London, 20 September 2012
EMA/CHMP/598935/2012
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment Report

IXinity (formerly IB1001)

International non-proprietary name: Recombinant coagulation factor IX (trenonacog alfa)

Procedure No. EMEA/H/C/002349

Applicant:

Inspiration Biopharmaceuticals, EU Limited[1]

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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

[1] EMA was informed about the change in applicant from Inspiration Biopharmaceuticals, EU Limited to Cangene Europe Limited on 26 April 2013.

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine transferase
aPTT	activated partial thromboplastin time
AR	assessment report
$AUC_{0-\infty}$	area under the plasma concentration time curve from 0 to infinity
AUC_{0-t}	area under the plasma concentration time curve from 0 to the time of the last measurable plasma concentration
BDS	bulk drug substance
BLA	biologics license application
BUN	blood urea nitrogen
CHMP	Committee for Human Medicinal Product
CHO	chinese hamster ovary (cells)
CHOP	chinese hamster ovary cell protein
CI	confidence interval or continuous infusion (depending upon context)
cGMP	current Good Manufacturing Practices
CJD	Creutzfeldt–Jakob disease
CNS	central nervous system
C_{max}	maximum plasma concentration post-infusion
dL	deciliter
DP	drug product
DS	drug substance
ED	exposure days
ELISA	enzyme linked immunosorbent assay
EMA	European Medicines Agency
EOP	end-of production cell
EPAR	european public assessment report
EU	European Union
F1+2	prothrombin fragment 1+2
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practices
GI	gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HCP	host cell protein
ICH	International Conference on Harmonization
IQR	interquartile range
ITT	immune tolerance therapy
IU	international units
IV	intravenous
IVR	in vivo recovery
kg	kilogram
L	liter
LoOI	list of outstanding issues
LoQ	list of question
MAA	marketing authorisation application
MCB	master cell bank
mg	milligram
NIBSC	National Institute for Biological Standards and Control (UK)

NOAEL	no observed adverse effect level
NOEL	no observed effect level
NOR	normal operating range
PDCO	Paediatric Committee (EMA)
Ph. Eur.	European Pharmacopoeia
pI	isoelectric focusing point
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PT	platelets
PTP	previously treated patient
PUP	previously untreated patient
Q	quarter
QbD	quality by design
qPCR	quantitative polymerase chain reaction
rFIX	recombinant factor IX
RVLPs	retrovirus-like particles
SAE	serious adverse event
SD	standard deviation
SOP	standard operating procedure
SPC (SmPC)	summary of product characteristics
t½α	distribution half-life
t½β	terminal half-life
TAT	thrombin antithrombin complex
Thr	threonine
TMB	tetramethylbenzidine
TSE	transmissible spongioform encephalopathy
WBCT	whole blood clotting time
WCB	working cell bank
WFI	water for injections
WHO	World Health Organization

1. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Rapporteurs consider that the application for IXinity (formerly IB1001), in the “treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency)” is not approvable since "new major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of outstanding issues.

Questions to be posed to additional experts

None.

Inspection issues

Proposal for Inspection

The drug substance manufacturer and the drug substance release testing and finished product stability testing site had not been GMP inspected by EU authorities within the last 3 years and a pre-approval GMP inspection was performed by UK Authorities in March 2012. GMP compliance of both facilities, has been confirmed.

A GCP inspection was proposed with regard to study IB1001-01 to address data-handling aspects.

Proposal for Pre-authorisation Testing

A proposal for pre-authorisation testing of IB1001 drug substance and finished product was made. A final pre-authorisation testing report has been presented to EMA in May 2012. All drug substance and drug product lots met release specifications.

New active substance status

The applicant considers that IB1001 fulfills the requirements for a “new active substance”.

The applicant is still requested to submit supporting data that the active substance of IB1001 can be qualified as a new active substance.

2. EXECUTIVE SUMMARY

2.1. Problem statement

Haemophilia B is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies. IB1001 is intended for treatment and prophylaxis of bleeding in patients with hemophilia B (congenital factor IX deficiency).

2.2. About the product

IB1001 is a 415 amino acid long recombinant human FIX expressed in CHO cells with a Mw of 55 kDa. The amino acid sequence of IB1001 is comparable to the human FIX-(Thr148 allelic form). The recombinant molecule contains 11 disulfide bridges. The IB1001 Drug Substance is a clear colorless solution, essentially free of visible particles.

2.3. The development programme/Compliance with CHMP guidance/Scientific advice

Inspiration's clinical development of IB1001 was based on the EU guideline available at the time the development program was initiated (*CPMP/BPWG/1561/99 rev 1*), as well as discussions with the US Food and Drug Administration (FDA). The strategy for the paediatric development has been revised in light of the publication of the new July 2009 draft CHMP Guideline on the *Clinical Investigation of Recombinant and Human Plasma-Derived Factor IX Products (EMA/CHMP/BPWPEMA//144552/2009)*.

In the fall of 2009, Inspiration met with the Danish Medicines Agency (DKMA), the French Agency (Afssaps), and the German Paul Ehrlich Institute (PEI) for national Scientific Advice on IB1001 development. On 18 March 2010, Inspiration received Scientific Advice on IB1001 from the CHMP. A MAA pre-submission meeting was held with the EMA on 28 July 2010 and with Rapporteur and Co-Rapporteur in October 2010. Additional feedback on the presentations, pharmaceutical forms and product information was provided by EMA on 19 April 2011.

Consistent recommendation contained (1) accordance with the clinical guideline as proposed, (2) advice from PDCO, and (3) questions regarding rather high dosage.

A Paediatric Investigation Plan (PIP) application for IB1001 was submitted to the Paediatric Committee (PDCO) in July 2009 and received an initial positive opinion on 11 June 2010, followed by minor modifications to the PIP with a positive opinion and positive EMA decision of 20 Sep 2011. The European Medicines Agency has deferred the obligation to submit the results of studies with IB1001. On 12 Aug 2011, a Compliance Report of the PDCO was adopted by the EMA. However, significance of paediatric studies is not to be assessed, currently.

The paediatric studies cover (1) a PK and treatment-phase study (IB1001-02) in 20 paediatric subjects according to the clinical guideline. 2nd proposed study (IB1001-03) covers 40 paediatric subjects <6 years who are previously untreated ("PUP-study").

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

GMP compliant manufacture of the DS and the DP is in principle demonstrated. A pre-authorisation inspection by Competent Authorities of the EEA of the drug substance manufacturer and the drug

substance release testing and finished product stability testing site has been conducted in March 2012. GMP compliant manufacturing conditions have been confirmed.

According to the applicant pharmacology studies were not GLP compliant except the study comparative thrombogenicity evaluation of IB1001 DP. Toxicology studies were all GLP compliant.

The clinical study supportive of the MAA dossier, IB1001-01, was conducted according to ICH E6 Good Clinical Practice (ref. 2.5.1.2 Clinical Development Program, p14).

However, general GCP issues have been raised regarding study IB1001-01. Grounds for a GCP inspection would be: small company, many contractors, single small pivotal study, incomplete documentation, e.g. patient diaries. These concerns have become more pronounced after receiving the applicant's responses to the LoQ, mainly due to general aspects related to data handling as database corrections by the company, data entry errors and different study report updates. Therefore, a need for GCP inspection for the clinical study IB1001-01 was discussed. However, it was considered premature at this point considering the remaining quality and clinical MOs.

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

- Legal basis

This is a full Marketing Authorisation Application (MAA) submitted by Inspiration Biopharmaceuticals EU Limited (Dublin, Ireland) as centralised procedure for the medicinal product IB1001, a recombinant human FIX. This MAA is submitted in accordance with Article 6 of Regulation (EC) No 726/2004, as amended and Article 8(3) of Directive 2001/83/EC, as amended.

3. SCIENTIFIC OVERVIEW AND DISCUSSION

3.1. Introduction

IB1001 is a single chain recombinant glycoprotein of 415 amino acids that is secreted by a genetically modified Chinese Hamster Ovary (CHO) cell line. The primary amino acid sequence is identical to the Thr148 allelic form of human factor IX with differences on some post translational modifications. The biosynthesis of functional factor IX requires vitamin K which serves as a cofactor in the enzyme-catalysed gamma-carboxylation of up to 12 glutamic acid residues. These glutamic acid molecules, which reside within the first 40 amino acid residues of the amino-terminal region of the protein, form the Gla-domain. Calcium binding to the Gla-domain results in a conformational change in the protein that is essential for factor IX function in the process of blood coagulation..

The manufacturing of IB1001 is a classical recombinant DNA technology process. Fermentation is followed by cell harvesting and solvent/detergent treatment to increase the margin of viral safety. Downstream purification process consists of three chromatography steps. After purification the solution is virus filtrated and finally ultra/diafiltrated. Bulk is filtrated, filled in plastic bottles and stored/shipped frozen.

The drug product (DP) is a powder for solution for injection. IB1001 contains no preservative and is intended to be administered to the patients by intravenous injection, after reconstitution with WFI. IB1001 DP is provided as a sterile non-pyrogenic cake in 5 mL glass vials with rubber stoppers. The present application includes three nominal DP strengths: 500 IU, 1000 IU and 1500 IU. The powder is to be reconstituted with 5 ml of WFI.

Currently there is a discussion ongoing about the labeling of modified proteins as reflected in a draft concept paper (EMA/CHMP/BWP/776563/2010). The concept paper refers to proteins which are intentionally modified in order to alter the in vivo properties of these molecules. IB1001 is labeled relative to a plasma-derived concentrate standard (which is calibrated against the 4th International Standard for Blood Coagulation Factor IX, Concentrate, 07/182). Labeling in International Units is acceptable, as it has been the case with the competitor product and other recombinant factor concentrates. Although IB1001 is not fully identical to pdFIX, it is a non-modified human recombinant rFIX, functionally and structurally similar to pdFIX. Therefore the declaration of FIX activity in IU is justified.

For each strength, IB1001 is proposed in the following presentations: Powder and solvent for solution for injection (powder in a vial and pre-filled syringe with sterile WFI in the same outer carton). This presentation in turn, can include: Either one vial of powder and one pre-filled syringe; or eight vials of powder and eight pre-filled syringes with solvent in the same outer carton. The Applicant has deleted the application for drug product only, and included a transfer device, as requested by CHMP. Sufficient information is presented in Module 3 regarding the compatibility of the device with the product; additional information regarding the quality of the devices is requested.

3.2. Quality aspects

Drug substance

Manufacture

The drug substance of IB1001 is manufactured and tested by contract manufacturers and test laboratories. The facilities involved in DS manufacture, MCB and WCB cell banking and testing are linked in the dossier.

Compliance with GMP is demonstrated by respective documents for all facilities involved in the manufacture, storage, transfer and testing of the drug substance or intermediates. The manufacture of IB1001 DS is accomplished using typical fermentation, harvest, and purification unit operations. WCB vials that are cultured in a sequential process in shake flasks, Spinner flasks, a seed fermenter and a production fermentation vessel. Some more details regarding cell culture handling during cell expansion and testing for microbial and foreign cell contaminates were requested to have assurance that the manufacturing process is in compliance with ICH Q5D. This has in principle been demonstrated. The cell supernatant is harvested by depth filtration followed by further filtration. The filtered harvest is subject to S/D treatment to eliminate enveloped viruses potentially present in the harvest.

The rFIX is purified through a series of three ion exchange chromatography steps, followed by a nanofiltration prior to concentration and buffer exchange into the formulation buffer.

The filtered bulk is stored in bulk storage bottles. The filled BDS bottles are stored until they are sent from the drug substance manufacturer to the drug product manufacturer by a shipping service specialized in cold chain transportation of biopharmaceuticals. At the drug product manufacturer, final formulation, sterile filtration, filling and lyophilisation take place. One batch of drug substance is produced from the harvest of a single fermenter. There is no pooling of harvests or intermediates. There is no re-processing of any chromatographic step.

