]	Humulin S	24	197.832 (32.4463)	194.996	16.4	197.186	113.74 - 245.80
	Solumarv	24	211.738 (40.5531)	207.769	19.2	214.271	134.93 - 280.11
$AUC_{ins.0-6h}$ [mU*h/L]	Humulin S	24	268.686 (34.3961)	266.441	12.8	276.158	183.08 - 338.55
	Solumarv	24	279.473 (37.9715)	276.875	13.6	283.082	192.15 - 360.76
$AUC_{ins.6-12h}$ mU*h/L]	Humulin S	24	72.881 (34.4864)	64.965	47.3	70.038	24.63 - 157.93
	Solumarv	24	69.065 (38.4992)	60.072	55.7	57.933	28.40 - 167.53
$AUC_{ins.0-\infty}$ [mU*h/L]	Humulin S	23*	360.619 (51.2454)	357.028	14.2	356.354	261.82 - 441.78
	Solumarv	24	371.505 (57.7884)	367.270	15.6	368.917	282.95 - 499.70
t_{max} [min]	Humulin S	24	137.5 (62.50)	NC	NC	120.0	30 - 330
	Solumarv	24	111.9 (51.58)	NC	NC	120.0	30 - 210
$t_{50\%-early}$ [min]	Humulin S	24	26.8 (6.63)	NC	NC	25.5	15 - 39
	Solumarv	24	27.5 (9.10)	NC	NC	25.0	15 - 50
$t_{50\%-late}$ [min]	Humulin S	24	343.0 (97.45)	NC	NC	331.5	193 - 583
	Solumarv	24	320.5 (115.13)	NC	NC	311.5	87 - 609
λ_z [1/min]	Humulin S	23*	0.305 (0.0965)	NC	NC	0.298	0.14 - 0.46
	Solumarv	24	0.313 (0.0703)	NC	NC	0.324	0.16 - 0.41
$t_{½}$ [min]	Humulin S	23*	153.6 (59.87)	NC	NC	139.7	90 - 293
	Solumarv	24	140.9 (39.12)	NC	NC	128.3	102 - 254
MRT [min]	Humulin S	23*	280.7 (66.97)	274.1	23.9	275.4	200 - 504
	Solumarv	24	270.5 (65.69)	263.5	24.3	261.5	184 - 414
CL/F [L/h]	Humulin S	23*	64.962 (11.9540)	63.899	18.4	61.736	39.49 - 91.58
	Solumarv	24	63.022 (12.2302)	61.903	19.4	58.940	46.03 - 84.78
V/F [L]	Humulin S	23*	236.606 (92.2963)	221.609	39.0	220.516	110.55 - 511.61
	Solumarv	24	207.069 (41.8230)	203.081	20.2	201.697	133.65 - 308.62

NC = Not calculated
* Humulin S profile of subject no. 111 excluded in case of λ_z and all λ_z dependent endpoints (for justification see Section 9.8.2).
Cross-reference: Tables 14.2.1.1.3.1, 14.2.1.1.4.1, 14.2.1.1.5.1, 14.2.1.1.6.1, 14.2.1.1.7.1, 14.2.1.1.8.1, 14.2.1.1.9.1, 14.2.1.1.10.1, 14.2.1.1.11.1, 14.2.1.1.12.1, 14.2.1.1.13.1, and 14.2.1.1.14.1, Section 14

After dosing, C-peptide concentrations decreased further from the fasting pre-dose levels and increased again towards baseline at the end of the clamp, reflecting the suppressive effect of the insulin administration on endogenous insulin secretion. There was no difference in mean C-peptide levels between both treatment groups

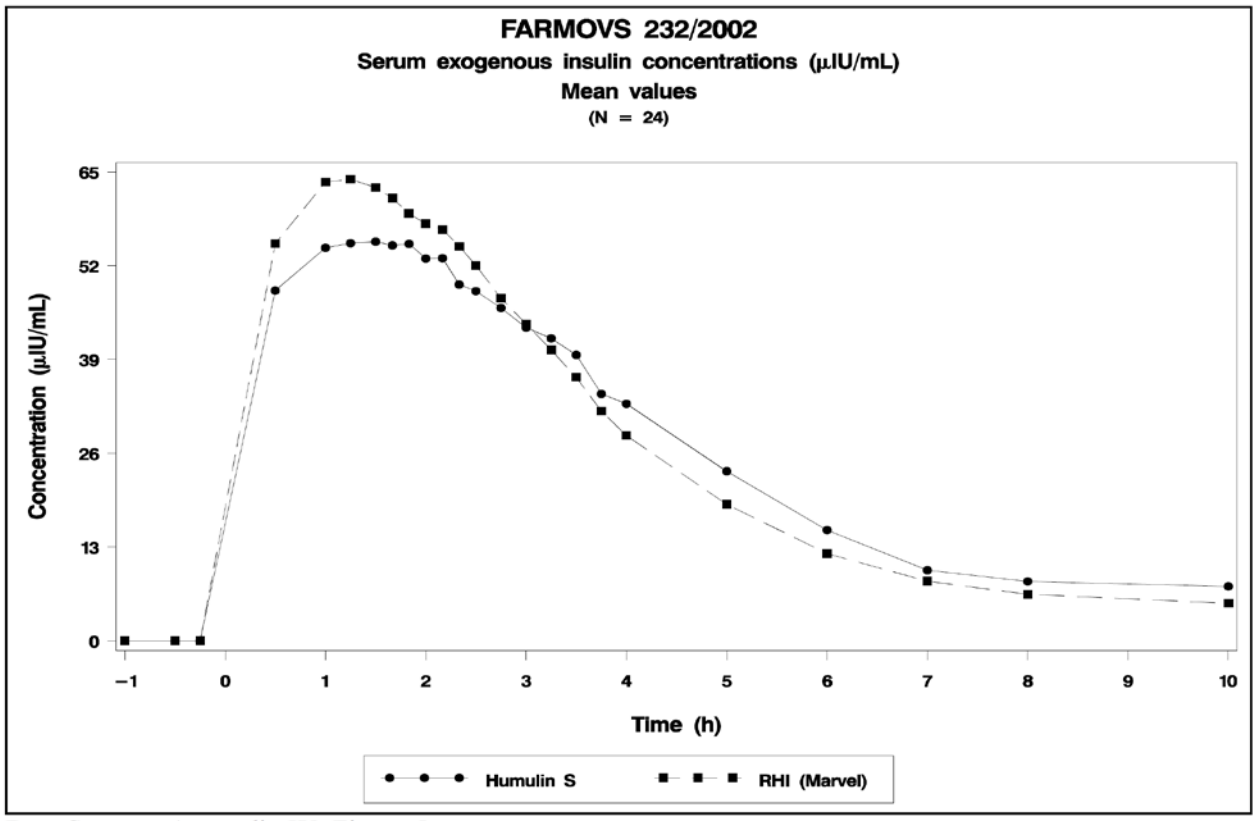
FARMOVS 232/2002 (short acting insulin; healthy subjects):

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:

Table 2.7.1-5: Summary of PK Parameters in HV at Farmovs, South Africa

Variable	Humulin S®	Soluble Marvel	Ratio	95% CI	90% CI
$AUC_{0\text{-}EoC}$	239.3 (245.5 ± 45.70)	242.6 (244.8 ± 33.18)	**101.4**	**91.8 – 112.0**	**93.3 – 110.1**
$AUC_{0\text{-}2}$	90.58 (92.74 ± 19.75)	102.6 (105.4 ± 25.81)	**113.2**	**104.0 – 123.3**	**105.5 – 121.5**
$AUC_{0\text{-}1.5}$	63.91 (65.41 ± 14.02)	72.85 (75.24 ± 20.44)	**114.0**	**104.5 – 124.3**	**106.1 – 122.5**
$AUC_{0\text{-}1}$	37.01 (37.90 ± 8.28)	41.73 (43.44 ± 13.37)	**112.7**	**102.6 – 123.9**	**104.3 – 121.9**
C_{max}	58.57 (59.99 ± 12.85)	67.74 (69.52 ± 16.38)	115.7	105.6 – 126.7	**107.3 – 124.7**
t_{max}*	1.51 (1.68 ± 0.81) *Median: 1.50*	1.23 (1.32 ± 0.47) *Median: 1.25*	81.8 -0.25	65.0 – 103.1 –0.58 – 0.00	67.6 – 99.1 –0.58 – 0.00
$T_{1/2,z}$	1.35 (1.52 ± 0.76)	1.16 (1.26 ± 0.60)	85.9	75.1 – 98.2	76.8 – 95.9
V_Z/F	124.5 (138.9 ± 66.5)	108.0 (120.1 ± 64.5)	86.7	74.8 – 100.5	76.7 – 98.0
MRT	2.82 (2.87 ± 0.56)	2.56 (2.61 ± 0.53)	**90.7**	**86.0 – 95.8**	**86.8 – 94.9**

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]



Data Source: Appendix IX, Figure 5

After dosing, C-peptide concentrations decreased from the fasting pre-dose levels and increased again towards baseline at the end of the clamp, reflecting the suppressive effect of the insulin administration on endogenous insulin secretion. There was some variability in both groups over the time. Overall, C-peptide levels tended to be slightly higher in the Solumarv group.

