

**Public Assessment Report**  
**for paediatric studies submitted in accordance**  
**with Article 45 of Regulation (EC) No1901/2006, as**  
**amended**

**Coagulation factor IX**

**CZ/W/0012/pdWS/001**

<b>Rapporteur:</b>	Czech Republic
<b>Finalisation procedure (day 120):</b>	8.6.2015
<b>Date of finalisation of PAR:</b>	14.9.2016

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## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	AlphaNine Factor IX Grifols/Novix Octanine F
INN (or common name) of the active substance(s):	Coagulation factor IX
MAH (s):	Instituto Grifols S.A., Grifols Deutschland GmbH, Grifols Italia S.p.A., Octapharma Pharmazeutika
Pharmaco-therapeutic group (ATC Code):	B02BD04
Pharmaceutical form(s) and strength(s):	Octanine F 500 inj. pso. lqf. Octanine F 1000 inj. pso. lqf.  Factor IX Grifols/Novix 50 UI/ml inj. Alphanine 500 inj. pso.lqf. Alphanine 1000 inj. pso. lqf. Alphanine 1500 inj. pso. lqf.

## **I. EXECUTIVE SUMMARY**

### **Summary of outcome**

☒ No change

## II. RECOMMENDATION

Based on the information provided in the application, the rapporteur is of the opinion that no regulatory action is warranted, and consequently no amendments to the product information are required.

## III. INTRODUCTION

On 29<sup>th</sup> October 2013, paediatric studies have been requested from relevant MAHs (Baxter, Vianex, Alk-Abello, LFB, Grifols, Sanquin and Octapharma) for coagulation factor IX according to Article 45 of the Regulation No 1901/2006.

Two MAHs have submitted paediatric data for coagulation factor IX in accordance with Article 45 of the Paediatric Regulation: Grifols s r.o. (Istituto Grifols S.A., Grifols Deutschland GmbH, Grifols Italia S.p.A.) and Octapharma Pharmazeutika.

Submission from Baxter is going to be evaluated via Type II variation with AT as RMS. The company Vianex cannot be reached and the companies Alk-Abello and Sanquin have stated that they do not have any relevant studies. Studies submitted by the company LFG concern von Willebrand factor therefore are not included into this pdWS.

Both MAHs (Grifols and Octapharma) submitted either published studies and/or unpublished study reports on paediatric data for coagulation.

The data package submitted by the MAH **Grifols** comprises of:

- Clinical overview
- MAH status overview of all coagulation factor IX products
- Coagulation factor IX Line listing (clinical studies conducted with paediatric population and previously not submitted to the regulatory agencies).
- PSUR (for the period from 7th of June 1996 to 31st of October 2013)

The MAH does not propose any changes to the PL and concludes that the benefit/risk profile for his coagulation factor IX products remains favorable when used within the approved indications.

The data package submitted by the MAH **Octapharma Pharmazeutika** comprises of:

- Clinical overview
- Coagulation factor IX Line listing (clinical studies conducted with paediatric population: YNE – 203 and YNE – 204)

The MAH does not propose any changes to the PL and concludes that the benefit/risk profile for his coagulation factor IX products remains favourable when used within the approved indications.

### **Assessor's comment:**

*In total, seven MAHs have been requested for submission of paediatric studies; however only two of these submissions were relevant for this pdWS. Non-submission of respective data by other MAHs is understandable and acceptable.*

*Both submitted packages are of a good quality. The clinical overviews are well written and clear.*

*Full body report of study YNE-204 (Octapharma Pharmazeutika) is missing (see LoQ)*

**Ad Grifols:**

*The authorship of the clinical overview is not known and should be ideally clarified by the MAH. However as there are no other comments raised to this MAH, this issue is not pursued further.*

**Ad Octapharma Pharmazeutika**

*The authorship of the clinical overview is not known and should be clarified by the MAH.*

*According to the MAH the studies YNE – 203 and YNE – 204 have been recently submitted within the MRP Re-Baselining DE/H/0213/01-02/IA/036. Submitted on February 28, 2012 and approved on March 14, 2012. No clinical assessment of these studies has been done and none is deemed necessary during this pdWS as these data have been already submitted to the regulatory authority.*

*Furthermore, the MAH states that all corresponding PSURs have already been submitted within the MRP (DE/H/0213/01-02); respectively the latest PSUR was submitted within the single PSUR assessment procedure (PSUSA/0001617/201307). It is agreed with the MAH that assessment of these PSURs is not deemed necessary during this pdWS procedure.*

## **IV. SCIENTIFIC DISCUSSION**

### **Pharmaceutical background**

Factor IX (FIX, Christmas factor) is a blood clotting factor, a zymogen of serine protease. Upon activation, FIX is converted into the active serine protease and, in the presence of  $\text{Ca}^{2+}$  and membrane phospholipids, it hydrolyses one arginine-isoleucine bond in factor X to form the activated factor X (Xa). The catalytic efficiency of activated FIX (FIXa) is greatly increased by the cofactor, the activated factor VIII (FVIIIa). The non-covalent complex of FIXa, FVIIIa and FX, bound to the phospholipid membrane, is called “the X-ase” or “tenase” and represents a major signal amplification loop in the blood coagulation cascade (Figure 1).