Cell banking system, characterisation, and testing

The Applicant is using a concept of two-tiered cell banking system that consists of MCB and WCB which are both stored at two different locations. The documentation provided is sufficient to conclude that the

cell banks have been generated mainly in compliance with ICH Q5D. The origin of the transfected and cloned production cells as CHO cell line has been characterised by isoenzyme analysis. The source, history and production of the CHO cells, RCB, MCB and WCB have been described and documented in detail according to ICHQ5B, including methods and reagents used during culture, in-vitro cell age, storage conditions and the size of the cell banks. Both MCB and WCB have been qualified and characterised by extensive testing for mycoplasma, sterility and adventitious viruses to establish purity. Specification for the preparation of future WCBs should be in line with the MCB specification. The measures to assure traceability of cell bank containers have been described in the dossier. The transgene copy number in the MCB, WCB, and end-of production cell (EOP) bank should be defined by a more precise procedure. Although the applicant considers the current qPCR method as sufficiently accurate to define an average gene copy number, he is encouraged to use an alternate method to define the true gene copy number more accurately. Characterisation reports for the EOP-cells provide evidence that the EOP cells meet acceptance criteria. The anticipated utilisation rate and expected interval of the WCB has been specified.

Characterisation

IB1001 has been extensively characterised by physical and biochemical methods, in compliance with ICH Q6B. Some additional data were requested, partially by means of complementary analytical techniques, to obtain a more complete physico-chemical characterisation of the active ingredient (complete primary amino acid sequence; disulphide bonds, sialylation; Gla residues). From the complete set of data available at submission and received with the responses to day 120 LoQ, IB1001 shows PTMs typical for recombinant proteins produced in CHO cells. It has been shown that with respect to physico-chemical properties IB1001 lots show a high degree of similarity.

Control of manufacturing process

The general approach to assure a consistent and reliable manufacturing process is in compliance with ICH Q6B. However, the control strategy was not sufficiently defined for the manufacturing of DS. This was regarded as a major objection at D120. The Company has determined the control steps according to quality by design (QbD) principles without applying QbD. The performance parameters are categorized into in-process controls, in-process limits, and in-process specifications. Based on an FMEA risk assessment, each process parameter was ranked from 1-10 on the severity, probability of occurrence, and the ability to detect an excursion and/or the impact of an excursion outside of the normal operating range (NOR). The categorization of a process parameter as critical or non-critical followed a risk based approach without a proper argumentation of the criticality of the parameters and this was not considered appropriate. With the responses to the LoQ D120 the Applicant discusses now more thoroughly their control strategy. The criticality of the parameters will be re-evaluated, but the final report will not be available until a given date. In addition the Applicant is applying a life cycle approach to the process validation, examining data after each lot and re-evaluating the adequacy of the current ranges. The first re-evaluation of the ranges will occur after a statistically sufficient number of batches. In general the Company´s strategy for process control is deemed acceptable. However a few points need to be clarified further:

i) A justification for the revised risk priority number RPN is needed.
ii) Clarification is needed how the protein load and yield will be routinely determined in the chromatographic steps and what is the basis for process and production parameters ranges (total protein or IB1001 protein content).
iii) The total amount of the protein in the load and in the elute should be determined and how much IB1001 accounts for. The clearance percentage should be calculated thereof.
iv) The ELISA method for quantitation of IB1001 protein and its validation should be submitted.

v) The reassessment of the criticality of process parameters and ranges limits as well the ranges limits for production parameters are awaited.

Process Development

The development of IB1001 DS commercial manufacturing process was performed by the contractor for Inspiration Biopharmaceuticals. The process development involved two rounds of process refinement that took place in three phases designated as follows:

- Original Process
- Refined Process
- Commercial Process

The Master Cell Bank (MCB) was used in the original process whereas the Working Cell Bank (WCB) was established and used in the refined and commercial processes. The cell culture and purification process principles were not changed through development. The fed batch production scale remained unchanged through the clinical development and is the same as for the proposed commercial scale. Similarly, all batches manufactured to date and used in the nonclinical and clinical studies or planned for commercial use have been manufactured at the same manufacturing site.

The original manufacturing process was first changed to the refined process by implementing certain changes. The refined process was changed in a step wise fashion to achieve the commercial process by implementing a new viral filter, changing the seeding density and adjusting chromatography steps. The rationale for process changes during development is adequately described in compliance with ICH Q5E. The commercial process results in an rFIX with physico-chemical properties comparable to rFIX of the previous processes. The comparability of the quality, safety and efficacy of the DS from the original process, the refined process and the commercial process is demonstrated.

Control of Drug Substance

The DS is subject to an extended list of release testing, including tests for integrity, purity, and activity. Acceptance criteria are mostly based on historical data, including preclinical and clinical lots, rely on pharmacopoeial requirements, or take into consideration the maximum allowed daily uptake. In principle, the release parameters and their specifications are adequate and meet requirements as outlined in ICH Q6B. Inspiration changed the approach of setting specifications. Now these are based on batch release data, on the commercial manufacturing process capability (CpK analysis) and takes into consideration the *Ph. Eur.* Monograph 01/2011:1223, Human Coagulation Factor IX and the in-house experience with the important quality attributes of the factor IX protein.

Analytical testing was conducted according to the specifications applied at the time. The comparability study from the refined process to commercial was conducted based on the same principles as previously. The comparability of the processes is sufficiently addressed. Whether the observed differences in posttranslational modifications have any impact on efficacy and safety is referred to clinical assessment.

Validation of analytical test procedures is considered adequate for most assays. Comparability of some tests with EP methods has been demonstrated. For the HCP-ELISA the source of the immunogen used appears inadequate to identify HCP impurity in the DS and DP. The sensitivity of the assay may be improved as well and the validation report should be presented.

Impurities

With respect to product-related impurities, the applicant has sufficiently tightened all specifications at DS and DP level, assuring that a product with a consistent high level of functional rFIX is obtained. An additional specification should be implemented at least at DS stage for better control of a variant.

The data indicate that IB1001 has a low level of process-related impurities, with the exception of residual HCP present in DS and DP. In the Response to the Day 120 LoQ the applicant reports that HCP impurities are present in IB1001 DS at a certain level, when measured with a more IB1001-specific HCP-ELISA. The level of HCP in all GMP lots (pre-clinical and clinal lots) is higher, compared to the data obtained with a previous, non-specific commercial assay (data provided in original submission). The high level of HCP in IB1001 DP is not acceptable**.** The development of anti-CHO protein antibodies in 26 % of participants of a clinical study provides further evidence that currently the impurity profile of the DP with respect to HCP is not approvable (**Major Objection).**

Possibly, the assay for the Determination of Antibodies to CHO Host Cell Proteins in patients could be more sensitive for co-purifying HCPs. Thus, more information is needed on the actual antigen and its´ specificity and sensitivity to detect a wide range of CHO-antibodies in patient sera and on the HCP-antibody to detect HCP-impurities in drug product. Eventually two assays, one broad range assay and one more IB 1001-specific assay may be employed.

Additional HMW protein impurities react with a goat polyclonal anti-HCP antibody, providing further evidence for the presence of residual HCP in IB1001 DS that should be eliminated prior to approval. The applicant reports that the introduction of an additional active substance purification step strongly reduces residual HCP level without affecting the integrity of the active substance.

The insufficient removal of HCP is considered as a Major Objection, which needs to be resolved before a marketing authorisation can be granted.

Reference Standards or Materials

The reference materials are adequately described and acceptable. In DS potency testing, as in house standard, the 6th British working standard (NIBSC) is used that has been calibrated against the 4th WHO IS for FIX concentrate 07/182. Beside this potency standard, currently only one in house reference standard of IB1001 is in use. The currently set specifications of the reference material have been justified and comparability of different reference materials has been shown.

Stability

The stability protocol for the BDS includes commercial lots and is in general in accordance with ICH Q1A(R2). The currently specified shelf life of the DS is supported by stability data from commercial DS lots, and by DS stability data from earlier GMP lots. Stability of the DS under accelerated storage is demonstrated.

Drug product

Manufacturer

IB1001, Coagulation Factor IX (Recombinant), drug product is manufactured, tested and released for Inspiration Biopharmaceuticals for commercial distribution using contract manufacturers and contract test laboratories. cGMP compliance of the facilities involved in manufacture and stability testing has been demonstrated.

Description and Composition of the Drug Product

IB1001 drug product is a sterile lyophilized powder intended for parenteral administration after reconstitution with water for injections (WFI). IB1001 exists in 3 presentations, 500 IU, 1000 IU and 1500 IU/vial. The solvent for reconstitution of one vial of IB1001 DP is 5 ml sterile Water for injections (WFI), resulting in 100 IU/ml to 300 IU/ml for intravenous administration. The WFI is in compliance with the *Ph. Eur.* (monograph 0169).

A transfer device and application set are part of the secondary packaging of the product. Compatibility of the devices with the drug product is in principle demonstrated, but more detailed information in the Medical Devices section of the dossier is requested.

DP is presented in a Type I borosilicate glass vial with rubber stopper and aluminum overseal with a polypropylene flip off cap in a matrix composed of histidine, mannitol, trehalose, NaCl and polysorbate 80, containing the labelled amount of Factor IX activity. All excipients are in compliance with Ph. Eur. and are commonly used compounds that serve to stabilize the active ingredient, to allow the formation of the cake during lyophilisation and to obtain adequate tonicity upon reconstitution. There are no materials of animal or human origin in the DP formulation.

The final formulation supported by stability studies has been the only formulation used in the preclinical and clinical trials of IB1001 DP and remains the same as the commercial DP formulation. The type of container and closure for dosage form and reconstitution solvent (water for injection) has been adequately described, too.

Manufacturing process

The DP manufacturing process uses operations that are commonly used for the production of biological parenterals. A comparability study has been performed according to ICH Q5E demonstrating that the DP lots manufactured at different sites are very similar.

The DP manufacturing process involves thawing of frozen DS, pooling of the thawed aliquots, mixing with the formulation buffer, filtration steps, filling into vials, lyophilisation, stoppering and visual inspection of vials. The Applicant has described the manufacturing process development (P.2.3) of DP focussing on the description of the formulation and lyophilisation cycle development. The lyophilisation development has been described adequately. The individual manufacturing steps have been described and the target limits for the in-process controls have been shown. The holding times for the steps have been justified.

Comparability of the equipment used at either site or cGMP compliant manufacturing conditions at the commercial drug product manufacturing site have been addressed in on-site audits by Inspiration. A risk analysis of the impact of minor differences between the sites on quality attributes of the product was made.

Release testing results of DP do not reveal any significant differences between testing sites. The specifications for DP from one site are partially only interim, and are further tightened after process transfer had been completed and the process is fully validated. Additional characterization of DP for specific parameters does not show any significant manufacturing site-differences. In process testing provides evidence that the process is consistent.

The DP is formulated to achieve three nominal potencies of 500 IU, 1000 IU, and 1500 IU of factor IX per vial. A change in the fill target from protein to potency was instituted so that the potency (instead of protein content) can be stated on the DP label to be consistent with the practice of other marketed coagulation products.

Validation

Criticality of each process step was evaluated in a risk assessment and acceptance ranges for critical parameters have been defined during process validation. The manufacturing process for IB1001 DP has been validated at full scale. The full scale process validation lots were produced using the same batch formula, container closure system, equipment, batch size, utilities and manufacturing process as to be used for the production of the commercial batches. The validation covered each individual step of the manufacturing process and the cleaning process, following respective SOPs in compliance with cGMP. The validation protocol addresses challenging conditions to demonstrate that the manufacturing

process is sufficiently robust. Maximum hold times are specified for each process step and are applied during the validation. The expected maximum process time at each step under routine conditions is used as minimum processing time during validation. Test parameters confirmed that the lyophilisation process leads to a uniform product.

The batch release test results for the batches in the validation study are coherent and within the acceptance criteria. The validation demonstrated consistent performance of the process and consistent production of IB1001 DP lots that meet release specification. The filters used for the sterile filtering of the formulated DS have been validated for bacterial retention, non-volatile residues, total organic carbon and leachable substances by the vendor. Furthermore, the maximum filtration pressure to rule out the risk for aggregation and precipitation of IB1001 during the filtration process has been specified. The filling accuracy and the temperature of the DS solution during filling are appropriately controlled. The filling weight and filling line speeds have been validated.