2.4.3. Pharmacodynamics

Results

PROFIL001SoluMarvHV:

Figure 7 shows the overlaid mean GIR profiles of the two insulin preparations.

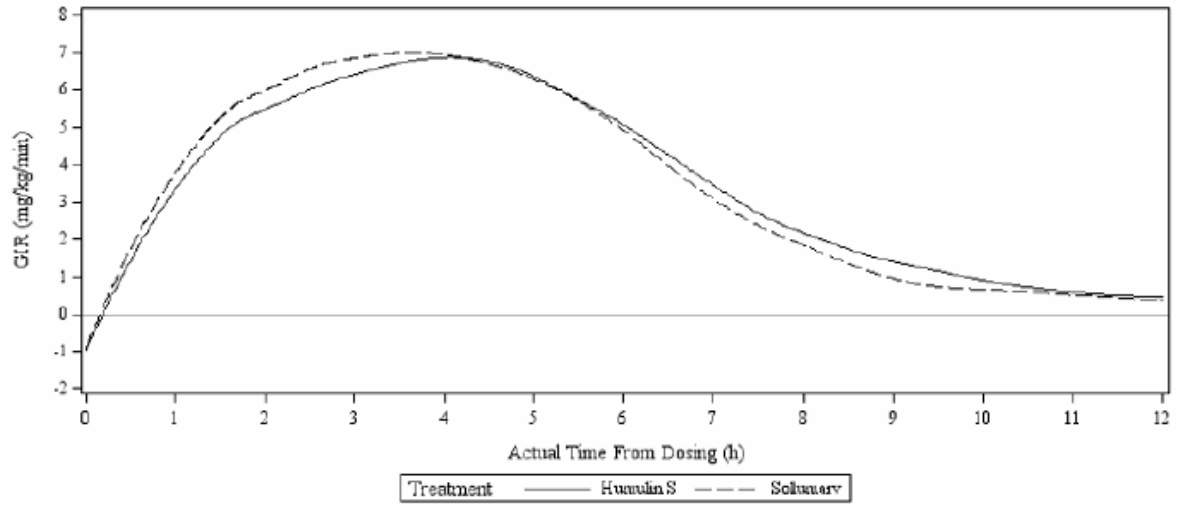


Figure 7 Mean smoothed GIR profiles (smoothing factor 0.3) after s.c. administration of 0.3 IU/kg Solumarv and Humulin S (PD analysis set)

Cross-reference: Figure 14.2.4.6, Section 14

Summary statistics of the **primary PD endpoints** are displayed in Table 11 below. Since GIRmax was derived from the smoothed curve, different smoothing factors (0.25, 0.30, and 0.35) were employed, whereby factors 0.25 and 0.35 were used for a supportive sensitivity analysis. Table 12 summarises the results of the statistical analyses.

Table 11 Summary statistics of primary PD endpoints (PD analysis set)

Parameter	Treatment	N	Mean (SD)	GeoMean	CV%	Median	Min - Max
$AUC_{GIR0\text{-}last}$ [mg/kg]	Humulin S	24	2543.395 (822.9878)	2426.959	32.4	2464.613	1316.31 - 4521.36
	Solumarv	24	2530.190 (701.8009)	2437.930	27.7	2349.345	1512.37 - 3779.90
GIR_{max} [1] [mg/kg/min]	Humulin S	24	7.387 (2.5513)	6.990	34.5	6.910	2.96 - 12.92
	Solumarv	24	7.466 (2.1698)	7.157	29.1	7.048	3.24 - 12.12
GIR_{max} [2] [mg/kg/min]	Humulin S	24	7.503 (2.6028)	7.101	34.7	7.005	3.08 - 13.23
	Solumarv	24	7.549 (2.2233)	7.231	29.5	7.055	3.25 - 12.30
GIR_{max} [3] [mg/kg/min]	Humulin S	24	7.303 (2.4961)	6.915	34.2	6.866	2.95 - 12.52
	Solumarv	24	7.402 (2.1317)	7.101	28.8	7.013	3.23 - 12.00

[1] Smoothing factor 0.30; [2] smoothing factor 0.25; [3] smoothing factor 0.35

Cross-reference: Tables 14.2.3.1.1.1, 14.2.3.1.2.1, 14.2.3.1.2.2, and 14.2.3.1.2.3, Section 14

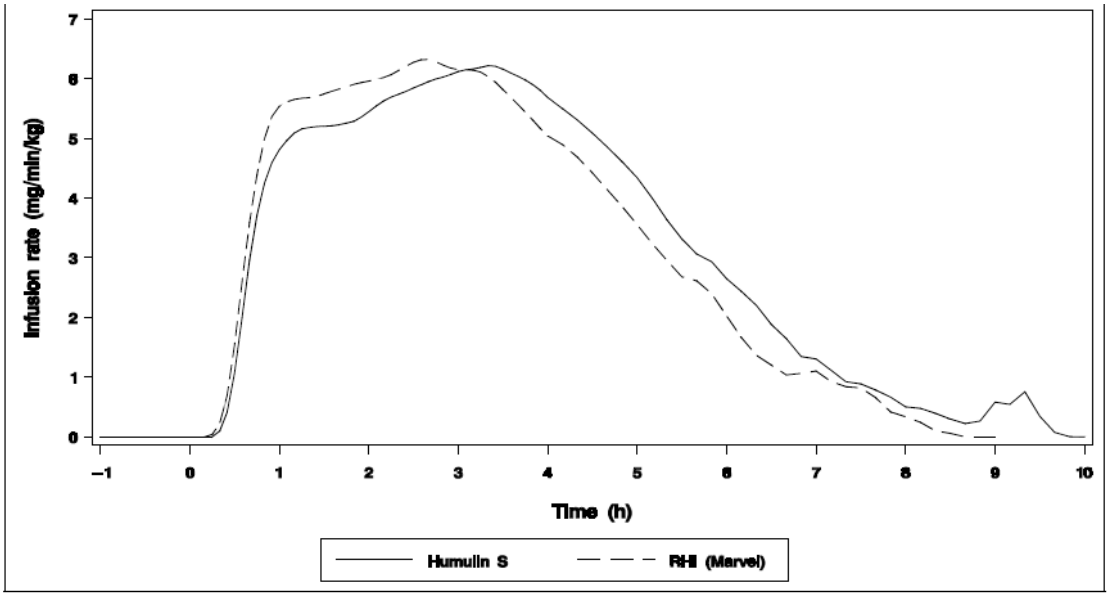
Table 12 Treatment comparisons of primary PD endpoints (PD analysis set)

Parameter	N	Ratio test/reference [1]	95%-CI	P-value [2]
$AUC_{GIR0\text{-}last}$	24	0.996	(0.906; 1.093)	0.9216
GIR_{max} (SF 0.30)	24	1.015	(0.933; 1.105)	0.7138
GIR_{max} (SF 0.25)	24	1.010	(0.927; 1.101)	0.8070
GIR_{max} (SF 0.35)	24	1.018	(0.938; 1.105)	0.6570

[1] Geometric LS mean of ratio of treatments (Solumarv/Humulin S)
[2] Two-sided t-test from ANOVA
SF = Smoothing factor for GIR curve
The log-transformed values were normally distributed.
Cross-reference: Tables 14.2.3.2.1.1, 14.2.3.2.2.1, 14.2.3.2.2.2, and 14.2.3.2.2.3, Section 14

FARMOVS 232/2002 (short acting insulin; healthy subjects).

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



Data Source: Appendix IX, Figure 25

Table 11-1 ANOVA for Primary Pharmacodynamic Endpoint

Variable	Arithmetic Means		Point estimate (95% CI)*
	Humulin S	RHI (Marvel)	RHI (Marvel)/Humulin S
$AUC_{(0\text{-end of clamp})}$ of GIR (mg/kg)	1792.09	1709.51	95.4% (83.1; 107.7)%

Data Source: Appendix VIII, Table 13

Table 11-2 ANOVA for Secondary Pharmacodynamic Endpoints

Variable	Arithmetic Means		Point estimate (95% CI)*
	Humulin S	RHI (Marvel)	RHI (Marvel)/Humulin S
$AUC_{(0\text{-}1h)}$ of GIR (mg/kg)	94.977	116.388	122.5% (100.3; 144.8)%
$AUC_{(0\text{-}1.5h)}$ of GIR (mg/kg)	247.282	285.586	115.5% (100.5; 130.5)%
$AUC_{(0\text{-}2h)}$ of GIR (mg/kg)	404.713	461.404	114.0% (100.8; 127.2)%
GIR_{max} (mg/min/kg)	6.690	7.118	106.4% (93.1; 119.7)%
t_{max} of GIR (h)**	3.108	2.482	-0.48h (-1.12; 0.04)h**
t_{onset} (h)**	0.384	0.321	-0.07h (-0.14; 0.01)h**
Early $t_{50\%}$ (h)**	0.736	0.725	-0.06h (-0.13; 0.03)h**
Late $t_{50\%}$ (h)**	5.672	5.153	-0.59h (-0.88; -0.21)h**
t_d (h)**	4.845	4.470	-0.55h (-0.86; -0.18)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.