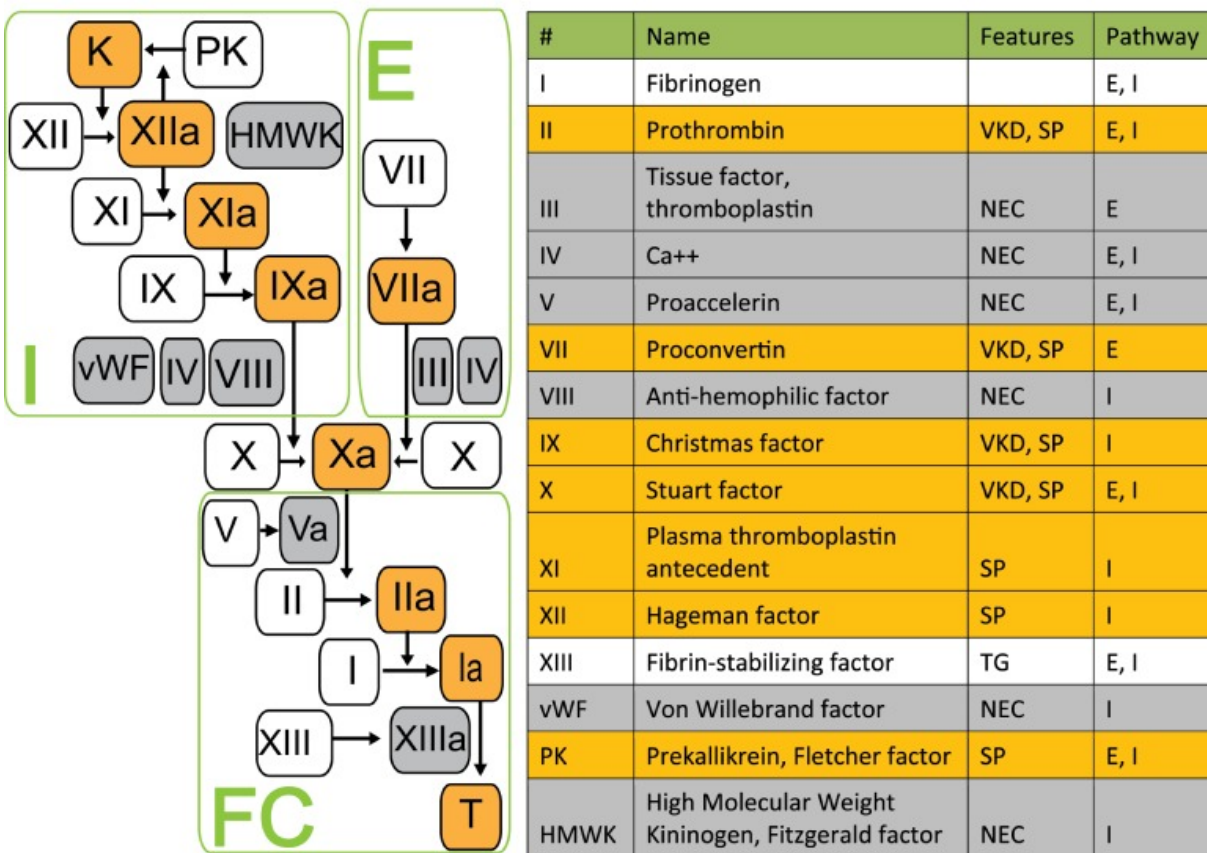


Figure 1: Scheme of blood coagulation cascade and international nomenclature of coagulation factors. VKD - vitamin K dependent; SP - serine protease, TG - transglutaminase; E – extrinsic pathway; I – intrinsic pathway; NEC - non-enzymatic cofactor, FC - final common pathway. (Orlova et al., Acta Naturae. 2012 Apr-Jun; 4(2): 62–73.)