Control of the drug product

The finished DP specification both for release and shelf life were considered insufficient at D120 and have been tightened based on batch history with the response to the D120 LoQ. The product related impurities are adequately controlled and no significant trends in DP impurities or aggregates were detected. The remaining product related impurities are controlled at DS level. Consistent low level of these product-related impurities in the DP has been demonstrated in confirmatory studies. Therefore, omission of release specifications at DP stage is considered acceptable.

A specification for a variant at DS level and in DP stability testing is still requested to better control this non-functional FXI variant.

Stability

None of the lots manufactured at the commercial production site have completed 24 month under real time/real temperature conditions. The manufacturing process conditions and quality of product manufactured at different sites are comparable, although different glass vials (both Ph. Eur. type I quality, but different suppliers) are used. However both suppliers received the vials from the same glass manufacturer.

Satisfactory in use stability data are presented justifying the currently proposed in use shelf life. The in use shelf life should also be investigated at the end of shelf life. Any out of specification or critical negative trend should be reported to EMA immediately.

Facilities and equipment

IB1001 production facility is run under cGMP conditions, as confirmed by a respective GMP inspection in March/April 2012. IB1001 is the first product manufactured in this facility for commercial purposes. There are two cell expansion suites A and B and two bioreactor suites A and B. In addition there is a harvest/capture suite, a purification suite 1, a purification suite 2 (post-viral filtration), and a bulk filling suite. Expansion suite B and Bioreactor suite B are not used for IB1001 and are not part of this submission.

Quality Control test labs are located in Building 1, as well as laboratories for developmental purposes or protein characterisation.

All facilities where activities in the manufacturing process of IB1001 DS are performed are described in a brief summary. For each suite all rooms with their environmental standards are described. Water supply and cleaning and sanitization equipment is described as well. Floor plans with personnel and material flow are provided. All equipment in contact with product is listed and specified as dedicated or non-dedicated. The cleaning follows approved procedures.

Post-validation quality assurance improvements have been made or are planned. These changes include improved segregation of raw materials, personnel, product and waste flows, and improved separation of process operations. The DS manufacturing process remains unchanged and is performed in the same building. Based on a risk assessment the improvements are considered by the applicant to have no significant impact on the IB1001 DS manufacturing process.

Processing areas are dedicated areas for a single product at a time. Manufacturing rooms and equipment are quarantined until all cleaning and material clearance and documentation are completed.

Adventitious agent's safety evaluation

In summary, a sufficient level of virus and TSE safety of IB1001 has been indicated and no health concerns have been identified.

No human or animal-derived reagents or excipients have been identified in the cell banks and in the manufacturing process. Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been indicated. The testing programme of cell banks and un-processed bulk harvest for virus contamination is considered adequate and in compliance with ICH Q5A. No adventitious viruses have been detected. Retrovirus-like particles (RVLPs) were found in some of the harvested cell culture supernatants. Such RVLPs are frequently found in CHO cells and this is acceptable if sufficient retrovirus clearance at down-stream manufacturing steps can be demonstrated.

The virus reduction capacity of the down-stream purification process has been adequately investigated with four model viruses. The manufacture includes two dedicated and robust steps for virus reduction, i.e. inactivation of enveloped viruses at SD-treatment and removal of enveloped and non-enveloped viruses at virus filtration. At virus filtration, an upper limit has been specified in order to avoid a potential overloading of filters. One of the three chromatographic purification steps additionally contributes to virus safety with moderate virus reduction capacity.

DRUG PRODUCT (Sterile Water for injection)

The manufacturing process for the WFI has been adequately described, tested and validated. There is no formulation development as the preparation contains only sterilised water. The manufacturing process is controlled using appropriate in-process controls and manufacturing controls. Product release and shelf-life specifications have been established complying with Ph. Eur. 0619. Satisfactory information with respect to equipment, filtration pressure validation, compatibility of filter materials with WFI, as well as studies of any leachable substances that might be associated with filter elements have been presented.

Medical device

IB1001 is presented together with solvent WFI for reconstitution and administration of IB1001. The devices and its compatibility with the drug product are in principle demonstrated, but more detailed descriptions of the devices and respective CE certificates are requested.

Discussion on chemical, pharmaceutical and biological aspects

IB 1001 is a full length recombinant FIX produced in CHO cells. It is structurally and biochemically similar to plasma-derived FIX. The rFIX has been sufficiently characterised with respect to physico-chemical and biochemical properties. Differences in post translational modifications are seen compared to plasma-derived FIX, but these differences are well known for recombinant products. The gene construct, the production of the transgenic CHO cell line and the cell banking has been performed in accordance with relevant guidance documents.

The upstream fermentation process and the downstream purification process have been adequately validated, although a few points regarding the chosen validation approach still require clarification. The entire drug substance manufacturing process appears in general well controlled, leading to a drug substance of consistent quality with a low level of residual product-and process related impurities, except a relatively high level of HCPs, which need to be substantially reduced before a marketing authorization can be granted. cGMP-compliant manufacturing conditions and DS testing have been confirmed by GMP inspections through Competent Authorities of the EEA. The risk for viral contamination is minimized through a well-controlled cell banking system and fermentation process and through two effective virus-reduction steps.

The drug product is manufactured under well controlled cGMP conditions, resulting in a finished product of consistent quality. The DP has been produced at different facilities during development, but sufficient data from the commercial production site are available to demonstrate that IB1001 is adequately formulated, filled, and lyophilized to obtain a product of consistent purity and stability.

Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the data on quality, it is considered that the application for IB1001 cannot be recommended for positive opinion at present time since a major quality objection and other quality concerns are raised, which preclude a recommendation for marketing authorisation.

The major objection is related to the insufficient reduction and control of HCP which led to a high number of patients developing anti-CHO protein antibodies and therefore is considered as a quality related safety concern. Further action to reduce the HCP content in the DS is required. To address this major objection from a quality point of view, the MAH should, for example, either show that this can be achieved by improving the performance and control of the current chromatographic steps or add an additional purification step to the manufacturing process. Clearance of HCP throughout the purification process should be shown by appropriate validation studies. In case an additional purification step is introduced comparability and characterization data will be required besides process validation data, as this change might alter the quality attributes of the active substance and the efficacy and safety profile of the product. Comparability of the post-change product with previously used clinical trial material should be investigated in order to address the question whether additional clinical studies will be needed.

3.3. Non clinical aspects

Pharmacology

Concerning primary pharmacodynamics several in-vitro and one in vivo study have been performed comparing IB1001 with commercial recombinant FIX product, as well as with a plasma-derived FIX product.

The in-vitro studies conducted with IB1001 aimed to evaluate the functional properties of IB1001 and to identify unexpected interactions between activators, inhibitors, substrates, and cofactors. These studies demonstrated that the potency of IB1001, as indicated by its specific activity of 200 to 230 IU/mg, falls within the expected range for marketed factor IX products (200 to 280 IU/mg). Further, there was no evidence found that IB1001 is more procoagulant than plasma-derived or recombinant comparator.

The in vivo study was performed in a canine model of haemophilia B. In this study, it was demonstrated that IB1001 DS and DP preparations produced clotting time responses comparable to recombinant and plasma-derived Factor IX products.

In order to investigate the thrombogenic potential the applicant performed four studies. In the "pivotal" in-vivo pharmacodynamic study in haemophilia B dogs, there was no evidence of thrombogenicity due to any of the tested factor IX preparations as judged by measurements of biochemical markers and observations of overt thromboembolic events.

The objective of the second study was to evaluate the thrombogenicity of IB1001 DS and lyophilized DP in comparison to recombinant and plasma-derived FIX products and FEIBA following a single intravenous bolus administration in Sprague Dawley rats. In brief, the positive control groups exhibited a clear response, while all of the other groups were essentially equivalent while they did not exert overt signs of thrombogenicity.

The third study aimed to evaluate the thrombogenicity of IB1001 containing 1.5% factor IXαβ following a single intravenous bolus administration in Sprague Dawley rats. Factor IXαβ is the fully active enzyme form of factor IX and thus has high coagulation activity. There was no mortality in any treatment group and no signs of toxicity were observed in any animal at the observation time points. Two animals of the 300 IU/kg group had a single small blood vessel with a thrombus. However, according to the pathologist it is not unusual to observe a small thrombus in a blood vessel of the lung. Since no thrombi were observed in higher dosed animals a test article effect was considered unlikely. Determinations for thrombotic markers were negative.

In the fourth study, the thrombogenicity of five different lots of IB1001 drug product formulations was tested in comparison to a control IB1001 DP lot which has been evaluated for thrombogenicity in the previous study. In brief, intravenous bolus administration of 5 test formulations of IB1001 DP at a dose level of 1000 IU/kg, which is 10 times the human clinical dose, to male Sprague Dawley rats did not produce any toxic effects.

Pharmacokinetics

The pharmacokinetic properties of IB1001 drug substance and lyophilised drug product have been evaluated by single dose intravenous administration to Sprague Dawley rats and haemophilia B dogs previously tolerized to human factor IX.

The rats were used to evaluate the recovery and half-life of IB1001 drug substance and drug product and commercially available factor IX recombinant and plasma-derived products. The results of the first study demonstrated that the IB1001 manufacturing process is reproducible. No differences were observed between the various DS lots. In addition, the final lyophilisation and filling of the product had no effect on the pharmacokinetics and the IB1001 drug product showed similar pharmacokinetics in comparison to the commercially available recombinant factor IX product.

The pharmacokinetics of DS lots manufactured according to the original and the refined process were also evaluated in normal rats in comparison to the commercially available recombinant factor IX product. This study showed that the level of N-glycan sialylation of IB1001 DS lots and systemic exposure to factor IX following injection of IB1001 DS did not exceed but was comparable to that determined for the commercially available recombinant factor IX product.

A further pharmacokinetic study evaluating the original, the refined and the commercial processes again in normal rats showed comparability among them and to the commercially available factor IX product and all lots tested are not significantly different from the IB1001 lots used for human PK data studies.

In the tolerized haemophilia B dog it was demonstrated that IB1001 DS and DP had PK characteristics consistent with those of commercially available recombinant factor IX product.

Toxicology

The toxicology programme for marketing authorisation application of IB1001 included three single dose and two repeat dose toxicity studies using rats and dogs as well as the evaluation of the local tolerance in New Zealand White rabbits in two studies.

The acute intravenous toxicity after single dose injection of IB1001 was evaluated over a 14 day clinical observation period in both Sprague Dawley rats and Beagle dogs. No test article related safety issues were observed in dogs; an apparent increase in perivascular inflammatory infiltrates and thrombosis was observed in rats. These animals had venous cannulae inserted to facilitate test article administration. While it seemed likely that the pathological changes observed were associated with the inserted venous cannulae, it was not possible at that time to conclusively rule out association with the test article. Consequently, the thrombogenic potential of IB1001 was evaluated by repeating the rat study in non-cannulated animals and administering the product via tail vein injection to avoid potentially misleading cannula related artefacts. In this study rats were dosed intravenously with IB1001 Drug Substance, IB1001 Drug Product, commercially available recombinant or plasma-derived factor IX product at protein dose levels up to 1000 IU/kg (10-fold the maximum human clinical dose). The previously observed lesions were not seen as there were no thrombotic lesions or perivascular infiltrates documented at the end of the study at 14 days after dosing. This was considered as evidence that the previously observed pathology was caused by faulty cannulation of the rats as performed in the first study.

The intravenous toxicity after repeat (twice weekly) dose of IB1001 was compared to commercially available recombinant and plasma-derived Factor IX over a 28 day clinical observation period in Sprague Dawley rats. There were no signs of toxicity seen during the clinical observation period. Statistically significant differences between treatment groups were seen in some haematology, coagulation, serum chemistry, and urinalysis data. These differences varied across groups and were consistent with normal animal variability. No trends within or between groups were observed. No test article related lesions were observed in this study. Expected antibody development to factor IX was similar for the various preparations.

The local toxicity of IB1001 was evaluated by para- and intravenous administration to New Zealand White Rabbits. No significant visible difference was noted between the test article and buffer control at any of the observed time points and no test article related microscopic lesions were observed in the studies. Furthermore, with the second local tolerance study it was demonstrated that refinement of the drug substance manufacturing process and the change of the product fill and finish site did not negatively impact the local tolerance of the IB1001 drug product

Ecotoxicity / environmental risk assessment

Environmental risk assessment was not performed. IB1001 is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment, and therefore, is not expected to pose a risk to the environment.