2.4.4. Discussion on clinical pharmacology

The commercially available ECLIA Test Kit was used to determine plasma insulin levels in the pivotal study PROFIL001SoluMarvHV. This assay was shown to be suitable for its intended purpose and was successfully validated.

In study PROFIL001SoluMarvHV in healthy subjects, 90% CIs for AUC and Cmax fell within the BE acceptance range of 80-125% as recommended in the draft revision of the Guideline on biosimilar insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005 Rev. 2). Cmax was numerically about 10% higher for Solumarv compared to the reference product Humulin S. This finding was consistent with the numerically higher Cmax and the numerically higher AUC values over the first 2 hours observed in the supportive FARMOVS study. However, this difference has been considered clinically not relevant. The results of the PROFIL study are consistent with the assumption of bioequivalence between Solumarv and Humulin S. In FARMOVS 232/2002 in healthy subjects, 95% CIs had been predefined, which are not required for PK parameters in the EU, and for which BE with regard to Cmax could not be shown. The post-hoc calculated 90% CIs for AUC and Cmax, however, fell within the acceptance range of 80-125%. The differences in tmax and T1/2 are considered clinically not relevant and thus acceptable. Despite some shortcomings, the FARMOVS study reasonably supports BE between Solumarv and Humulin S.

Pharmacodynamics

In the PROFILstudy, blood glucose was determined by a super GL glucose analyser which is an established CE certified device.

In PROFIL001SoluMarvHV, the primary pharmacodynamic endpoints AUCGIR0-last and GIRmax, Solumarv showed equivalent responses to Humulin S. The 95% confidence intervals of the ratios test/reference were within the range 0.8 to 1.25.

The secondary pharmacodynamic endpoint AUCGIR0-6h supported the assumption of pharmacodynamic equivalence (i.e., the 95% confidence interval of the ratio test/reference was also within the range 0.8 to 1.25). AUCGIR0-4h and AUCGIR6-last did not meet the pharmacodynamic equivalence criterion but showed no statistically significant difference between the treatments. AUC GIR0-4h was numerically higher for Solumarv and the upper margin of the 95%CI level was slightly above 1.25 for this secondary endpoint. This finding corresponds to the about 10% higher Cmax value for insulin PK and was mirrored by a lower AUCGIR-last. The results indicate that the overall exposure is similar but the time course of the effect is slightly different. These findings are in line with those in the FARMOVS study and the observed differences were considered small and neither relevant for safety nor for efficacy.

Overall, based on the results of this study, Solumarv and Humulin S can be considered pharmacodynamically equivalent.

In the FARMOVS 232/2002 the values of total AUC0-EoC and GIRmax for Solumarv and Humulin S (95% CI; range 80-125%) were comparable. However, the test insulin showed a slightly faster absorption and onset of action with a somewhat higher early but shorter effect on blood glucose. However, these differences were judged as being of no clinical relevance and can be considered to be within the day-to-day variability of short-acting insulins. In addition, since short-acting insulin is taken with meals, the slightly larger Cmax is not considered a safety issue. From about 2 1/2 hours post-dose onward the mean serum insulin concentrations are highly similar. The FARMOVS study supports the results of the pivotal PROFIL study, although, the design of this study (not blinded) could have biased the PD results.

In both studies, the small amount of endogenous insulin secretion in fasting healthy volunteers was further suppressed by the injected insulin and is thus unlikely to have had a relevant influence on PK or PD results. No relevant differences in C-peptide levels were observed between treatment groups, which supports similar suppression of endogenous insulin.

Both studies showed consistent results and similar pharmacokinetic and pharmacodynamics profiles of Solumarv and Humulin S. Overall, based on the results of both studies, Solumarv and Humulin S can be considered to have equivalent efficacy.

2.4.5. Conclusions on clinical pharmacology

The PK results of both studies, the pivotal PROFIL study and the supportive study FARMOVS 232/2002, taken together support the assumption of bioequivalence of Solumarv and Humulin S, with regard to the test material used in those studies. Also, the PD results of these studies allow the conclusion of similar time action profiles and thus similar efficacy of Solumarv and Humulin S. However, as a limitation, the studies, including the pivotal trial PROFIL001SoluMarvHV, were conducted with test material (Marvel insulin) which in the view of the CHMP has not been demonstrated as being representative for the material intended for commercialisation. Therefore, the relevance of the study results is uncertain.

2.5. Clinical efficacy

Supportive studies

In addition to the pivotal insulin clamp studies, the efficacy of Solumarv is further supported by the following studies:

- study 411-BK-03-001-0000 (24-week comparison with Humulin), 24-week single-arm open-label extension

- study 411-MA-08-001-0000 (28-week comparison with Humulin), 28-week, single-arm open-label extension

These studies aimed to compare the safety and efficacy of three types of Marvel Insulins (tentative names: Insulin Human 30/ 70 Mix Marvel, Insulin Human Long Marvel (Isomarv) and Insulin Human Rapid Marvel (Solumarv) to the respective reference products (Humulin S, Humulin I and Humulin M3, Eli Lilly. This application only concerns Solumarv.

Study 411-BK 03-001-0000 was designed as an efficacy study with HbA1c as the primary endpoint. Since such a study is not a formal requirement according to the Guidance on similar medicinal products containing recombinant human soluble insulin (EMEA/CHMP/BMWP/32775/2005) or its revision and 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 comparable efficacy.

Study 411-MA-08-001-0000 was designed as a safety study investigating immunogenicity in line with the requirements as set out in the Guideline on biosimilar insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005 Rev. 1). Only results with respect to secondary endpoints (HbA1c, weight gain, insulin dose) are presented 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

The study was conducted as a double-blind, randomized, multicenter study in two parallel groups of patients. A total number of 480 patients (120 patients per group: test and reference product in type 1 and type 2 diabetes) had to be randomized with the aim to reach 400 patients (100 patients per group: test and reference product in type 1 and type 2 diabetes) who could be evaluated in respect of the primary endpoint HbA1c.

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, stratified by diabetes type, to reference (Humulin insulin) or test medication (Marvel insulin, *for details on the test and reference products please refer to the Clinical AR*). 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.

The primary endpoint of the present study was the glycosylated haemoglobin (HbA1c) measured after 24 weeks of treatment in a blinded fashion by a central laboratory. HbA1c measurements were performed centralised and in a blinded manner.

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.

Baseline data

Type 1 diabetes:

The mean age (± SD) of the Type 1 diabetes patients enrolled in Study 411-BK-03-01-0000 in the test and reference group was 34.3 ± 11.9 years and 34.7 ± 12.2 years, respectively. In total, 142 patients were male and 101 were female. All patients enrolled were Caucasians. The mean weight (± SD) was 71.1 ± 9.9 kg in the test group and 72.9 ± 8.9 kg in the reference group. The mean BMI was 24.0 ± 3.5 kg/m2 and 24.3 ± 3.5 kg/m2 in the test and reference groups, respectively. Both treatment groups were comparable regarding their demographic data.

The HbA1c values at baseline were slightly different between the two study groups (8.80% ± 1.27 in the Marvel insulin group and 8.53% ± 1.38 in the Humulin group.

Type 2 diabetes:

The mean age (± SD) of the Type 2 diabetes patients enrolled in Study 411-BK-03-01-0000 in the test and reference group was 58.5 ± 9.1 years and 59.3 ± 8.0 years, respectively. In total, 146 patients were male and 137 were female. All patients enrolled were Caucasians. The mean weight (± SD) was 82.2 ± 12.6 kg in the test group and 84.0 ± 12.8 kg in the reference group. The mean BMI was 29.1 ± 3.5 kg/m2 and 30.0 ± 3.7 kg/m2 in the test and reference groups, respectively. Both treatment groups were comparable regarding their demographic data.

The HbA1c values at baseline were lower than those in patients with Type 1 diabetes and practically identical in both study groups (8.12% ± 1.35 in the Marvel insulin group and 8.14% ± 1.38 in the Humulin group).

Summary of Main Efficacy Results

Data sets analysed

Type 1 diabetes mellitus

A total number of 243 (safety population, Marvel insulin n=123, Humulin n=120) started treatment with the trial medication. The number of patients who completed week 24 was 95 patients in the recombinant human insulin treatment group and 101 patients in the Humulin treatment group. The number of patients who dropped out was 26.

Type 2 diabetes mellitus

A total number of 283 (safety population, Marvel insulin n=142, Humulin n=141) started treatment with the trial medication. The number of patients who completed week 24 was 112 patients in the recombinant human insulin treatment group and 124 patients in the Humulin treatment group. The number of patients who dropped out was (n=25).

Primary endpoint

The results on HbA1c at week 24 are presented in the tables below by diabetes sub-type and by type of insulin.

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)

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.

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.

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.

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. Subjects entered study 411-BK-03-01-0001 directly from the end of the 24-week double-blind treatment phase of study 411-BK-03-01-0000. All 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. The secondary objective was to provide supportive information regarding the continuing efficacy and safety of Marvel insulin and to evaluate the interchangeability when switching from Humulin to Marvel insulin. The total number of patients who completed the double-blind treatment period was 217. Out of those, 196 patients started and 185 patients completed the open-label extension.