Factor IX is produced in the liver and is secreted into the bloodstream as pro-peptide. Circulated mature FIX, 57 kDa and app. 90 nM, takes part in the blood coagulation cascade after specific proteolytic cleavage by the activated factor XI (of the contact pathway) or the activated factor VII (of the tissue factor pathway). Activated FIX is slowly deactivated by multiple factors – binding to antithrombin III, nexin-2, the protein Z-dependent protease inhibitor, and endocytic hepatocyte receptors or degraded by neutrophil elastase.

The gene of human FIX lies in the X chromosome and various mutations in this gene can impair the functioning of the FIX protein, resulting in bleeding-disorder hemophilia B.

The rate of incidence of severe hemophilia B, requiring regular replacement therapy, is 1 in every 30,000 men, which represents approximately 20% of all hemophiliacs.

In some cases, mutations in the promoter region of the gene result in the less severe hemophilia B Leiden, characterized as a nearly complete absence of FIX in childhood and steady increase in the level of endogenous FIX during puberty to the near-normal values.

#### IV.1 Clinical background

Haemophilia B is a coagulation disorder which is transmitted by X-chromosomal-recessive inheritance and which is caused by a deficiency in FIX activity (FIX:C). Haemophilia B accounts for about 12% of the total cases of haemophilia and occurs in approximately 1 case per 30.000 males.

The disease becomes manifest in recurrent bleeding episodes without obvious cause or in continuous bleeding after minor surgeries or traumatism. The diagnosis of haemophilia B is made based on family history, bleeding history and specific assays for FIX. It is variable in phenotype, and the degree of bleeding severity usually correlates with the level of FIX activity present in the patient's plasma.

The disease is clinically manifested almost exclusively in males. Haemorrhages are located in the muscles, soft tissues, articulations and viscera. Articular haemorrhages and haemarthroses are typical manifestations of haemophilia that occurs chiefly in children and adolescents and may lead to severe handicap and disability. The most frequently affected articulations are weight-bearing joint, as the knees, ankles, and elbows. Intracranial haemorrhage is one of the major causes of death, and may occur even in the absence of recognisable trauma. Peripheral nerve compression by a haematoma is a particularly common problem, as the femoral nerve palsy secondary to retroperitoneal haematoma. Haemorrhages are not too frequent in the skin and the mucosae. They are more common in muscular masses and soft tissues, which must be treated with care due to the risk of progression and result in serious complications. The most frequent visceral haemorrhages are haematurias. It is sometime self-limited in a few days, but it may persist for weeks or months if untreated. Patients with severe haemophilia B have spontaneous haemorrhagic episodes and recurring haemarthroses.

Patients with moderate or severe haemophilia B require specific replacement therapy. This is sometimes conducted prophylactically on a regular basis or is sometimes administered if required as a result of a haemorrhagic episode. Desmopressin is of no value in haemophilia B. Antifibrinolytic agents are useful following dental extractions but are of no value in treating haemarthroses and are contraindicated in the treatment of haematuria due to the risk of urethral obstruction.

Until recently pure preparations of FIX were not available, and preparations referred to as prothrombin complex concentrates (PCCs) were used. PCCs contain variable quantities of FVII, FIX, FX, prothrombin, protein C and protein S. The purity of these products is in the range of 1-5 IU FIX/mg protein. Despite their utility, PCCs have the presence of clotting factors other than FIX, which are unnecessary for the treatment of haemophilia B and may contribute to the risk of thromboembolic phenomena. Recently, highly purified FIX concentrates have become available, allowing safer therapy. The purity of the FIX concentrates is higher than in PCCs, and contains 50-250 IU FIX/mg protein. Multiple studies have documented the clinical efficacy, the lack of thrombogenicity and the viral safety of the purified preparations.

Protein-replacement therapy is very expensive for patients and the healthcare system. Only 20% of the world's population can afford the treatment; so hemophilia B remains lethal in childhood in poor countries.

#### **IV.2 Overview of Factor IX products/formulations and approved indications**

This paediatric worksharing procedure concerns only products with plasma-derived human coagulation FIX (AlphaNine, Factor IX Grifols/Novix and Octanine F).

All concerned products are indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B. In general, these products are approved for administration to children above 6 years.

#### **Assessor's comments:**

*The current SmPC of AlphaNine states that there are insufficient data to recommend the use of AlphaNine in children less than 6 years of age.*



*Therefore of the main interest during this pdWS would be studies conducted with AlphaNine in children below 6 years.*

*The current SmPC of Octanine states in the posology section: "In the study conducted in 25 children under 6 years of age, the median dose administered per exposure day was similar for prophylaxis and treatment of bleeding, i.e. 35 to 40 IU/kg BW." This means that recommendation for prophylaxis and treatment dosing in children below 6 years of age is already provided.*

### **IV.3 Non-clinical aspects**

Not applicable as no non-clinical studies have been submitted.