Discussion on non-clinical aspects

Concerning the in vivo pharmacodynamics the applicant performed one study in haemophilia B dogs, only. Though the results are clearly favourable, the use of haemophilia B dogs is limited in the number of animals that can be studied. On the other hand the FIX ko mice model is established allowing for more thoroughly testing of efficacy in terms of number of animals and parameters like e.g. tail-tip bleeding. The applicant was asked to give a justification for using solely the haemophilia B animal model. The applicant argued that a more thoroughly characterisation of non-clinical pharmacodynamics would have been performed if a novel coagulation product would have been developed. However, IB1001 was designed in close relationship to the marketed recombinant FIX product BeneFIX. Thus,

there was an expectation that IB1001 would be very similar to BeneFIX which was intended to be confirmed only by using the haemophilia B dog model. In conjunction with the safety profile of IB1001 as documented in the reported toxicology studies, the evaluation of the efficacy of IB1001 in humans was considered to be more relevant than performing additional animal studies with surrogate efficacy endpoints. Though the establishment of a second and/or more meaningful pharmacodynamic model would have been endorsed, the argumentation of the applicant might be considered acceptable at this point of product development.

Several in-vitro pharmacodynamic studies were performed aiming to evaluate the functional properties of IB1001 and to identify unexpected interactions between activators, inhibitors, substrates, and cofactors. However, in these in-vitro studies several methodological pitfalls had been identified. So, the applicant was asked to clarify the aspects on robustness and reproducibility of the assays used for in-vitro functional characterisation of IB1001. However, the requested details of the in-vitro characterisation assays were not provided and therefore no conclusions on functional similarity between IB1001 and other marketed factor IX products can be made based on these assays. Though the clinical PK data provide evidence that IB1001 is functionally active, in the light of the fact that the applicant is claiming that IB1001 is a new active substance the lack of robust pharmacological characterisation data is still considered a deficiency.

Further, the applicant was asked to provide missing data on thrombin generation potential (i.e. a description of suitability and qualification of the analysis methods for the thrombotic markers). According to the response document it appears that the data are derived from at least three different laboratories using different experimental conditions and references. However, methodological details were not provided. Therefore, the data do not allow drawing any conclusions. Also, the requested integrative discussion on the data on hemostatic activity of IB1001 was not provided. Thus, the pharmacological characterisation data are still considered inconclusive.

In terms of safety pharmacology no separate studies have been performed. Thus, the applicant was asked to justify the omission of any kind of safety pharmacology investigations. The applicant argued that the only undesirable pharmacological activity for this test article and class, i.e. recombinant factor IX, might be related to the thrombogenic potential. Accordingly, studies were designed to evaluate the thrombogenic potential. Other parameters were not chosen as there is obviously no indication of cardiovascular, respiratory or CNS system risks with marketed plasma derived and recombinant Factor IX products. The preclinical and clinical studies performed with IB1001 are considered to support this finding.

In order to investigate the thrombogenic potential the applicant performed four studies. In two of these studies FEIBA was used as positive control. Despite a similar study design and dose levels the positive control gave completely different results in these studies. The applicant was asked to discuss this apparent discrepancy and the possible impact on the interpretation of the data. However, the weaknesses in the analytical methods and uncertainty related to their suitability remained an issue, and therefore the value of this non-clinical data might be considered low.

The pharmacokinetic properties of IB1001 drug substance and lyophilised drug product have been evaluated by single dose intravenous administration to Sprague Dawley rats and haemophilia B dogs. After first assessment two issues were identified which were considered relevant to be addressed by the applicant prior to final conclusion. So, the suitability of the chosen ELISA method for comparative PK analysis and the impact on interpretation of data should be discussed by the applicant. The applicant provided a short description of assay parameters but the validation report was not included. Further, the information provided in the applicant's response is not in line with the information provided in the initial submission (Section 2.6.4 and the respective study reports). Also, in contrast to what the applicant states in the response, the initial submission included a description of usage of

correction for variation and standards but justifications were not provided. In conclusion, the initial uncertainty related to the assay suitability together with the contradictory information provided in the applicant's response make it impossible to draw firm conclusions on the rat and dog PK data.

Furthermore, the applicant was asked to provide a description of the qualification of the ELISA method for detection of anti-IB1001 antibodies in rat plasma and suitability of the assay for comparative analysis of antibodies. However, a validation or qualification report was not provided. The approach to qualify the assay as described is not considered acceptable. Removal of data points from the analysis based on high variability does not qualify the method. The applicant did not clarify whether the assay was qualified for rat plasma or which molecule (IB1001, BeneFIX, or other) was used for qualification. Thus the value of the immunogenicity data is considered questionable and no conclusions can be made.

In general, type and amount of toxicity studies are considered appropriate for marketing authorisation application of IB1001 as recombinant blood coagulation factor IX. Key elements of ICH S6 Guideline have been followed by e.g. selection of rodent and non-rodent species for acute toxicity, following by repeat-dose toxicity in the rodent species, only. As known, the duration of repeat-dose toxicity studies is limited due to the development of antibodies against the foreign protein. Though the dose chosen in the repeat-dose toxicity study was not as high, i.e. only 75 IU/kg, already 3-4 of 15 rats had antibodies after 28-days following applications twice a week (=eight injections). Accordingly, further extended application beyond 28 days will not reveal useful results.

However, within the repeat-dose toxicity study several methodological pitfalls have been identified. So, in the repeat dose toxicity study only one dose level has been tested. The applicant was asked to give a justification for studying one dose level, only, including a rationale for the dose selected. Concerning the chosen (single) dose level (i.e. 75 IU/kg BW) as tested in the Repeat dose toxicity study in rats, the applicant clarified that this dose was selected to approximate the maximum clinical dose and scheduled to be used for prophylaxis. Though this rationale is comprehensive on one hand, this does not explain why no higher doses have been tested. To address this issue, a second 28-day study was conducted where a higher dose, approximately 200 IU/kg, given on a daily basis was tested. In this study IV administration of IB1001 to male Sprague Dawley rats nominally up to 206 IU/kg daily for 28 consecutive days did not result in any indications of systemic toxicity. The results of this new study reveal no safety concerns up to doses 6-10-fold higher in terms of total monthly dose (on a per weight basis) compared to the average hemophilia patient on prophylaxis.

Concerning the omission of recovery groups in the repeat dose toxicity studies, the applicant argued that the lack of any untoward findings obviated the need for recovery groups. This explanation might be considered acceptable in this case as indeed no safety signals have been observed in non-clinical as well as clinical studies which necessitate the inclusion of recovery group animals.

Toxicokinetic data were not provided for the pivotal Repeat-dose toxicity study. The applicant was asked to justify how the safety margins to IB1001 were established, especially in regard to the finding of cardiomyopathy in all test article-treated groups and the possibility that the development of anti-human factor IX antibodies could influence the exposure of the animals to the product. The applicant provided a study report of a new repeat dose toxicity study which however did also not include evaluation of toxicokinetics. Thus, safety margins based on exposure could not be established. The results from this newly performed study are mainly in line with previous data with the exception of occurrence of anti-FIX antibodies. In the new study, anti-FIX antibodies were not detected whereas in the previous rat repeat dose study some of the animals tested positive. It appears that the same assay for detection of anti-FIX antibodies that was previously used in non-clinical studies was also used in this new study. However, due to deficiencies in the analytical methods it is still unclear whether the

animals were adequately exposed in the toxicity study. Therefore, establishment of safety margins based on dosing levels only is considered speculative.

Conclusion on non-clinical aspects

Overall, the data implicate that functional activity and pharmacokinetic properties of IB1001 are similar, both to another recombinant Factor IX product and to the plasma derived Factor IX product. Nonclinical data did not show any clinically relevant treatment related adverse effects. However, the evaluation of non-clinical data is hampered by insufficient, unclear or contradictory information on the analytical methods and their suitability. This deficiency pre-empts final conclusions on pharmacological characterisation, pharmacokinetic behaviour, and risk of thrombogenicity and establishment of safety margins. As a whole the non-clinical data package appears premature and inconclusive. The applicant is asked to provide compelling justification for the appropriateness of the available non-clinical data for the marketing authorisation application of IB1001.

3.4. Clinical aspects

Hemophilia B is an x-linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. Using replacement therapy, the plasma level of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

IB1001 is an intravenous recombinant factor IX produced in Chinese hamster ovary (CHO) cells. It is a 415 amino acid glycoprotein with a molecular weight of approximately 55,000 Daltons. The primary amino acid sequence of IB1001 is comparable to the Thr148 allelic form of plasma-derived factor IX, contains approximately 13% carbohydrate by weight, and has 11 disulfide bonds.

After completion of a PK-phase of the study or, alternatively, a recovery evaluation subjects were included into a treatment phase of prophylaxis or on-demand therapy with safety and efficacy to be evaluated. In addition or independently, subjects were included into a surgical sub-study.

Tabular overview of clinical studies

Tabular Listing of all Clinical studies (ref. 5.2):

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	IB1001-01 PK study	5.3.3.2	define PK and compare with marketed recombinant factor IX	randomized blinded cross-over active controlled	75±5 IU/kg of test drug or comparator , intravenous followed 5-28 days later by 75±5 IU/kg of the other repeat PK in 13 subjects after ≥3 months of treatment to compare with initial PK; IB1001 only 75±5 IU/kg	32 (subset of 13 for repeat PK)	hemophilia B	single dose of IB1001 and comparator; approximately one months	Complete; Full
Efficacy	IB1001-01 surgery substudy	5.3.5.2	Efficacy and safety in the perisurgical setting	single arm	Up to 120 IU/kg IV within 1 hour prior to the start of the procedure, followed by ~ 60 IU/kg 12 hours after the first infusion, and up to 120 I U/kg 24 hours after the first infusion; continue every 12 hours for a minimum of 3 days. If continuous infusion, the plasma level of factor IX should range between 70% and 110%	10 major surgical procedures in 10 subjects	hemophilia B	up to 1 month	Complete; Full
Efficacy	IB1001-01 treatment phase (20 subjects for 50 ED)	5.3.5.2	evaluate the safety and efficacy with respect to breakthrough bleeding during prophylaxis and with respect to control of hemorrhaging in the prophylaxis and on demand groups	single arm	Prophylaxis: intravenous 50-75 IU/kg of IB1001 twice weekly; may be modified as determined by investigator On demand: 50-100 IU/kg of IB1001, as determined by the investigator at the time of bleed; may be repeated as needed	25 (21 prophylaxis; 4 on demand)	hemophilia B	5-20 months	Complete; Full

Participant flow is described graphically in the following figure covering all phases of IB1001-01:

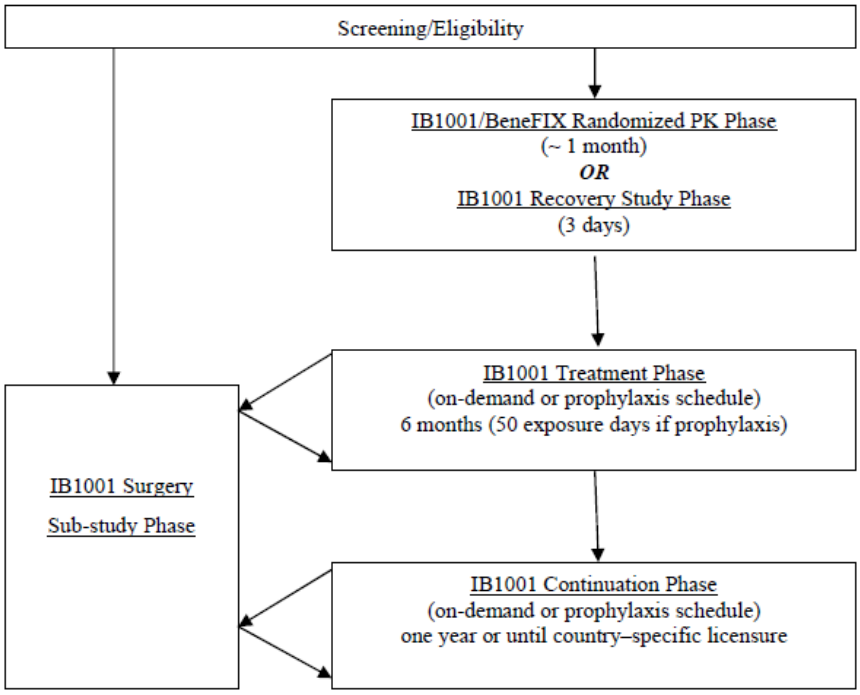

Figure 1: Overview of Study IB1001-01

Pharmacokinetics

Objective of the PK study phase was to evaluate the pharmacokinetics (PK) of IB1001 in subjects with hemophilia B.