Results (efficacy)

Type 1 Diabetes

The mean values of HbA1c for all patients at start and final visit of the extension study were 8.44 ±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 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 (regular insulin: start follow-up period 25.7 IU, end of follow up period 26.1 IU for test, start follow up period 26.2 IU, end of follow up period 26.2 IU for reference product).

Type 2 Diabetes

The mean values of HbA1c for all patients at start and final visit of the extension study were 7.69 ± 1.21 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 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 (regular insulin: start follow-up period 16.5 IU, end of follow up period 17.1 IU for test, start follow up period 19.5 IU, end of follow up period 18.8 IU for reference product).

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 (primary endpoint, power calculation based on this endpoint). Please note that all results relating to safety (immunogenicity) are presented in the Clinical Safety section.

This study was a multicentre, randomised, double blind (according to the study report, the pre-filled cartridges containing test and the reference medication were identical in any respect and additionally collective batch numbers were used for the preparations, the pens to be used were also identical), active-controlled study and included both type 1 and type 2 diabetes patients, in two parallel groups of patients. The study lasted from 15 July 2011 to 20 December 2011 (end of follow-up treatment period).

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. The statistical analysis for these secondary endpoints was

performed according to the type of distribution of the respective target parameters. Continuously distributed parameters are characterised by summary statistical measures for each treatment group. Discrete variables are presented as frequency tables by treatment group.

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 receive a free or fixed combination of either Marvel insulin or Humulin in a double-blind fashion. In insulin pretreated patients 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 was maintained. 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.

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 characteristics

The mean age (± SD) of the patients enrolled in Study 411-MA-08-01-0000 was 54.36 ± 11.47 years (recombinant human insulin) and 54.29 ± 11.56 years (Humulin). In total, 247 patients were male and 231 were female. All patients enrolled were Caucasians. The mean weight (± SD) of patients treated with Marvel insulin was 73.72 ± 15.49 kg and 73.02 ± 16.45 kg for patients treated with Humulin. The mean values for the body mass index (± SD) were 26.86 ± 4.41 kg/m2 for Marvel insulin and 26.98 ± 4.42 kg/m2 for Humulin. Both treatment groups were comparable regarding their demographic data.

The mean time since the patients had been diagnosed with diabetes mellitus was 93 months in patients treated with recombinant human insulin, with a median of 73.5 months, and 99 months in patients treated with Humulin, with a median of 73.0 months. Twenty seven patients with type 1 and 217 patients with type 2 diabetes were treated with Marvel insulin. Twenty two patients with type 1 and 212 patients with type 2 diabetes were treated with Humulin.

Disposition of patients:

A total number of 478 patients were randomised to one of both study drugs (Human insulin or recombinant insulin) and received treatment. A total number of 92 patients were excluded from the PP set due to major protocol deviations (n=48 in the test group and n=44 in the reference group. In general only an insufficient duration of treatment (less than 20 weeks) and factors having a potential effect on immunogenicity were regarded as major protocol deviations. The most frequent reasons for exclusion from the per protocol population were similar in both treatment groups: positive results for antibodies against insulin at the randomization visits (n=19 in the test group and n=23 in the reference group), total treatment duration with double-blind medication of less than 20 weeks (n=21 in the test group and n=15 in the reference group), followed by lack of post-baseline data regarding immunogenicity (n=9 in the test group and n=7 in the reference group) and other reasons (n=6 in each group). The per-protocol set consists of 386 patients. A total number of 422 male and female patients who completed the blinded treatment period of the trial (main study) started treatment with the test product recombinant human insulin the follow-up extension period.

Summary of main efficacy results

Glycosylated haemoglobin (HbA1c) measured after 28 weeks of treatment (not change in HbA1c): The mean values (±SD) in the respective groups for the per-protocol set (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%.

In the study reports no changes from baseline were calculated. The following table (with mean baseline data has been submitted as an appendix to the report).

Table 100 Time course of HbA1c [%] measurement - descriptive statistics, per protocol set

HbA1c	description						
	MD	N	Mean	SD	Min	Median	Max
Week -2 / Entry							
Test	0	196	9.26	2.40	5.9	8.80	23.0
Reference	1	189	9.49	2.36	5.9	9.00	19.5
End of week 12							
Test	3	193	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	2	194	7.93	1.48	5.4	7.67	12.7
Reference	4	186	7.90	1.39	5.2	7.80	14.1

Results were also presented in the safety population. HbA1c results were very similar to those in the PPS.

Dosage of insulin (for the duration of the trial the patients documented dates and times of the amounts of daily administered regular and NPH insulin): The mean daily dose (±SD) of regular insulin was 15.6 IU (11.66) for the test group and 17.1 IU (11.89) for the reference group in the PPS. The mean daily dose of NPH insulin was 24.0 IU (12.61) for the test group 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

Incidence and severity of hypoglycaemia: 39.8% of the patients in the test group vs. 50% of the patients in the reference group experienced minor hypoglycaemic episodes. The proportion of

patients who experienced major hypoglycemic episodes was also comparable in both treatment groups: 2 patients (1.0%) in the test group vs. 3 patients (1.6%) in the reference group.

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.

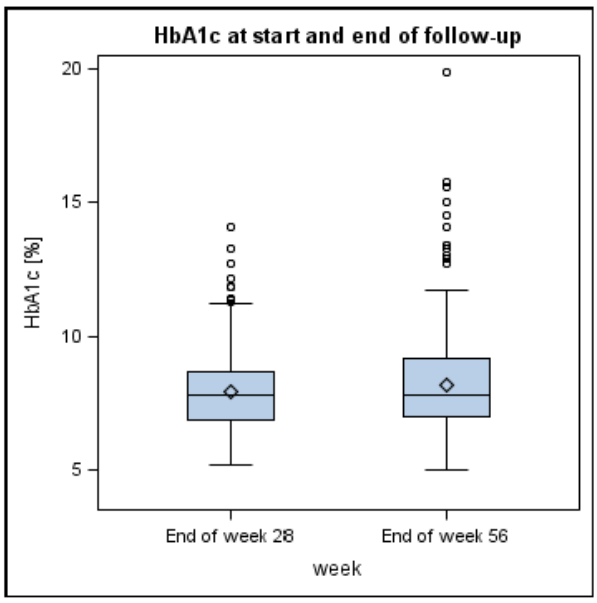
Results of secondary endpoints measured during follow-up treatment

A total number of 422 patients (212 treated with test drug and 210 treated with reference drug) completed the double-blind treatment period. All of these patients started treatment with follow-up medication (only test product and 412 patients completed the follow-up period.

HBA1c results at the end of the follow-up period were comparable to those at the end of the double blind treatment phase:

Table 131 Time course of HbA1c [%] measurement - descriptive statistics, all patients entered open treatment

HbA1c	description						
	MD	N	Mean	SD	Min	Median	Max
End of week 28	0	422	7.90	1.40	5.2	7.80	14.1
End of week 56	10	412	8.16	1.83	5.0	7.78	19.9



TF 12 Comparison of HbA1c at the end of double-blind treatment and at the end of follow-up

Body weight did not change markedly from the end of the double blind treatment period to the end of the follow up period (e.g. in Type 2 DM: 82.9 kg to 83.0kg).

2.5.1. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant is required to demonstrate in this application that Solumarv is biosimilar to the reference product Humulin S. The PK/PD clamp studies are therefore considered to be pivotal for the demonstration of equivalent efficacy. Efficacy data from clinical trials using HbA1c as endpoint are too insensitive to detect potential, clinically relevant differences and can therefore only be considered supportive. No dose-finding studies have been performed which is acceptable for a biosimilar product application.

The efficacy studies aimed to compare the safety and efficacy of three types of Marvel Insulins (tentative names: Insulin Human 30/ 70 Mix Marvel, Insulin Human Long Marvel (Isomarv) and Insulin Human Rapid Marvel (Solumarv) to the respective reference products (Humulin S, Humulin I and Humulin M3, Eli Lilly). This application only concerns Solumarv.

In both clinical studies, either a free or a fixed combination of the test and reference products were administered, thus all patients were exposed to both the short-acting and long-acting components. While including all insulin preparations in the same clinical trial is fully acceptable for the comparison of immunogenicity between the test and the reference insulins, this design limits the comparison of the efficacy of a specific test insulin to its respective reference insulin (here Solumarv vs. Humulin S), unless the study is powered for the respective subgroup analysis, which is not the case here.

The overall study design of clinical **study 411-BK-03-01-0000**, which was designed as an efficacy study, is generally acceptable and is in line with the Scientific Advice given. Inclusion and exclusion criteria are acceptable. Patients with significant cardiovascular disease were excluded. This is acceptable considering that human insulin is a well-known substance and that the goal of the comparability exercise is to establish biosimilarity and not patient benefit or safety *per se*.

Patients were either treated with a free or a fixed combination of regular and isophane insulins and approximately 50 % in the group randomised to test insulin were treated with Solumarv.