### **IV.4 Clinical Aspects**

#### **IV.4.1 Introduction**

Two MAHs have submitted paediatric data for coagulation factor IX in accordance with Article 45 of the Paediatric Regulation: Grifols and Octapharma Pharmazeutika.

Submitted data from Grifols have not been previously submitted to the regulatory agencies. Submitted studies by Octapharma Pharmazeutika (YNE – 203 and YNE – 204) have been previously submitted within the MRP Re-Baselining DE/H/0213/01-02/IA/036. Submitted on February 28, 2012 and approved on March 14, 2012. Though, no clinical assessment has been done previously.

Assessment has been done separately for each MAH.

#### **IV.4.2 Studies conducted with Factor IX Grifols/Novix**

The company has provided study reports of following trials with paediatric subjects. These trials provide additional information on the safety of AlphaNine and Factor IX Grifols/Novix:

**ACT 91-11: Coagulation Factor IX (Human) AlphaNine SD Affinity Purified, Solvent Detergent Treated. An Open Label Study of Viral Safety in Previously Untreated Individuals with Hemophilia B.**

#### Methods

This study was a phase IV, multicenter, open-label, uncontrolled clinical study designed to investigate the safety of AlphaNine in previously untreated or minimally treated subjects diagnosed with hemophilia B, performed in 26 male hemophilia B subjects in 12 sites in USA over a 52 week period.

- Objectives
  - Viral safety of AlphaNine SD in previously untreated or minimally treated haemophilia B subjects
  - Incidence of adverse experiences during and following the infusion of AlphaNine SD
  - Incidence of factor IX inhibition formation
- Study population /Sample size

Twenty-six male haemophilia B subjects were enrolled and successfully completed the study. Sixteen were diagnosed with moderate haemophilia B (2-5% FIX level) 10 with severe haemophilia B (<2% FIX level). Fifteen of the twenty-six patients were previously untreated, 11 had previous exposure to plasma products (AlphaNine, AlphaNine SD,

Mononine, Konyne, single donor cryoprecipitate plasma). Of the twenty-six (26) subjects enrolled in the study, twenty-one (21) were pediatric. A summary of the pediatric subjects is presented in the Table 1 below:

<b>Patient No</b>	<b>Date of Birth</b>	<b>Date of First Infusion</b>	<b>Weight (kg)</b>	<b>Height (cm)</b>
0101 EMB	4-ago-82	3-sep-93	37.6	136.3
0102 BED	9-ene-94	19-jun-95	10.5	74.0
0201 RCW	23-may-90	1-oct-93	34.0	38.0
0301 CAT	24-jul-94	14-jun-95	10.0	ND
0601 CF	27-feb-93	30-abr-93	6.4	60.0
0602 JS	1-abr-90	23-may-95	13.4	99.5
0603 KAS	7-jul-93	12-dic-94	ND	ND
0801 JAM	1-jun-84	4-ago-94	28.5	136.1
0802 KMF	22-ago-94	27-may-95	7.6	72.0
0901 DDF	28-ene-95	19-jun-95	8.1	67.5
1401 DJB	2-jun-90	2-sep-93	16.3	99.6
1402 JDE	6-may-85	2-nov-93	23.4	ND
1403 CE	27-jul-79	8-sep-93	68.0	ND
1404 RFA	13-jun-93	21-sep-93	6.5	60.0
1411 MLC	20-jun-82	12-sep-94	43.3	147.0
1413 ARC	24-oct-94	19-may-95	7.2	64.5
1601 MGP	14-ago-88	27-jul-93	21.4	117.0
2301 KJK	24-ago-92	23-dic-93	12.3	85.1
2601 CAB	17-jul-93	23-may-95	11.4	87.5
2602 JMB	9-nov-91	23-may-95	15.1	102.3
2603 NMP	24-jul-92	15-jun-95	15.0	97.5

**Table 1: Summary of pediatric Subjects in ACT 91-11**

- **Treatments**  
AlphaNine SD was provided as a lyophilized powder in vials containing at least 20 IU Factor IX/ml after reconstitution. Dose was dependent upon reason for the infusion (prophylaxis or treatment of a bleeding episode)
- **Outcomes/endpoints**  
Efficacy was not considered in the design of the study  
Safety: The main criterion used to evaluate safety was the incidence of seroconversions for blood-borne viruses. The incidence of inhibitor formation was the second criteria to evaluate safety.
- **Statistical Methods**  
N/A

### Results and conclusions

- **Efficacy results**  
The study was not designed to evaluate efficacy of AlphaNine SD.
- **Safety results**  
Subjects received 389 infusions of 360,700 units of AlphaNine from 30 different lots (13,873.07 IU/subject, range 500 to 137,940 IU; 927 IU/infusion) during 52 week follow-up for various reasons. Three hundred and fifty (350) of the total infusions were

administered to pediatric patients (Table 2: 11,982.38 IU/subject, range 500 to 137,940 IU; 719 IU/infusion).