Studies have compared the pharmacokinetics (PK) of a recombinant factor IX product, with plasma-derived factor IX and have reported that recovery was approximately 30% lower when using recombinant factor IX than recovery when using a plasma-derived factor IX product[2]. As a result of lower recovery, the dose required to achieve the same effect as plasma-derived factor IX product may be increased.

PK study phase of IB1001-01 was designed as a randomized double-blind cross-over PK study of IB1001, compared with the marketed recombinant factor IX. Non-inferiority of IB1001 over the comparator was concluded for the AUC-ratio.

Factor IX activity in plasma PK samples is performed at the central lab by the one-stage assay. Determined FIX potencies have been found to be higher than the labelled potencies for IB1001 as well as for comparator product. However, results are comparable in an inter-laboratory test.

32 male patients were enrolled in the PK study phase with ages ranging from 15 to 64 years (mean 32 years. All subjects had moderate to severe hemophilia B with factor IX ≤2%.
All 32 patients completed the PK study and were considered evaluable, defined as having at least 80% of the planned time points.

Either a single intravenous 75 ± 5 IU/kg dose of comparator product or a single intravenous 75 ± 5 IU/kg dose of IB1001was administered. A pre-infusion level of factor IX and the presence of inhibitors and non-inhibitory antibodies were assessed. Factor IX levels were determined at the following time points post-infusion: 30 minutes, 1, 3, 6, 9, 12, 24, 36, 48, 60 and 72 hours. Thrombogenicity markers (D-dimer, F1+2, and TAT) were evaluated pre-infusion, at 30 minutes post-infusion, and at 3 and 24 hours post-infusion. After a minimum washout of 5 days and up to a maximum of 28 days after the last assessment (assuming no other treatment with factor IX), a single intravenous 75 ± 5 IU/kg dose of the opposite product was administered, and an identical set of factor IX and thrombogenicity markers was assessed.

C_{max}, $AUC_{0-\infty}$, Clearance, initial and terminal half-life, MRT and V_{dss} were determined from FIX-Serum concentrations.

4 to 18 months after completing the comparator rFIX/IB1001 PK Study, 13 subjects participated in a follow-up PK study with IB1001.

[2] Roth et al: Human recombinant factor IX: safety and efficacy studies in haemophilia B patients previously treated with plasma-derived factor IX concentrates; Blood, 15Dec2001 Vol 98 no 14 pp1665-1671

Results of the determination are presented in the following table:

Table 1: Pharmacokinetic Parameters BeneFIX and IB1001

Parameter	BeneFIX N=32	IB1001 N=32
Alpha-phase half-life (hr)		
mean ± SD	10.4±1.7	9.6±2.7
median	10.2	9.9
range	7.0-14.7	2.8-14.3
Beta-phase (terminal) half-life (hr)		
mean ± SD	33.4±21.2	29.7±18.2
median	27.9	25.8
range	17.5-126.7	13.2-118.4
$AUC_{0-\infty}$ (IU/dL/hr)		
mean ± SD	1723±465	1674±605
median	1680	1601
range	1061-3170	886-3682
AUC_{0-t} (IU/dL/hr)		
mean ± SD	1419 ±340	1401±367
median	1366	1399
range	969-2317	831-2188
Clearance (L)		
mean ± SD	0.05±0.01	0.05±0.02
median	0.04	0.05
range	0.02-0.07	0.02-0.08
Mean residence time (hr)		
mean ± SD	39.7±18.7	35.9±18.5
median	35.3	31.7
range	23.9-114.9	18.4-124.4
Volume of distribution-steady state (mL/kg bodyweight)		
mean ± SD	180±70	160±40
median	170	160
range	90-480	90-290
C_{max} (unadjusted recovery) (IU/dL)		
mean ± SD	72.5±17.0	74.0±17.1
median	70	70
range	46-112	51-113

Drug concentration-decay of both products was similar.

Repeat PK assessments demonstrated no significant reduction in baseline factor IX recovery or elimination half-life.

Due to the known impact of N-glycan sialylation on PK behavior of factor IX that was supported by PK rat studies with IB1001, an exploratory PK analysis of key parameters was performed by dividing the subjects into three subgroups based on the sialylation levels of the drug substance that was used to manufacture the drug product used in the PK study. The presented comparative PK-parameters show a trend towards increased half-life, increased AUC and increased c_{max} with increasing sialylation-level .

The number of represented subjects in each sialylation-dependent subgroup was similar (10-11 subjects) allowing descriptive comparison of the 3 subgroups. However, when comparing the lowest with the highest sialylation-subgroup, e.g. $AUC_{0-\infty}$ increases from a mean of 1206 to a mean of 2122 IU/dl/h. The comparator product-controls similarly show such increasing values – which might substantiate the suggestion of inter-individual variation being the most effective parameter of the

presented findings. However, the variation within the comparator controls (e.g. $AUC_{0-\infty}$ increases from a mean of 1455 to a mean of 1810 IU/dl/h) is much less than in the IB1001 group.

Special populations: Impaired renal function and impaired hepatic function were excluded by the inclusion criteria. Gender was male for all subjects. 30 were of white race, one black, one "other". Subjects with a weight of 51 to 144 kg were included in the PK-study.
Children 12 to 18 years of age have been included into the MAA. IB1001 has not been studied in children below the age of 12 years. Safety in the paediatric population including previously untreated patients (PUPs) will be studied post-authorisation.

Pharmacodynamics

N/A

Discussion on clinical pharmacology

The described PK in general follows the purpose of the clinical guideline. The presented results for PK-parameters and Re-Test PK support the assumption of IB1001 treatment-response being comparable with comparator product and stable over time.

The purpose of the currently valid clinical guideline (Guideline on the clinical investigation recombinant and human plasma-derived factor IX products, 21July2011, EMA/CHMP/BPWP/144552/2009) has been met with the presented study, in general. Overall the study-design has been changed from single to cross-over with the comparator, which is acknowledged. Comparison of IB1001 with comparator was to be demonstrated in a non-inferiority model, which is acceptable. Dose of 75 IU/kg is considered to be high, but is within the maximum margin of the guideline and is compared with the same dose for the comparator.

The study results support the assumption of no clinically meaningful differences between IB1001 and comparator rFIX with respect to pharmacokinetic behavior. Main pharmacokinetic parameters are within expected margins though less favorable than PK parameters derived from pd-FIX-products.

The applicant described their laboratory methods and potency reliability analyses. Determined FIX potencies have been found to be higher than the labelled potencies for IB1001 as well as for the comparator. However, results are comparable in an inter-laboratory test.

Statistical analysis follows current standards and is therefore considered to be acceptable.

Repeat PK study of IB1001 in a subset of 13 subjects who participated in the initial randomized PK demonstrated stability of the PK-results over time.

Impact of sialylation-levels on PK behavior in rats was a trigger for conducting subgroup-PK analysis based on the sialylation levels of the Drug Substance. The presented comparative PK-parameters show a trend towards increased half-life, increased AUC and increased c_{max}.with increasing sialylation-level.

Within **specials populations** the following additional issues have been identified:

The included subjects presented with a weight-range of 51 to 144 kg corresponding with an absolute dose of 3825 to 10800 IU (75 IU/kg). This wide range of applied doses might be source of significant variation of the reproduced PK-results with a tendency to artificially "improve" PK-characteristics.

It has been acknowledged, that clinical studies in the paediatric population have been deferred to the post-authorisation phase as agreed within the adopted PIP-opinion. However, this is in contrast to the currently valid clinical guideline (Guideline on the clinical investigation recombinant and human

plasma-derived factor IX products, 21July2011, EMA/CHMP/BPWP/144552/2009) which requests pre-authorisation evaluation in children. Scientific advice from authorities and the COMP have discussed that lack of paediatric clinical data to be a significant gap in clinical evaluation. Section 4.1 of the SmPC has been adapted, accordingly.

Within the presented PK trial patients from 12 to 18 years of age are included. A stratified PK-evaluation of this paediatric sub-population in comparison with the adult population has been provided.

Regarding details of the planned paediatric studies, further adaptation is encouraged.

Conclusions on clinical pharmacology

In general, the presented data support the assumption of non-inferiority of IB1001 with regard to the authorised comparator. Pharmacokinetic parameters reflect a similar profile as the comparator product but are less favourable than pd-FIX-products, as expected.

Impact of sialylation-levels on PK behavior in rats was a trigger for conducting subgroup-PK analysis based on sialylation levels of the Drug Substance. The presented comparative PK-parameters show a trend towards increased half-life, increased AUC and increased c_{max}.with increasing sialylation-level .

The included subjects presented with a weight-range of 51 to 144 kg corresponding with an absolute dose of 3825 to 10800 IU (75 IU/kg). This wide range of applied doses might be source of significant variation of the reproduced PK-results. Impact has been reflected within the SmPC (section 5.1)

Clinical studies in the paediatric population have been deferred to the post-authorisation phase as agreed within the adopted PIP-opinion. Use of IB1001 in children should therefore not be encouraged before reliable data is available according to the guideline.
Regarding details of the planned paediatric studies, further adaptation is encouraged.

Clinical efficacy

Dose-response studies and main clinical studies

Study design: Patients with moderate or severe forms of the disease (factor IX levels ≤0.02 IU/mL) participated in various study phases. The protocol was designed as a Phase I/II/III enrolling subjects in an initial PK or recovery study (see above) further progressing to a treatment- and continuation-phase. Surgery sub-study was open for subjects on other study-phases or independently.

Participants received IB1001 for treatment or prophylaxis of haemorrhage and were assessed at 3-month intervals for up to 20 months. 25 subjects were treated, including 21 enrolled in prophylaxis, 3 in on-demand and one subject in “targeted prophylaxis” (included in the on-demand group for analytic purposes). Subjects were allowed to switch between prophylaxis and on-demand regimens When this occurred, subjects were evaluated in each group for the time period in which they participated in the relevant treatment.

Subjects with confounding clinical or laboratory evidence regarding hemostatic control such as the presence or an history of an inhibitory antibody to factor IX, antiplatelet therapy or liver disease were excluded from the cohort.

Participants on prophylaxis therapy received an intravenous dose of 50-75 IU/kg IB1001 twice weekly. If clinically indicated, variation of the frequency or the recommended dose was prescribed at the discretion of the investigator. Frequency of breakthrough bleeding was determined, along with other subject-reported diary assessments. Investigator assessments of efficacy were performed at each three month visit.

Five patients who participated in an on-demand schedule during some period of time were prescribed doses of 20 IU/kg, 25 IU/kg, 55 IU/kg, 72 IU/kg and 75 IU/kg for bleeding episodes.

In addition, a surgery sub-study was performed in ten subjects undergoing ten major surgical procedures. Use of either bolus or continuous infusion was permissible; continuous infusion was used in 3 procedures and bolus in 7 surgeries. For bolus infusions, up to 120 IU/kg was to be given within 1 hour prior to the start of the procedure, followed by approximately 60 IU/kg 12 hours after the first infusion, and up to 120 IU/kg 24 hours after the first infusion. This regimen was continued every 12 hours as long as requested by physician and surgeon, but for a minimum of 3 days post-procedure. For continuous infusion, the plasma level of factor IX was targeted between 70% and 110% for a minimum of 3 days post-procedure. Vital signs including pulse, blood pressure, and respiratory rate were routinely monitored at the time of surgery, and post-operatively, with additional monitoring in cases of excessive bleeding.

Perioperative factor IX replacement was by pulse replacement in 7 major procedures and by continuous infusion in 3 procedures.