The chosen endpoints are acceptable. In addition, development of insulin antibodies was recorded and these data are discussed in the safety section of this report.

The strategy to include about 50 % patients with T1DM and 50 % with T2DM is endorsed as is the strategy to include similar proportions of patients on free and fixed combination. Randomisation procedures were adequate as were blinding procedures for the respective insulin preparation. Adequate statistical methods were applied.

In the extension part (411-BK-03-01-0001), patients originally treated with the reference products were switched to the test products. The design and objectives of the extension part of the study are acceptable.

Evaluation of efficacy was included as a secondary endpoint of **study 411-MA-08-01-0000,** whereas the primary objective was to describe the development of insulin antibodies in patients treated with the test products compared to the reference products. This is in line with the respective guideline on biosimilar insulins. Shape and labelling of the cartridges have been sufficiently similar to ensure double-blinding in the study. Reference cartridges were not re-filled for the purpose of blinding, which is supported from a safety point of view (sterility). The measures taken to ensure and to maintain double blindness are considered adequate.

Efficacy data and additional analyses

In **study 411-BK-03-01-0000**, baseline data were largely comparable between treatment groups and indicate that a representative population had been recruited. However, the baseline HbA1c in the T1DM group treated with the test product was slightly higher (8.8%) compared to the reference group (8.5%).

The non-inferiority margin chosen (0.6%) is considered unacceptably wide. A margin of 0.3-0.4 % would have been more appropriate. However, the upper limit of the 95 % CI for the treatment difference in the overall study population is below an acceptable non-inferiority limit of 0.4% (mean difference 0.16%, 95% CI [-0.04, 0.36]).

In all analysed subgroups, except for the free combination in T2DM patients, the mean differences in HbA1c were numerically in favour of the reference group. All but one subgroup (patients with type 1 diabetes treated with the fixed combination) met the pre-specified non-inferiority margin, while only 3 subgroups met the more stringent margin of 0.4%. However, some of the subgroups were very small and none of the subgroups was powered for formal non-inferiority testing. In addition, in patients with T1DM mean baseline HbA1c values were higher in the test compared to the reference group (8.80% versus 8.53%), which may have disadvantaged the test group. The reduction from baseline for test and reference was in the same range, roughly calculated at 0.29% and 0.23%, respectively, suggesting similar efficacy.

When data were analysed for the T2DM subjects (on both free and fixed combination), the reduction in HbA1c from baseline was in the same range for both test and reference products. In the T2DM subjects, the 95% CI for the difference in HbA1c at 24 weeks between test and reference was - 0.15% and +0.32%, thus also when applying a stricter non-inferiority margin of 0.4 %, non-inferiority could be shown for the T2DM group. No clinically relevant differences were observed between test and reference product when HbA1c was analysed by background treatment with oral antidiabetics as requested in the Scientific Advice.

The patients continuing in the extension phases (411-BK-03-01-0001, open –label extension phase of study 411-MA-08-01-0000) did not differ from the patients included in the main part of the study, with regards to baseline characteristics. In both T1DM and T2DM patients, HbA1c levels were largely maintained throughout the study period. Data has been presented to show that, overall, there was no deterioration in HbA1c in patients who switched from reference to test during the extension periods. Insulin requirements also did not increase over time, further supporting maintenance of effect.

Results of **study 411-MA-08-01-0000** numerically favoured reference treatment with respect to the results on HbA1c (test: 7.93%; reference: 7.90%; change from baseline roughly estimated at -1.33% and -1.59% for test and reference, respectively). However, both treatments led to a clinically relevant reduction within the double blind treatment period which was maintained through week 56 (end of open label extension phase). 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 Scientific Advice procedure EMEA/ H/ SA/1118/1/ FU/ 2008/ SME/ II.

As recommended in the relevant guideline (CPMP/ EWP/ 1080/ 00 rev. 1) and requested by the CHMP, change in HbA1c from baseline were also evaluated post-hoc for both trials. These analyses did not change the conclusions drawn from the evaluation presented above.

2.5.2. Conclusions on the 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-03-01-0000 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 24 or 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. 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 Humulin to Marvel insulin in the open-label extension and no change in insulin dose requirements was noted. Taken together, the data from the clinical trials, with some limitations, reasonably support similar efficacy of the test insulin used in those studies and reference insulin as demonstrated in the pivotal clamp study.

However, the efficacy trials were conducted with test material (Marvel insulin) which in the view of the CHMP has not been demonstrated as being representative for the material intended for commercialisation. Therefore, the relevance of the study results is uncertain.

2.6. Clinical safety

The Applicant performed three short-term PK and PD studies to demonstrate similar efficacy of Solumarv as compared to Humulin S, of which two produced valid results that can be considered for the current application. The safety database essentially consists of two phase 3 trials, i.e. study 411-BK-03-01-0000 (with extension phase 411-BK-03-01-0001) and study 411-MA-08-01-0001 (for further details on the studies' design see previous section "Clinical Efficacy"). The latter trial had a stronger focus on immunogenicity. In the following, the study IDs will be abbreviated as **BK-03** and **MA-08**, respectively, to improve readability. Details on the two phase 3 studies are provided in the efficacy section above.

Patient exposure

In **study BK-03** 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. 196 patients with T1DM and 213 patients with T2DM completed the extension phase; all patients received the Marvel product during extension. In this trial, care was taken to include approximately the same number of T2DM and T1DM patients. The average daily doses of regular and NPH insulin were similar between both treatment groups (Marvel and Humulin), among the T1DM as well as among the T2DM patients.

Study MA-08 recruited patients without special regard to the type of diabetes; hence, the ratio of Type 1 diabetics and Type 2 diabetics corresponds to the ratio in the general population of diabetics. In consequence, T1DM patients were a minority and were not evaluated separately. In total, 478 patients contributed to the safety set, 244 of these received Marvel insulin and 234 comparator. Actually, around 10% of the safety population were Type 1 diabetics, and they were rather well balanced between the treatment groups (11.1% vs. 9.4%, Marvel vs. Humulin).

The mean treatment duration in the comparative phase was 26.4 and 26.9 weeks in the Marvel and comparator group, respectively; 422 patients entered the non-comparative extension phase. The average daily doses of regular and NPH insulin were similar in both treatment groups.

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.

MA-08 (TT 10 of study report): Summary of treatment emergent adverse events, safety population

Number of -...	Test	Reference
	(N=244)	(N=234)
AEs reported	171	193
Patients with AEs	86 (35.2%)	87 (36.7%)
Serious AEs	17 (7.0%)	16 (6.8%)
Patients with SAEs	12	10
Deaths	0	0
Patients withdrawn due to AE	4	0

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 (24.4%)	15 (12.5%)
Serious AEs	1 (0.8%)	2 (1.7%)
Patients with SAEs	1	2
Deaths	0	1
Patients withdrawn due to AE	0	2

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 (25.3%)	44 (31.2%)
Serious AEs	16 (11.3%)	16 (11.3%)
Patients with SAEs	8	7
Deaths	0	0
Patients withdrawn due to AE	4	2

There was a marked imbalance in the number of patients suffering an AE among Type 1 diabetics in study BK-03 (30 vs. 15 patients, Marvel vs. Humulin). According to the study report, influenza and hypertension relevantly contributed to this imbalance (6 vs. 1 and 4 vs. 1 patient, respectively). Hence, a relationship to Marvel insulin is unlikely.

In the T2DM patients of study BK-03 the AE imbalance was in the other direction, i.e. in favour of Marvel. Random fluctuation is the most likely cause for imbalances observed among this rather small groups of patients.

In study MA-08, overall AEs were similar between treatment groups. Four patients vs. none withdrew due to AE in study MA-08. These cases included potential immunologic events which are discussed in detail in the respective section below.

Serious AEs were fairly balanced between Marvel and Humulin in both studies.

AEs by organ system: In study MA-08 there were some imbalances in respect to certain AE entities, but the total number of AEs was fairly balanced. The most salient imbalances are GI and general disorders, which were markedly more frequent in the Marvel group. Among these events were cases of potentially allergic origin (tongue oedema, generalised oedema); these are further discussed in the context of immunologic events below. Vascular disorders occurred more than two times more often in the reference than in the test group. Most of these vascular disorders were arterial hypertension.

The observed imbalances in the two studies are most likely chance findings due to the limited number of subjects in each group.

Hypoglycaemia is an important side effect of insulin therapy. The following table compares the incidence of hypoglycaemia in patients receiving Marvel insulin vs. the reference product Humulin in the two phase 3 trials. Hypoglycaemia was more frequent in Type 1 than in Type 2 diabetics, but

there is no hint that hypoglycaemic events were more frequent or more serious with Marvel than with Humulin insulins.

Incidence of hypoglycaemia during double-blind period

	411-BK-03-01-0000				411-MA-08-01-0000	
	Marvel		Reference		Marvel	Reference
	Type 1 diabetes N=95	Type 2 diabetes N=112	Type 1 diabetes N=101	Type 2 diabetes N=124	N=196	N=190
minor episodes n(%)	61 (64.2)	45 (40.2)	60 (59.4)	59 (47.6)	78 (39.8)	94 (49.5)
major episodes n(%)	3 (3.2)	1 (0.9)	3 (3.0)	3 (2.4)	0	2 (1.1)

Serious adverse events and deaths

Two deaths were reported in the clinical trial programme, one due to stroke and the other because of traffic accident.