Efficacy of IB1001 to control bleeding was evaluated using the surgeon's assessment of:
a) estimated blood loss at the time of surgery (less than expected, expected, or more than expected)
b) post-surgery blood loss, defined as haemostasis adequate, haemostasis superior, or haemostasis poorly controlled.

Most subjects participated in more than one study phase. With the exception of 3 subjects who participated in the PK study phase, only, and 4 who participated in the surgery sub-study, only, the other subjects continued on to the treatment study phase receiving IB1001 in either on-demand or prophylactic regimen.

The sample of study subjects in all study phases varied in age from 10 to 64 years (one subject in the USA <12 years), with all but one subject being male, showing a historical factor IX level ≤0.02 IU/mL and/or a clinical history of frequent bleeds consistent with severe disease. The exception was a female with mild hemophilia B who required a hysterectomy and for whom the investigator considered surgical support with factor IX concentrate a necessity. He requested from the Sponsor and was granted a waiver to allow him to use IB1001 to support this subject's surgery.

With one exception in the surgery sub-study who had <150 prior exposure days, subjects included adolescents and adults with at least 150 prior exposures to factor IX products and who were immune-competent (CD4 > 200/µL).

Endpoints: Overall, Clinical efficacy of IB1001 to treat and prevent bleeding in patients with hemophilia B was assessed in several ways:

• Recovery and AUC were used in the pharmacokinetic study as surrogates to predict the efficacy of IB1001 in comparison to the marketed recombinant factor IX. This was the only randomized, blinded, controlled study phase.
• Annualized bleeding rates were calculated for subjects using on-demand and prophylaxis treatment regimens.
• Response per infusion for bleeding episodes was assessed subjectively by patients and reported according to a four-point scale ("excellent", "good", "fair", and "poor"). Subjects also assessed the time for pain, swelling and bleeding to stop.
• Efficacy for each participant was assessed subjectively by investigators at each three month visit and reported according to a three-point scale ("effective", "partially effective", "not effective") covering the documented subjective assessments of concerned patients. A rating of not applicable was intended to be used for any interval in which no bleeds occurred, but was instead used to indicate an interval that

was not rated. Instead, if no bleeding occurred, investigators typically rated the interval as 'effective' control, in line with the conventions with which they were familiar.
• In the surgical setting, efficacy parameters included estimated total blood loss during the procedure and adequacy of hemostasis following the procedure as assessed by the surgeon; transfusion requirements were also documented.
• Consumption of factor IX was calculated to detect any trends in usage change over time.

Statistical methods: Descriptive statistical analyses were planned with regard to efficacy and safety; parameters were described by means of statistical characteristics (count data: absolute and relative frequencies; continuous data: mean, SD, median, range).

Results: Annual bleed rate: 17 of 24 subjects who were on prophylaxis regimens and all subjects who were on on-demand regimens for all or part of their treatment reported bleeding episodes. The median number of bleeding episodes for individuals on prophylaxis was 2, compared with a median of 8 for subjects on on-demand regimen. However there were three subjects with several bleeding episodes resulting in annualized bleed rates of >6 during prophylaxis:

- One subject had switched from on-demand to prophylaxis regimens, resulting in a reduction in his annual bleeding rate from 42.3 to 7.0; after switching to prophylaxis, he was relatively non-compliant with the twice weekly regimen

- One subject was on a once weekly infusion schedule

- One subject was non-compliant with the twice weekly regimen and experienced several bleeding episodes that resulted from trauma.

11 of 24 subjects on prophylaxis experienced ABR above 3 with individual justifications for bleeding.

7 of 24 subjects did not experience breakthrough bleeding while on prophylaxis. The other 17 subjects had a total of 89 bleeding episodes.

5 subjects experienced a total of 42 bleeding episodes while using an on-demand schedule (30 spontaneous, 9 traumatic, 3 unknown).

Subject assessment of efficacy: Of 84 total bleeding episodes (on-demand or prophylaxis) recorded in the subject bleeding diary logs that were spontaneous or of unknown cause, 67 occurred ≥3 days after the prior dose of IB1001. Most bleeding episodes (n=92; 70%) were controlled with only one dose of IB1001.

8 bleeding episodes required ≥5 doses of IB1001.

Of the bleeding episodes where IB1001 efficacy was rated by study subjects, the efficacy was considered to be good or excellent 87% of the time. However there were 5 instances where efficacy was rated fair and two instances where efficacy was rated poor with individual justifications.

For the surgery sub-study all efficacy-related assessments were judged by the surgeon. For all surgical procedures, the estimated blood loss was as expected (n=5) or less than expected (n=5); this is supported by the lack of requirement for transfusions during any of the procedures. At 12 and 24 hours post-surgery, hemostasis was assessed as superior (n=1) or adequate (n=9) for the surgical sites in all subjects.

Drug Dose and relationship to response: Assigned prophylaxis regimens for the patients included here can be divided roughly into the following three ranges

- <30 IU/kg; 3 subjects
- 47-60 IU/kg; 16 subjects
- 60-75 IU/kg; 5 subjects

The average dose for prophylaxis was 53.5 IU of factor IX per kg of body weight (median 50 IU/kg, range 24 to 75 IU/kg) at intervals of 3 to 4 days.

There were three exceptions to the twice weekly frequency recommended for prophylaxis dosing, including two subjects who started on once weekly regimens and one subject who started on a 3x weekly regimen.

Occasional doses above 75 IU/kg were recorded for treatment of specific bleeding episodes, include up to 83 IU/kg for elbow trauma (60-001), up to 91 IU/kg for a muscle bleed (60- 002) and up to 105 IU/kg for a trauma that resulted in minor surgery (60-003).

4 subjects were switched to prophylaxis regimens after unacceptable bleeding rates using on-demand (n=3) or targeted prophylaxis (n=1), in all cases to help reduce the number of bleeding episodes.

2 out of 25 subjects on prophylaxis were reported to require an increased frequency or/and dose due to bleeding or unsatisfactory response.

There are insufficient data to draw any conclusions about the lowest dose range, since only two subjects in the range have been on prophylaxis for at least 6 months.

The protocol-recommended dose for a bleeding episode for patients using on-demand treatment ranges from 50-100 IU/kg. 5 subjects who participated in an on-demand schedule were prescribed doses between 20-75 IU/kg (20, 25, 55, 72 and 75 IU/kg).

In the surgery sub-study continuous infusion was used in 3 procedures and bolus in 7 surgeries. For bolus infusions, an infusion of up to 120 IU/kg was to be given within 1 hour prior to the start of the procedure, followed by an infusion of approximately 60 IU/kg 12 hours after the first infusion, and up to 120 IU/kg 24 hours after the first infusion. This regimen of bolus infusions was continued every 12 hours as long as the physician and surgeon deemed necessary, but for a minimum of 3 days post-procedure. For continuous infusion, the plasma level of factor IX was targeted between 70% and 110% for a minimum of 3 days post-procedure.

Consumption of IB1001 stayed relatively constant over the course of the observation period as demonstrated by the total monthly consumption or average dose of subjects under observation.

Numbers have been updated from the ongoing extension study and included into the SmPC.

Summary of efficacy for trial IB-1001-01

Title: : A randomized study to evaluate the efficacy and safety of Inspiration's Recombinant Factor IX Product, IB1001, in Subjects with Hemophilia B			
Study identifier	IB1001-01		
Design	PK study: Randomized, blinded, cross-over Treatment Phase: non-randomized, parallel design Surgery sub-study: non-randomized, open-label design		
	Duration of main phase:	72 hours	
	Duration of Run-in phase:	5-28 days	
	Duration of Extension phase:	6 months	
Hypothesis	PK study: Non-inferiority of IB1011 compared to Benefix		
Treatment groups	PK study: IB1001: 15; Benefix: 17		
	Treatment phase: 25		
	Surgery sub-study: 10		
Objectives and definitions	PK study	PK characterisation AUC0-∞ ratio	Area under the serum concentration time curve from time 0 to infinity
	Treatment phase	Control of haemorrhages Annualized bleeding rate	annualized bleeding rate = (# of bleeding episodes x 12) / (# months of observation)
	Surgery sub-study	Coverage of bleeding under surgical circumstances	
Database lock:	Treatment phase: 26/10/2010 Surgery substudy: 20/05/2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	**PK Populations:** All subjects who receive both doses during these PK studies and who provide at least 80% of the follow-up factor IX levels. These will be separate PK populations, but will include the same study subjects (n=32). **Intent-to-Treat (ITT) population:** All subjects who enroll in the Treatment Phase of the trial and who provide any post-screening data (n=21 for the prophylaxis and n=4 for the on-demand phase).			
Descriptive statistics and estimate variability	Treatment group (PK study)	IB1001	Benefix	
	Number of subject	15	17	
	AUC0-∞ ratio	1601	1680	
	1-sided 95% CI			
	Treatment group (Treatment phase)	IB1001 (prophylaxis)	IB1001 (on-demand)	
	Number of subject	21	4	
	Annualized bleeding rate mean	1.41	3.54	
	95% CI	(0.92-1.90)	(1.32, 5.76)	

Clinical studies in special populations

N/A

Analysis performed across trials (pooled analyses AND meta-analysis)

N/A: one single trial IB1001/01

Supportive study(ies)

N/A

Discussion on clinical efficacy

Design and conduct of clinical studies

After completion of the PK-phase of the study or, alternatively, a recovery evaluation subjects were included into a treatment phase of prophylaxis or on-demand therapy. In addition or independently, subjects were included into a surgical sub-study.

In total, 42 subjects were included in this submission. 32 subjects in the PK study, 25 (4 on-demand, 21 prophylaxis) in the treatment study-phase and 10 subjects in the surgery sub-study.

Inclusion and Exclusion criteria follow currently accepted *state of the art* for Coagulation Factor replacement.

Mode of treatment (treatment prevention, “prophylaxis” and treatment based upon occurrence of bleeding “on-demand”) reflects the current state of FIX-replacement-therapy in haemophilia and follows the currently valid clinical guideline. Numbers of subjects have been updated from the ongoing extension study.

The surgical procedures were, with few exceptions, typical orthopedic procedures that are required by many severe hemophilia patients as a result of the arthropathies resulting from years of bleeding episodes, especially into target joints. Perioperative factor IX replacement was by pulse replacement in 7 major procedures and by continuous infusion in 3 procedures.

The primary efficacy variables were control of breakthrough bleeding during prophylaxis and control of bleeding episodes in either the prophylaxis or on-demand treatment regimens. The specific objective of the surgery sub-study was to evaluate the ability of IB1001 in providing coverage against bleeding under surgical circumstances. The objectives follow the requirements of the currently valid clinical guideline.

Overall, clinical efficacy of IB1001 to treat and prevent bleeding in patients with hemophilia B was assessed in several ways:

• Recovery and AUC were used in the pharmacokinetic study as surrogates to predict the efficacy of IB1001 in comparison to the marketed recombinant factor IX.
• Annualized bleeding rates were documented
• Response per infusion for bleeding episodes was assessed subjectively by patients and reported according to a four-point scale (“excellent”, “good”, “fair”, and “poor”). Subjects also assessed the time for pain, swelling and bleeding to stop
• Efficacy for each participant was assessed subjectively by investigators at each three month visit and reported according to a three-point scale (“effective”, “partially effective”, “not effective”)
• In the surgical setting, efficacy parameters included estimated total blood loss, adequacy of hemostasis and transfusion requirements

• Consumption of factor IX was calculated

In general, the objectives of the clinical guideline regarding clinical efficacy documentation have been followed.

The background criteria for including subjects into the presented studies are in general accepted. The issue of inhomogeneity has been discussed within the PK-section. Severity of haemophilia is one crucial issue when describing safety and efficacy of Factor IX products. Inclusion of other than true severe (residual FIX-activity <1%) haemophiliacs requires justification which has been provided.

Efficacy data and additional analyses

Main efficacy results are presented above. The presented results are plausible and support the assumption of effective prophylaxis as well as on-demand treatment and protection during surgery.