The incidence of SAEs was fairly balanced between the treatment groups in both trials, BK-03 and MA-08, see summary in the previous section. The rate of SAEs was higher in T2DM patients than in T1DM patients. This is plausible because of increased co-morbidity in the generally older Type 2 diabetics. There was no accumulation of specific types of SAEs. Two patients in the Humulin group experienced severe hypoglycaemia. Otherwise, relation to insulin treatment or to Marvel insulin in particular appears unlikely in most cases due to the nature of the events (e.g. bone fracture, CV event or infection). There were salient cases of face oedema which might reflect hypersensitivity. These cases are discussed in detail in the section on immunological events below.

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 insulin or Humulin nor were there any clinically relevant differences between Marvel insulin and Humulin.

The primary endpoint of study MA-08 was defined as the incidence of newly developed **anti-insulin antibodies** (IgG) during the double-blind treatment phase. 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 a 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.

Antibody measurements from the older study BK-03 were considered unreliable due the use of an insensitive assay. In brief, around 20% of the Type 1 diabetics were tested positive at the beginning of the study in each treatment group. 21.9% in the test and 14.0% in the reference group developed new antibodies during the study. In Type 2 diabetics, around 13% of patients were positive in each treatment group at study start. 10.7% and 12.5% turned positive during the study in the test and reference group, respectively.

Analytical methods for antibody determination

In study MA-.08, the following determination method for antibodies was used and validated:

A commercially available RIPA (Euroimmun, Lübeck) was used for the detection of **binding antibodies to insulin** (screening and confirmation) and is in general considered appropriate in design. Assay principle: 125I- labelled human insulin is used to bind anti-insulin antibodies. Bead-bound goat anti-human IgG is added to precipitate immune complexes. The radioactivity of the

samples is measured using a γ-counter. Acceptable validation was performed. However, it is not able to discriminate between antibodies against native and modified Lys insulin.

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. It was an ECL-based competitive ligand binding assay. In this assay, the plates are pre-coated with anti-penta-His antibodies (R&D systems) to straighten the insulin receptor which contains a C-terminal penta-His-tag. Sulfo-tag™(purchased from Meso Scale Discovery)-labelled insulin is pre-incubated with serum containing neutralising antibodies against insulin forming an immune complex that will be immobilized on the insulin-receptor coated microtiter plate. In the presence of neutralising anti-insulin antibodies binding of sulfo-tagged insulin to the insulin receptor will be inhibited. The electronic stimulation of the sulfo-label will lead to the emission of signals which inversely correlate with the concentration of neutralising antibodies against insulin.

Neutralising anti-insulin antibodies have not been identified with currently licensed recombinant insulins. Therefore, a screening assay for neutralising antibodies is not considered essential.

Furthermore, an assay for **antibodies against host cell protein (HCP)** was developed. This assay was a direct ELISA. HCP lysate purchased by Diosynth was immobilized on the surface of microtiter plates. Bound antibodies against HCP were detected by adding a specific anti-human IgG conjugated with horseradish peroxidise (HRP) for the detection of human anti-HCP antibodies. Anti-rabbit IgG conjugated with HRP was added to detect the rabbit standards and controls. Commercially available rabbit antibodies against E.coli lysate at three concentrations was used as positive control. The validation results indicate that the assay is most probably suitable for its intended use.

Antibody incidence in study MA-08

The proportions of patients with new anti-insulin antibodies during double-blind treatment (per protocol set) were 28.06% in the test group and 28.42% in the reference group (see table below). The 95% confidence interval for the difference between the test and the reference group was between -9.31 % and +8.57%, i.e. within the pre-defined non-inferiority margin of 10%.

The following two tables summarise the incidence of newly formed antibodies in the participants of study MA-08 in total and separated for type of diabetes. No meaningful differences between treatment groups became obvious.

TT 1 Proportion of patients with new anti-insulin antibodies during double-blind treatment phase, per protocol set

Incidence						Treatment effect			
Test			**Reference**						
n	new	rate	n	new	rate	Statistic	Value	Lower	Upper
196	55	0.2806	190	54	0.2842	Difference	-0.0036	-0.0931	0.0857
						Odds ratio	0.9824	0.6154	1.5688

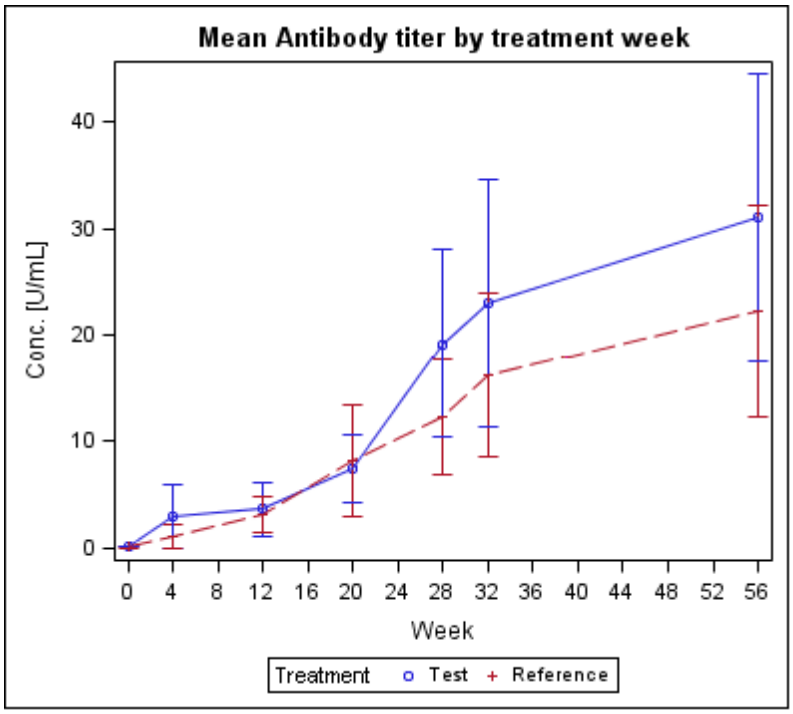
Table 2.7.4- 19 of SCS: Antibody AB results in the per protocol set according to type of diabetes

	TEST DRUG			**REFERENCE DRUG**			**95% CI for difference**
	N (total)	**N (+)**	**% (+)**	**N (total)**	**N (+)**	**% (+)**	
T1DM	22	7	31.82	18	4	22.22	-18.11 - +34.30
T2DM	174	48	27.59	172	50	29.07	-10.91 - +7.97

Antibody titres in study MA-08:

Not only incidence but also titre of antibodies was followed over time. Being antibody-negative at the beginning of the trial was an inclusion criterion so that the curve displaying the time course of

the titre starts at zero. As depicted in the figure below, the mean titre increased over time in both treatment groups, numerically more in the Marvel group but with large confidence intervals in either group. Thus, no meaningful differences between the groups became obvious. In the open label extension period (beyond Week 26), where all participating patients received Marvel, the increase was weaker than in the double-blind period. Notably, no stronger increase was observed in patients that switched to Marvel insulin at week 28 (red broken line) compared to patients who received Marvel insulin throughout the study (blue line).



TF 9: Mean titer (±95% confidence intervals) of anti-insulin antibodies for the duration of the whole trial in patients who became positive for antibodies during double-blind treatment.

Neutralising antibodies in MA-08:

Results of further Ab analysis of ab-positive patients exceeding a certain Ab cut-off point in the screening assay, using a neutralising (inactivation) assay, identified 6 patients on **Marvel (3.06%)** and 4 on **reference product (2.11%)** positive for neutralising antibodies. The comparison of all relevant clinical parameters (HbA1c, dosage of insulin, minor and major hypoglycaemic episodes) between the patients with neutralizing antibodies and all other patients revealed no clinically relevant difference.

Although the mean/median HbA1c values at week 28 and at week 56 were approximately 8%, some patients revealed very poor glycaemic control (HbA1c >10%), especially during the extension phase. One patient presented with the extremely high HbA1c of around 20% at the end of the extension phase. There is no hint that these cases of poor glycaemic control were due to neutralising antibodies; a deficit in compliance or supervision in individual cases is more likely.

Safety in special populations

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

Immunological events

In study MA-08, there were several potentially immunological events, in most cases in patients receiving marvel insulin. However, not all of these events were regarded as allergic/immunologic by the investigators.

The investigators had to answer at each visit the question whether any local or systemic allergic reactions occurred. There were six patients with a positive answer to this question.

Two patients in the Marvel insulin group:

- tongue oedema, face oedema (recovered/resolved)
- urticaria (recovered/resolved)

Four patients in the Humulin group:

- eyelid oedema (recovered/resolved)
- lipodystrophy acquired (recovered/resolved)
- urticaria (recovered/resolved)
- dry skin (recovering/resolving)

In order not to miss relevant potential allergic reactions, an additional check of all AEs was performed irrespectively from the answers from the investigators regarding local or systemic allergic reactions based on the MedDRA Standardised MedDRA Queries (SMQs). The following SMQs (MedDRA version 15.0) were taken into account in order to achieve the broadest possible definition:

- Anaphylactic reaction (broad)
- Angioedema (broad)
- Astma/bronchospasm (broad)
- Anaphylactic/anaphylactoid shock conditions (narrow)

A total number of 17 AEs identified as local or systemic reaction by the investigator and/or belonging to any of the SMQs defined above were registered in 16 patients treated with the test drug and 17 AEs were registered in 14 patients treated with the reference product. Urticaria, a typical sign of allergy, was balanced between test product and reference, one case per group. A lack of balance between both groups in favour of the reference drug was revealed for the following events:

1. Periorbital oedema (1 case in the test group, no case in the reference group; however, one case of eyelid oedema was reported in the reference group)
2. Tongue oedema and face oedema (1 case in the test group, no case in the reference group)
3. Face oedema (2 cases in 2 patients in the test group, no case in the reference group)
4. Generalized oedema (1 case in the test group, no case in the reference group)
5. Oedema peripheral (1 case in the test group, no case in the reference group)
6. Drug hypersensitivity (1 case in the test group, no case in the reference group)
7. Rash (1 case in the test group, no case in the reference group)

Peripheral oedema is most likely no sign of hypersensitivity; for the case of drug hypersensitivity, a link to sulfonylurea background medication could be established. For the remaining cases brief narratives of the cases in the test group are provided in the following:

Periorbital oedema:
male, 52 years
6 days after treatment start
not regarded allergic by investigator
non-serious
probably related
antibody-negative

Tongue oedema and face oedema:
female, 58 years
36 days after treatment start
not regarded allergic by investigator

serious
probably related
antibody-negative

Face oedema
male, 50 years
1 day after treatment start
regarded allergic by investigator
serious
certainly related
antibody-negative

Face oedema
male, 37 years
78 days after treatment start
not regarded allergic by investigator
non-serious
not related
antibody-negative

Generalized oedema
female, 44 years
15 days after treatment start
not regarded allergic by investigator
non-serious
not related
antibody-negative

Rash
female, 59 years
2 days after treatment start
not regarded allergic by investigator
non-serious
probably related
antibody-positive

In two of the three cases of oedema in the head region, the event was not regarded as being an allergic reaction by the investigator.

No new events of oedema were observed in the extension period of study MA-08. There was one event of injection site pruritus which was regarded by the investigator as allergic. No other AEs occurring in the extension period were regarded as allergic by the investigator.

One cases of face oedema was reported in the earlier study BK-03. This event is unlikely to be related to insulin. It was accompanied by gastrointestinal symptoms, and there was no clear oedema in the face but only the subjective impression of feeling turgor in the face. On the other hand, pruritus was also reported which cannot readily be explained. Nevertheless, there were no other signs for an immunological event so that the latter is unlikely.

The Applicant compiled the number of ab-positive patients among the subjects having had a potential immunologic reaction and having not had such a reaction. In a following step, the ab titres were compared between these two groups. No meaningful correlation between antibody status and potentially allergic reactions (broad definition) was observed.

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

The number of patients discontinuing a study due to AEs was small (see section on AEs). The AEs leading to discontinuation included the potential immunological events which are discussed in the respective section above.

2.6.1. Discussion on clinical safety

Three types of Marvel Insulins (tentative names: Insulin Human 30/ 70 Mix Marvel, Insulin Human Long Marvel (Isomarv) and Insulin Human Rapid Marvel (Solumarv) were used, which were compared to the respective reference products, Humulin S, Humulin I and Humulin M3, from Eli Lilly.The overall tolerability of Marvel insulin and the reference product Humulin was comparable. The number of AEs, SAEs and hypoglycaemia events was in general fairly balanced between test and reference product in both phase 3 trials conducted. Numerical imbalances in AE incidence occurred in both directions and were most likely due to random fluctuation among the rather small groups of patients. E.g., a rather high imbalance in AE incidence between test and reference product was observed in the T1DM subgroup of the study. This imbalance was mainly caused by events of influenza and hypertension in the test group and is therefore most likely not related to insulin treatment.

The primary endpoint of the newer study MA-08 was formation of new antibodies against insulin (the study was conducted in patients who were antibody-negative at the time of inclusion). No meaningful differences were observed in respect to ab incidence and mean ab titre between Marvel and Humulin insulins; also, the increase in titre over time was not relevantly different in both treatment groups. Neutralising antibodies as defined by the applicant were detected in a small fraction of patients of study MA-08 but were not associated with clinical consequences such as worsening glycaemic control or increasing insulin demand. From study BK-03, no reliable antibody measurements are available.

There were three events of oedema in the head region (face, tongue and periorbital) in the Marvel group of study MA-08 for which the cause was unclear and which could be potentially allergic in nature. There was also theoretical concern that Marvel insulin could be more immunogenic than other human insulin preparations because Marvel insulin, due to its specific production process, contains two impurities which are absent in other insulins. A non-clinical test for increased immunogenicity of these terminally substituted insulin impurities did not yield unambiguous results. The relevance for humans of this non-clinical approach is questionable since an artificial stimulator of the immune response was used.

Notably, two out of the three events of head region oedema were considered to be non-allergic by the investigator. In the remaining case (a combination of face and tongue oedema), allergic origin was suspected; however, the patient also took several medications which are known to potentially cause angioedema so that other reasons than Marvel insulin are possible.

It has also to be considered that oedema is a known (albeit rare) side effect of insulin therapy. In fact, one event of oedema in the head region (eyelid in this case) was also observed in the comparator group. Although the mechanism of insulin-induced oedema is not fully understood, rapid improvement in glycaemic control could play a role. For this reason, this side effect might occur more frequently in a clinical trial than in general practice.

Taken together, there is no clear indication from antibody testing or clinical use that the test product used in the clinical trials is associated with undue immunogenicity.

It is notable that a number of patients had very poor glycaemic control at end of the extension phase of study MA-08 (HbA1c >10%) with the highest HbA1c measured being 20%. The latter patient's glycaemic control deteriorated during the second half of the double-blind phase and further worsened during the follow-up phase but obviously, no actions (e.g. increase in insulin dose) were taken, questioning compliance and supervision. No further information could be provided by the Applicant. For the other patients with poor glycaemic control the pattern was similar. During the double-blind period glycaemic control improved (HbA1c decreased by around 2% in mean) but deteriorated again during the extension phase of the study. This was observed in both treatment groups so that poor glycaemic control was most likely not related to Solumarv but to deficiencies in supervision and compliance. However, the rationale of the extension study was following-up the immunogenicity results. Glycaemic control was not the focus.

Of note, studies BK-03 and MA-08 were conducted with test material (Marvel insulin) which has not been demonstrated to be representative for the material intended for commercialisation (see section on pharmaceutical quality for details).

2.6.2. Conclusions on the clinical safety

The general safety profile of Marvel insulin, with regard to the test material used in those studies, appears comparable to that of the reference product Humulin. Antibody incidence and titres, AE incidence and hypoglycaemias were similar. However, more unusual cases of oedema were reported with Marvel than with Humulin insulins (face, tongue and periorbital oedema were observed in the Marvel group; one similar case (eyelid oedema) occurred in the comparator group). The cause of these events is not clear and is not necessarily immunogenic. Taken together, no conclusion is possible on whether the observed cases were hypersensitivity reactions or were related to insulin Marvel. During the extension studies, no further (potential) hypersensitivity reactions occurred. Thus, there are no clear hints for an increased immunogenicity of Solumarv. Hypersensitivity reactions are also known for other insulins and are included as important identified risk in the RMP.

An important limitation of the safety data is that the clinical trials were conducted with test material (Marvel insulin) which in the view of the CHMP has not been demonstrated as being representative for the material intended for commercialisation. Therefore, the relevance of the study results is uncertain.

2.7. Risk Management Plan

The CHMP received the updated PRAC Rapporteur Risk Management Plan Assessment Report dated 13/10/2015.

The PRAC considered that the risk management plan version 3.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. Product information

2.9.1. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

For a biosimilar medicinal product, it is required to demonstrate similarity with the reference product with regard to quality safety and efficacy,. Based on demonstrated similarity, the biosimilar application can refer, to the efficacy and safety experience gained with the reference product. 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.

Both studies, the pivotal investigator-blinded automated clamp study PROFIL001SoluMarvHV and the open-label supportive manual clamp study FARMOVS 232/2002 in healthy volunteers support the assumption of similar time-concentration and time-action profiles of the test insulin used and Humulin S. Although in study FARMOVS 232/2002 the predefined 95% CI for the comparison of the PK results did not meet the equivalence margins of 80-125%, the 90% CI, usually required for demonstration of bioequivalence, did. However, the 90% CI was not predefined and calculated post-hoc.