Dosage within this efficacy study has been subject to Scientific Advice, and requires further discussion:

The prophylaxis-dosage of 50-75 IU/kg twice weekly does not follow the recommendation of the Core SPC (20-40 IU at intervals of 3-4 days). When comparing with the marketed rFIX, the average prophylaxis-dose has been reported to be 40.3 versus 53,5 IU/kg (IB1001).

The protocol-recommended dose for a bleeding episode for patients using on-demand treatment ranges from 50-100 IU/kg. This is – similar to the prophylaxis regimen – above the recommendations of the Core SPC, where *60-100 IU/kg are advised for life-threatening haemorrhages*, only. *More extensive hemarthrosis, muscle bleeding or haematoma* are recommended with *30-60* and *early hemarthrosis, muscle bleeding or oral bleeding with 20-40 IU/kg*. Further critical analysis of the dosage within the study should be reflected within the SmPC (sections 4.2 and 5.1).

In the surgery sub-study for bolus infusions, a dose of up to 120 IU/kg was to be given within 1 hour prior to the start of the procedure, followed by an infusion of approximately 60 IU/kg 12 hours after the first infusion, and up to 120 IU/kg 24 hours after the first infusion. This regimen of bolus infusions was continued every 12 hours as long as the physician and surgeon deemed necessary, but for a minimum of 3 days post-procedure. For continuous infusion, the plasma level of factor IX was targeted between 70% and 110% for a minimum of 3 days post-procedure.

Dosage within the surgery setting of the study deviates from the recommendations of the Core SPC, where 8*0-100 IU/kg* are advised *pre- and post-operatively for Major surgery* to be *repeated every 8-24 hours (…)*. Dosage should be reflected within the SmPC, adequately.

Result of this further discussion is recommended to be taken into account when designing regimens in the paediatric age-groups (refer to Paediatric Population, Pharmacokinetics): more rapid clearance, shorter half-life and consequently the need for higher and more frequent dosage in prophylaxis should be assumed with decreasing subject's age.

Conclusions on clinical efficacy

In general, clinical efficacy of IB1001 of treatment and prophylaxis of bleeding episodes in Haemophilila B patients has been documented through the adequately designed phases of clinical evaluation.

Main uncertainty has been distilled to be dosage and dose-interval for on-demand treatment as well as for prophylaxis and surgical intervention and should be reflected in the SmPC.

Clinical safety

IB1001 is a purified recombinant form of the human coagulation factor IX protein produced in Chinese Hamster Ovary (CHO) cells. It is a 415 amino acid, single chain glycoprotein with a molecular weight of approximately 55,000. The primary amino acid sequence of IB100l is comparable to the Thr148 allelic form of plasma-derived factor IX.

Safety aspects of factor IX products include viral safety, immunogenicity and other adverse events (AEs). The safety of IB1001 with regard to viral contamination is reasonably assured by the application of virus testing within the manufacturing process and assessment of virus inactivation and removal during the manufacturing process. Similar principles apply for all transmissible agents including TSE and other emerging pathogens.

Patient exposure

32 subjects were enrolled in the comparator rFIX/IB1001 PK study. All subjects were randomized and completed both study periods. For the PK study phase, all subjects received the same exposure to IB1001 and comparator on a per kg basis (75 IU/kg each IB1001 and comparator). Body weights recorded during the PK study phase range from 51-145 kg, thus the total PK dose ranged from approximately 3825-10875 IU per subject.

At study entry 25 subjects were basis of the safety and efficacy analyses of IB1001 treatment in this report. All subjects are ongoing at the time of data cut-off, with one exception, a subject who was lost to follow up. The total number of exposure days documented for all 25 subjects in the treatment phase as of the data cut-off date for this phase is 2199.

A total of 10 major procedures in 10 subjects were documented in the surgery sub-study. 4 of 10 subjects were enrolled in the surgery sub-study only, 4 subjects were already participating in the study and 2 subjects entered the treatment phase after the surgical procedure. The 10 subjects received an average of 740.7 IU/kg (range 482 IU/kg to 1320 IU/kg) over a period of 3-10 days. Total number of infusions ranged from 7-19. The average dose used for the three subjects on continuous infusion was 43-96 IU/kg/12 hr for a period of 72-140 hours following the initial pre-surgery dose.

Numbers of subjects have been updated from the ongoing extension study.

Adverse events

Eight adverse events were reported in each group in the PK phase and included mild-moderate reports of back pain, headache, diarrhea, vomiting, fever, and viral gastroenteritis.

With the exception of two reports of headache, none were considered to be related to study drug. The frequency of subjects experiencing adverse events during the IB1001 and comparator PK study periods was similar.

There were no life-threatening AEs reported during this study phase. The only event reported in either PK study period as severe (ref. AE-listing 16.2.7) was an episode of hemarthrosis in the ankle associated with the comparator.

Within the treatment-phase, there were 120 events reported in 15 subjects during prophylaxis and 11 events reported in 3 subjects during on-demand schedule.

Most reported AEs were mild or moderate in severity covering unspecific symptoms. Exceptions were several events in three subjects, including (i) severe pain due to kidney stones (preexisting condition),

(ii) severe pain associated with a device (prosthesis) dislocation and (iii) severe knee pain in a subject who needed minor surgery to remove a stone embedded in his knee as a result of a fall.

In the surgery sub-study, 38 AEs in 4 out of 10 subjects were documented. Adverse events included pain, swelling, fever, nausea, and some bleeding or oozing at the surgical site. No transfusions were required in any subjects and no significant perioperative hemorrhages or other significant adverse events were reported.

Serious adverse events and deaths

No deaths occurred.

Two serious adverse events (SAEs) have been reported to date for all phases/subjects, both due to hospitalization and considered unrelated to IB1001. The first SAE included hospitalization that resulted from a motorcycle accident in which the subject was involved. The second SAE was for abdominal pain, later diagnosed as diverticulitis.

Laboratory findings

In the PK phase of Study IB1001-01, laboratory parameters monitored included thrombogenicity-markers [prothrombin fragment 1+2 (F1+2), d-dimer and thrombin-antithrombin complex (TAT)], high sensitivity C-reactive protein (hsCRP), and factor IX. There was significant variability in the results of the thromobogenic marker assays, however there were no cases of or a pattern indicative of clinically relevant thrombogenicity in subjects treated with both IB1001 or comparator rFIX, and none were associated with AEs.

In the treatment study phase, laboratory parameters for blood chemistry, hematology, and urinalysis have been observed over the course of study participation for all subjects. There were no clinically meaningful trends in individual lab values over time.

Antigenicity has been assessed throughout the study. As of the cut-off date of the last study report (Surgery Study Report, May 2011), no inhibitors have been detected in any of the subjects. Additionally, there have been no reports of anaphylaxis or other serious allergic type reaction, nor has nephrosis been documented in any treated patient.

Vital signs (respiration rate, pulse, blood pressure and temperature) were measured in each phase of the study. In general, abnormal vital sign values were consistent with pre-infusion values, not considered clinically significant and therefore unremarkable.

Safety in special populations

N/A

Immunological events

Long-term safety

The clinical safety and efficacy study is ongoing. Patients will continue to be enrolled and followed with the goal of treating at least 50 subjects for 50 exposure days to further evaluate inhibitor development. In addition subjects are encouraged to progress to the continuation study after 50 ED so that a total of 100 ED for 50 subjects can be obtained. These data, together with any additional data from the continuation phase of the recently initiated pediatric study (IB1001-02) are intended to provide long term safety data.

Additional Major Objection regarding CHO-antibodies

Late breaking information has been submitted in a clinical hold letter of the FDA regarding both IB1001 studies. In Europe, urgent safety restriction was circulated, but only 1 subject seems to be on IB1001 in clinical studies, currently.
Information on current status (e.g. number of included patients, sites, still active?) of study IB1001-02 in paediatric subjects should be submitted together with updated overall numbers of subjects in IB1001-01, and, separately, in Europe.

Of concern is a non-anticipated rise in CHO-antibodies observed overtime in clinical trials in 26%of patients on IB1001. Escalating titers occurring in approximately half of anti-CHO positive subjects with relevant rise and no subject returning to negative are further sensitizing findings. The accelerating dynamics, percentage and non-transient character of the antibodies differ significantly from the known and published phenomenon of anti-host-cell antibodies with other recombinant anti-hemophilic medicinal products.

The Applicant identified two potential sources of the findings: Change of soy supplier and changes of final DP formulation, filling and lyophilization. However, identity of the proteins responsible for inducing the anti-CHOP-antibodies, has not been identified, yet.

Furthermore, details of the assay-description suggest that the actual HCP assay used for batch release is not able to detect all HCPs that may end up into the product. It also raises a question about the production process and how well it is able to remove impurities. Further, the sensitivity of the anti-HCP-antibody assay to detect antibodies in patient sera may be questioned, as the antigen used in the assay does not represent all putative CHO-proteins.

The Applicant has started improvement of the ELISA technique and introduction of an additional CHOP-removing chromatography step.

Adaptations of the Risk-management plan and SmPC adaptations have been suggested. Those should be postponed until the above mentioned changes have been finalized. Wording suggestions, however, require adaptation.

Furthermore, the planned post-marketing extension phase of the clinical study according to the clinical guideline is assumed to be challenging as all subjects on the study switched to other products. The Applicant is asked to comment.

Up to date no clinical signs have been identified indicating adverse effects of the immunological response (positive anti-CHOP-titres). However, it is unknown how CHOP-antibodies further develop, if there is cross-reactivity with other proteins or if they return to normal after withdrawal from IB1001.

Taking these issues together, an **additional clinical Major Objection** has to be raised. Until manufacturing and testing issues are not solved, convincingly, **authorization of IB1001 should not be recommended**. From a clinical point of view, it will be relevant for the future, if the proposed chromatography step will potentially affect efficacy and safety of the final medicinal product in comparison with the product used in the initial clinical trials until now.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to AES

None

Post marketing experience

N/A

Discussion on clinical safety

Rationale, background and conduct of the safety evaluation within the clinical trial on IB1001 follow the currently valid clinical guideline.

Patient exposition in general follows the suggestions of the study protocol supplemented by individual patient's and investigator's decisions. Within the PK study, large inter-individual differences of dosages (3825-10875 IU per subject) have been identified. Analysis and discussion has been requested within the PK part of this AR. Within the treatment and surgery phases, dosages are in an unexpected high range, which has also been discussed within the efficacy part of this AR.

Adverse Event reports are in general considered to be within the expected range of the anticipated safety-profile of FIX-products.
Frequency of headache-episodes within all study-phases might be noticeable. Together with the reported subject who lowered his prophylaxis dose for headaches, the issue should be evaluated further (see LoOI).

Serious Adverse Events did not generate a safety signal.

Thrombogenicity markers – as documented for the PK-phase – are considered to be of high individual safety-related value when assuming thrombogenicity to be a significant adverse effect of FIX-administration. Thorough analysis and interpretation of the results has been exercised. However, further effort for documentation of such markers with respect to clinical relevance is encouraged.

Regarding laboratory parameters for blood chemistry, hematology, urinalysis, and antigenicity (inhibitor-development) the applicant presented anticipated results.

The applicant's projected study-conduct is considered to be in compliance with the clinical guideline. As discussed above, the evaluation of paediatric subjects has been postponed to the post-marketing phase in agreement with the PDCO. Long-term safety will be subject to further follow up of the product in the post-marketing phase. The low incidence of Hemophilia B and subsequently the low numbers of subjects followed in clinical-trials require close and continuing safety-reporting

Late breaking information has been submitted regarding non-anticipated rise in CHO-antibodies observed overtime in clinical trials in 26%of patients on IB1001. Escalating titers occurring in approximately half of anti-CHO positive subjects with relevant rise and no subject returning to negative are further sensitizing findings. The accelerating dynamics, percentage and non-transient character of the antibodies differ significantly from the known and published phenomenon of anti-host-cell antibodies with other recombinant anti-hemophilic medicinal products.

Fundamental gaps regarding HCP detection have been identified.

The Applicant identified two potential sources of the findings: Change of soy supplier and changes of final DP formulation, filling and lyophilization. However, identity of the proteins responsible for inducing the anti-CHOP-antibodies, has not been identified, yet.

The Applicant has started improvement of the ELISA technique and introduction of an additional CHOP-removing chromatography step.