The two phase 3 trials, study 411-BK-03-001-0000 and study 411-MA-08-001-0000, aiming at achieving similar HbA1c values in patients with type 1 or type 2 diabetes are considered only supportive for the purpose of demonstrating similar efficacy. In both trials 3 Marvel insulin preparations (short-acting insulin applied for, NPH and biphasic insulin preparations) and their respective reference products were used. Although in both studies results of HbA1c at week 24 or 28 (absolute HbA1c values as pre-defined) tended to favour reference treatment, the upper limit of the 95% CIs of the treatment differences for the overall study population were contained within the non-inferiority margin of 0.4% considered acceptable by CHMP (see EMEA/ H/ SA/1118/1/ FU/ 2008/ SME/ II). Daily insulin doses were also comparable between treatment arms. Therefore, the data submitted reasonably support the assumption of comparable efficacy between Marvel insulins and Humulin insulins.

HbA1c results of the 24-week extension study 411-BK-03-01-0001 (following study 411-BK-03-001-0000), in which all patients were treated with Marvel insulin, showed no trend for deterioration of glycaemic control. Insulin doses did not increase during the extension study. Similarly, patients continuing in the open-label extension phase of the parent study 411-MA-08-01-0000 largely maintained their HbA1c throughout the extension period in both T1DM and T2DM patients. Insulin requirements also did not increase over time, further supporting maintenance of effect of Marvel insulins.

Uncertainty in the knowledge about the beneficial effects

The major limitation regarding the conclusion of similar efficacy of the product applied for with the reference product is that the clinical trials, including the pivotal trial PROFIL001SoluMarvHV, were conducted with test material (Marvel insulin) which in the view of the CHMP has not been demonstrated as being representative for the material intended for commercialisation. Therefore, the relevance of the study results is uncertain.

The study FARMOVS 232/2002 was performed open-label, which could have introduced a bias in adjustments of glucose infusion rate in this manual clamp. However, since FARMOVS 232/2002 is considered supportive only, the issue is not relevant for the overall conclusion on biosimilarity.

Risks

Unfavourable effects

The undesirable effects of insulin therapy are well known and mainly consist of hypoglycaemia. Frequency and severity of hypoglycaemic events were similar for the test insulins (Marvel insulin)

used in the studies and Humulin. The AE profiles of test and reference insulins were comparable. The studies conducted with Marvel insulin did not reveal additional risks.

Immunogenicity of Marvel insulins, as measured by development of anti-drug antibodies and antibody titres, did not appear to be increased compared to reference insulins.

Uncertainty in the knowledge about the unfavourable effects

The major limitation of the safety data is that the clinical trials were conducted with test material (Marvel insulin) which in the view of the CHMP has not been demonstrated to be representative for the material intended for commercialisation. Therefore, the relevance of the study results is uncertain.

Compared to Humulin, there were a few more cases with the test insulins (Marvel insulin) used in the studies, potentially reflecting hypersensitivity reactions. There were four events of oedema in the head region (face, tongue, periorbital) in the Marvel group and one (eyelid) in the comparator group. The cause of these events is not clear and is not necessarily immunogenic. Oedema is a known but usually rare side effect of insulin which mainly occurs upon rapid improvement of glycaemic control. Theoretically, hypersensitivity due to low levels of Marvel-specific product-related terminally substituted insulin impurities could be the cause. In the most serious case (face oedema combined with tongue oedema), the patient received several other drugs beside insulin, many of which are known to potentially cause angioedema. Taken together, no conclusion is possible on whether the observed cases were hypersensitivity reactions or were related to insulin Marvel. During the extension studies, no further (potential) hypersensitivity reactions occurred. As for other insulins, hypersensitivity reactions are included as important identified risk in the RMP.

Balance

Importance of favourable and unfavourable effects

Safety and efficacy of a biosimilar product is required to be demonstrated by a targeted comparability exercise. The conclusion of biosimilarity from this comparability exercise allows the biosimilar application to rely, upon the extensive clinical experience gained with the reference product.

Prerequisite is the demonstration of analytical comparability between the biosimilar and the reference product. However, as fundamental questions remain with regard to the manufacturing process of Insulin Marvel the data submitted by the applicant do not allow the conclusion of physicochemical and biological similarity with the reference product. Since the quality of the product cannot be demonstrated, the benefit/risk balance cannot be established.

The two clamp studies submitted suggest equivalent time-concentration and time-action profiles of Solumarv and the reference insulin Humulin S and thus allow a conclusion of similar efficacy with regard to the test material used in those studies, but not with regard to the material intended for commercialisation. This conclusion is supported by the efficacy results of two clinical trials, in which three different preparations of Marvel insulins (including Solumarv) and the respective reference products were used. Similar effects on HbA1c using similar insulin doses could be achieved with these test and reference products. Maintenance of effect of these Marvel insulin preparations (including Solumarv) was obvious over the treatment duration of 1 year.

The AE profiles including hypoglycaemia were found to be generally comparable with regard to the test material used in those studies. An increased propensity of Marvel insulin to cause hypersensitivity reactions appears unlikely but cannot fully be excluded. Hypersensitivity is included as important identified risk in the RMP.

Benefit-risk balance

Discussion on the benefit-risk assessment

The conclusion on biosimilarity of a product with a reference product is based on the totality of data derived from a targeted quality, non-clinical and clinical comparability exercise.

The data from the non-clinical and clinical studies support the assumption of similar efficacy and safety of the test insulin used in those studies and the reference insulin. However, as the clinical trials were conducted with test material (Marvel insulin) which in the view of the CHMP has not been demonstrated to be representative for the material intended for commercialisation, no conclusion of similar efficacy and safety of the material intended for commercialisation with the reference product can be established.

The foundation of any biosimilar development is the extensive characterisation and comparison of structural and functional characteristics of the biosimilar and the reference product using state-of-the-art analytical tools. Active substance material of Solumarv (Marvel insulin) used for the analytical comparability exercise was produced between 2003 and 2010 The active substance manufacturing process has undergone changes over time but the applicant has failed to identify these process changes in detail and to evaluate them. Furthermore, the active substance manufacturing process which is intended to be commercialised has not been clearly identified and documented. Consequently the robustness and reliability of the intended commercial manufacturing process could also not be demonstrated as validation data for the commercial process was not presented.

Comparability of Solumarv product used for nonclinical and clinical studies with the commercial product has not been demonstrated. Thus, the relevance of the non-clinical and the efficacy and safety data obtained from the various studies for the product to be commercialized is uncertain. Moreover, a final conclusion on the actual amounts of the Solumarv specific terminally substituted insulin variants in clinical and commercial batches is currently not possible since equivalence of the different methods used has not been demonstrated. It also became clear that the applicant does not have full access to all process data on the active substance manufacturing process and could not provide sufficient reassurance that all future manufacturing changes would be made known to the applicant and consequently the EMA.

The unresolved major concerns on quality and the uncertainty regarding the relevance of the data from the biosimilarity exercise for the product intended for marketing present a major obstacle to the approval of Solumarv. In the absence of demonstration of the quality of the product, the benefit/risk balance of the product cannot be established.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Solumarv in the patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis, the CHMP considers by consensus that the quality of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product.

The CHMP considers that:

- The commercial manufacturing process for the active substance has not been clearly identified and documented. In particular, the intended commercial fermentation process and pooling procedures are not reflected by the flow chart and the manufacturing process description.

Reprocessing of undefined, non-complying RP-HPLC side-fractions and blending and homogenisation of batches are not acceptable and need to be removed from the dossier. Assurance that the Applicant has full access to manufacturing records held at the two active substance EU manufacturing sites and that he will be informed of manufacturing process changes have not been obtained.

- Process validation data supporting the intended manufacturing process for the commercial product have not been provided. Retrospective process validation data for the process as performed in 2008/2009 are considered insufficient to demonstrate validation of the intended commercial manufacturing process as performed in 2015. The data are insufficient to reflect splitting, pooling, blending of the maximum defined batches and batch traceability as proposed for the commercial process. Thus the reproducibility and robustness of the intended manufacturing process have not been demonstrated.

- Comparability of Solumarv product used for pre-clinical and clinical studies with the commercial product has not been established; therefore the relevance of the non-clinical and clinical data for the product intended for marketing is not demonstrated. Process history has not been documented and information on the differences between the intended commercial active substance manufacturing process and the active substance manufacturing processes used to generate material for nonclinical and clinical studies has not been provided. Process changes have not been evaluated in line with ICH Q5E requirements and a science based risk assessment on the changes implemented during the manufacturing process history is not available. The presented data are insufficient to confirm comparability of the different manufacturing processes.

- Reliability of analytical results for the specific variants of recombinant insulin in Solumarv has not been assured. Two analytical in house-methods have been established and validated in 2015 as active substance release methods. However, equivalence of the previously used methods with these new active substance release methods has not been fully demonstrated. This precludes a comparison of the batch results for clinical lots with the commercial batches and a final conclusion on the actual amounts of Solumarv specific insulin variants in the active substance batches.

- Following from the above grounds, analytical comparability between Solumarv and the reference product Humulin S has not been established. The data provided by the Applicant to support the biosimilarity of Solumarv and Humulin S are not sufficient to allow a final conclusion on analytical comparability.

The CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the quality of the above mentioned medicinal product is not properly or sufficiently demonstrated.

Since the quality of the product cannot be demonstrated, the benefit/risk balance cannot be established.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, and risk management plan cannot be agreed at this stage.