Impact on the extension phase and the paediatric study remains open.

Up to date no clinical signs have been identified indicating adverse effects of the immunological response (positive anti-CHOP-titres). However, it is unknown how CHOP-antibodies further develop, if there is cross-reactivity with other proteins or if they return to normal after withdrawal from IB1001.

Until manufacturing and testing issues are not solved, convincingly, **authorization of IB1001 should not be recommended**. It will be relevant for the future, if the introduced chromatography step will potentially affect efficacy and safety of the final medicinal product in comparison with the product used in the initial clinical trials until now.

Conclusions on clinical safety

Clinical safety has been analysed from the data of all clinical trial phases. Evaluation in general follows the currently valid clinical guideline. The presented results are considered to be acceptable. With regard to the limitations of the data-base due to the rareness of the underlying disease, further data is expected from the postmarketing-phase and yet planned clinical trials.

Late breaking information on non-anticipated rise in CHO-antibodies and fundamental gaps regarding HCP detection have been identified and raised an additional major objection.

Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A qualified person and a back-up qualified person for pharmacovigilance were named, contact data curriculum vitae and job descriptions are presented.

An organisation chart with units and teams and their responsibilities and internal and external activities are described in detail. Necessary facilities for the handling of any adverse events and adverse reactions are described. Flow charts to explain sequences of reporting procedures are included which give a sufficient overview over the handling of adverse events and adverse reactions. In general, the description of the pharmacovigilance system is considered appropriate, however, prior to marketing authorisation the open issues as listed in section 6 should be addressed.

Risk management plan

Identified risks:

There are no identified risks for IB1001 that are derived from clinical evidence with the product besides the newly identified clinical major objection.

Potential risk:

Immunogenicity, lack of efficacy, thrombogenicity, hypersensitivity (including anaphylaxis), and nephrotic syndrome.

Important missing information and planned action:

Important missing information	Planned action
Pregnant and lactating women	Routine Pharmacovigilance;
Elderly patients (>65 years old)	Routine Pharmacovigilance;

Patients with hepatic insufficiency	Routine Pharmacovigilance;
Patients with renal insufficiency	Routine Pharmacovigilance;
Children < 12 years old, previously treated patients (PTPs)	Routine Pharmacovigilance Clinical study IB1001-02 - Phase III/IV Paediatric Study in Paediatric Subjects with Haemophilia B Previously Treated with Factor IX products
Children previously untreated (PUPs), IB1001	Routine Pharmacovigilance Clinical study IB1001-03 - Phase III/IV Paediatric Study in Children with Haemophilia B Previously Untreated with Factor IX Products (PUPs)

Summary table of safety concerns and planned pharmacovigilance actions

Important potential risks	Planned action
Immunogenicity	Routine Pharmacovigilance; Long-term safety study IB1001-01 Continuation Phase; Clinical studies IB1001-02 and -03
Lack of efficacy	Routine Pharmacovigilance; Long-term safety study IB1001-01 Continuation Phase Clinical studies IB1001-02 and -03
Thrombogenicity	Routine Pharmacovigilance; Long-term safety study IB1001-01 Continuation Phase Clinical study IB1001-02
Hypersensitivity (incl. anaphylaxis)	Routine Pharmacovigilance; Long-term safety study IB1001-01 Continuation Phase; Clinical studies IB1001-02 and -03
Nephrotic syndrome	Routine Pharmacovigilance

Summary of outstanding actions, including milestones

Actions	Milestones/ exposure		
IB1001-01 Continuation Phase	55 prophylaxis subjects 20 on Demand subjects		
IB1001-02 Paediatric PTP Study (≤12 years)	20 subjects (10 < 6 years) and 10 (between 6 and 12 years)		
IB1001-03 Paediatric PUP Study (<6 years)	40 subjects (new born to < 6 years)		

Summary of planned minimisation actions

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide description of routine activity and justification
Important potential risks		
Immunogenicity	Yes	**SmPC: Section 4.4** Immunogenicity is a safety concern for all factor replacement products. Inhibitor development is one of the most significant safety concerns andmay be associated with anaphylaxis or immune mediated nephrotic syndrome in haemophilia B patients. There is a special warning in the SmPC on the correlation between the occurrence of a factor IX inhibitor and allergic reaction. Furthermore, it is recommended that the initial administration of factor IX in PUPs should be performed under medical observation.
Lack of Efficacy	Yes	**SmPC: Sections 4.2, 4.4 and 4.8:** Lack of efficacy may be caused by neutralising antibody development or by non-compliance with posology recommendations. Routine analysis and trending of spontaneous adverse events reported related to loss of effect and immunogenicity is sufficient to assess the frequency of occurrences with IB1001. Furthermore, the SmPC contains a precaution for providers and patients to draw attention to the potential for this adverse event.
Thrombogenicity	Yes	**SmPC: Sections 4.4 and 4.8:** Since the use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications, the risk being higher in low purity preparations, the use of factor IX-containing products may be potentially hazardous in patients with signs of fibrinolysis and in patients with DIC. Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic phenomena or DIC. In each of these situations, the benefit of treatment with IB1001 should be weighed against the risk of these complications. While there have been no reports of thrombotic events with IB1001, there is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity factor IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX is rarely associated with such side effects.
Hypersensitivity (including anaphylaxis)	Yes	**SmPC: Sections 4.3, 4.4 and 4.8:** Hypersensitivity to the active substance or to any of the excipients, or known allergic reaction to hamster proteins are contraindications in the SmPC Section 4.3. As with any intravenous protein product, anaphylaxis and hypersensitivity reactions are possible. This product may contain traces of hamster proteins. Patients should be informed of early signs of hypersensitivity reactions including difficult breathing, shortness of breath, swelling, hives, general urticaria, tightness of the chest, bronchospasm, laryngospasm, wheezing, hypotension, blurred vision, and anaphylaxis. If these symptoms occur, patients should be advised to discontinue use of the product immediately and contact their physician Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been

		observed infrequently in patients treated with factor IX-containing products. In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors (see section 4.4 SmPC). If allergic/anaphylactic reactions occur, the administration of IB1001 should be discontinued at once. In case of severe allergic reactions, alternative haemostatic measures should be considered. The treatment required depends on the nature and severity of side-effects. Patients known to have major deletion mutations of the factor IX gene should be observed closely for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of initial exposure to product. Furthermore, routine analysis and trending of spontaneous adverse events reported related to more severe allergic reactions (e.g. anaphylaxis) is sufficient to assess the frequency of occurrences with IB1001 due to the expected rarity of the event based upon post-market experience with a commercialised recombinant FIX.
Nephrotic Syndrome	Yes	**SmPC: Section 4.8:** Nephrotic syndrome is a rare adverse event observed with a commercialised FIX product in correlation with susceptibility to allergic reactions and antibody development. Routine analysis and trending of spontaneous adverse events reported related to renal impairment is sufficient to assess the frequency of occurrences with IB1001 due to the expected rarity of the event based upon post-market experience with a commercialised recombinant FIX. Furthermore, the SmPC contains a precaution for providers and patients to draw attention to the potential for this adverse event.
Important missing information		
Pregnant/ Lactating Women	Yes	**SmPC: Section 4.6:** Haemophilia B is an X-linked condition and occurs very rarely in women. The SmPC contains a warning against use in pregnant or lactating women unless clinically warranted. Routine analysis and trending of spontaneous adverse events reported related to use during pregnancy or lactation is sufficient due to the expected rarity of the event based upon post-market experience with a commercialised recombinant FIX.
Elderly patients	Yes	**SmPC: Section 4.4:** Haemophilia B is a rare condition that presents in early childhood in which lifelong prophylaxis of FIX therapy is administered. Moreover, comorbidities in elderly patients severely challenge the robust analysis of FIX safety in clinical trials. Therefore, the SmPC contains a precaution indicating that data in these patients are not available and routine analysis and trending of spontaneous adverse events is sufficient to capture safety information in this population.
Patients with hepatic insufficiency	Yes	**SmPC: Section 4.4:** Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease.
Patients with renal insufficiency	Yes	**SmPC: Section 4.8:** Although no renal events were observed with IB1001, nephrotic syndrome has been reported and is especially an issue following high doses of factor IX to induce immune tolerance in haemophilia B patients with factor IX inhibitors and a history of allergic reactions.
Children $\leq$ 12 years (PTP)	Yes	**SmPC: Section 4.2:** Paediatric patients were not studied in IB1001 clinical trials. However, two paediatric studies are planned according to the agreed Paediatric Investigational Plan (PIP).
Children (PUP)	Yes	**SmPC: Section 4.2:** The safety and efficacy of IB1001 in children aged less than 12 years and in previously untreated patients (PUPs) have not yet been established.

Overall the presented RMP gives a sufficient overview over the potential risks and the important missing information. The proposed planned actions as well as the warnings in the SmPC seem to be an adequate action in order to reduce the risks.

However, prior to marketing authorisation the open issues as listed in section 6 should be addressed.

4. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

IB 1001 is a newly developed recombinant Factor IX for treatment and prophylaxis of haemorrhage in Haemophilia B patients. Overall, efficacy has been established within a 3-phase clinical trial comprising pharmacokinetic analysis, a treatment phase covering on-demand and prophylaxis schedules, and a surgery sub-study reflecting major surgical procedures to be covered by Factor-IX replacement. IB1001 is designed similar to the authorised rFIX product and aims at identical target population.

Uncertainty in the knowledge about the beneficial effects

Impact of sialylation level of IB1001 on PK-parameters has been demonstrated. However, characterisation of the commercial product corresponds with the data as collected within the PK-trial within acceptable ranges.

Within the pharmacokinetic evaluation an “artificial” inhomogeneity has been created by extensive dose-range (3825 to 10800 IU) due to a wide weight-distribution of the subjects. Further data-analysis allows reflection of a more homogenous sample within the SmPC, in addition.

Data on paediatric population <12 years of age is lacking. In the light of this population being highly vulnerable but main target of replacement therapy, this significant gap covers a high level of uncertainty and will therefore be reflected in section 4.1 of the SmPC.

Dosage has been identified to be significantly above the recommendations of the Core-SmPC. On-demand-treatment, prophylaxis and surgery (bolus infusion and continuous infusion) are concerned, similarly. This issue requires further SPC adaption.

Risks

Unfavourable effects

Late breaking information has been submitted regarding non-anticipated rise in CHO-antibodies observed overtime in clinical trials in 26% () of patients on IB1001. Escalating titers occurring in approximately half of anti-CHO positive subjects with relevant rise and no subject returning to negative are further sensitizing findings. The accelerating dynamics, percentage and non-transient character of the antibodies differ significantly from the known and published phenomenon of anti-host-cell antibodies with other recombinant anti-hemophilic medicinal products.

Uncertainty in the knowledge about the unfavourable effects

Up to date no clinical signs have been identified indicating adverse effects of the immunological response (positive anti-CHOP-titres). However, it is unknown how CHOP-antibodies further develop, if there is cross-reactivity with other proteins and if they return to normal after withdrawal from IB1001.

Fundamental gaps regarding HCP detection have been identified.

Balance

Importance of favourable and unfavourable effects

In general, efficacy has been established by the provided clinical evaluation. The late-breaking information regarding anti-CHOP-antibodies, however, is considered to be of high impact. It will be relevant for the future, if changes to the manufacturing process will potentially affect efficacy and safety of the final medicinal product in comparison with the product used in the initial clinical trials until now.

Benefit-risk balance

Based upon the currently available data the Benefit-risk balance for IXinity / IB1001 is considered to be negative.

Discussion on the benefit-risk assessment

In general, efficacy of IB1001 in prevention and treatment of bleeding episodes in Haemophilia B is not doubted. However, the late-breaking objection regarding anti-CHOP antibodies together with corresponding shortages of the respective assays suggest the medicinal product to be subject of further improvement. Until major issues have been solved, benefit-risk is considered to be negative.

4.1. Conclusions

The Benefit/Risk ratio of IB1001 is negative, based upon newly available data on quality and clinical aspects. Major objections have been identified with respect to insufficient CHO protein removal and control during the manufacturing process and an unexpected rise of anti-CHOP antibodies in currently 26% of treated subjects.