Patient No	BASELINE FIX (IU/mL)	Total Units infused	Infusions Received (n)
0101 EMB	<0.01	2080	4
0102 BED	0.02	5300	8
0201 RCW	0.015	1520	3
0301 CAT	<0.01	8660	11
0601 CF	0.08	1350	9
0602 JS	<0.01	8530	15
0603 KAS	0.02	12820	13
0801 JAM	0.02	2800	2
0802 KMF	0.03	5700	8
0901 DDF	0.89*	500	1
1401 DJB	0.018	3540	11
1402 JDE	0.02	900	1
1403 CE	0.03	20820	11
1404 RFA	<0.01	11550	18
1411 MLC	0.029	1000	1
1413 ARC	<0.01	11170	23
1601 MGP	0.12	6360	10
2301 KJK	<0.01	4890	15
2601 CAB	0.10	2080	4
2602 JMB	0.14	2120	4
2603 NMP	<0.01	137940	184

\* Received AlphaNine infusion one day before baseline measurement.

**Table 2: Summary of AlphaNine infused in pediatric subjects of ACT 91-11**

During the clinical study no seroconversions occurred except those associated with hepatitis B vaccinations, nor clinical evidence of hepatitis infection was noted in any subject.

In the 25 subjects tested (subject 0901 DDF missed all four FIX inhibitor tests due to an error by the investigator), no inhibitors to FIX developed. One paediatric subject (1404 RFA) developed a low-titer inhibitor approximately 10 months following completion of the clinical study. This subject was subsequently immunotolerized with 100 IU/kg/day of AlphaNine after which no FIX inhibitor was detected for 15 months following the completed immunotolerance induction.

Overall, no serious adverse events occurred during the study. Three (3) subjects experienced a total of 5 adverse events (AEs) following 389 infusions. Three (3) of these AEs (nausea, sweating and increase in temperature) affected two subjects from the paediatric age group (Table 3) and were rated as mild and regarded as probably not related to AlphaNine. The remaining two AEs (dizziness and hypotension) occurred in an adult subject and were considered moderate and regarded as possibly related to AlphaNine.

PATIENT No	INFUSION #	SYMPTOM	SEVERITY	RELATION TO TEST DRUG
0101 EMB	3	nausea	mild	Probably not
		sweating	mild	Probably not
2603 NMP	42	1°C elevation in temperature	mild	Probably not

Table 3: Display of adverse events in pediatric patients

In the 5 subjects that re-enrolled for further monitoring, no adverse events were reported and no seroconversions or clinical evidence of hepatitis infection was noted. Four (4) of these reenrolled subjects were from pediatric age group.

**Assessor's comment:**

*Based on the provided demographic data and the dates of first infusion (please see Table 1) it can be concluded that subjects younger than 6 years have been included in this study. In total, it has been calculated by the assessor that this subgroup (younger than 6 years) counts fifteen subjects.*

*Taking into account that primary objectives of this study have been safety concerns, no conclusion on the efficacy in this pediatric subgroup can be made.*

*As regards to safety, no new safety signals have been observed during this study.*

*Therefore the assessor is of the opinion that the statement in the current SmPC of AlphaNine "there are insufficient data to recommend the use of AlphaNine in children less than 6 years of age" is adequate and no new efficacy and safety recommendations can be derived from the study ACT 91-11.*

**ACT 96-04:**

**Pharmacovigilance of AlphaNine SD (Solvent Detergent Treated/Virus Filtered): An Open-Label Safety Study in Previously Treated Hemophilia B Subjects**

Methods

- Objectives  
To evaluate the safety of AlphaNine SD in previously-treated hemophilia B patients, as determined by the incidence of the following:
  - Transmission of viral hepatitis, HIV-1 and 2, and Parvovirus B19
  - Factor IX (FIX) inhibitor formation
  - Adverse events, including thrombogenicity.
- Study design  
This was a post-licensing, non-randomized, open-label, unblinded and uncontrolled multicenter study (5 sites in the USA and 4 in the UK)
- Study population /Sample size  
Eligible patients were those that had been diagnosed with hemophilia B and had previously received FIX-containing products and were immunocompetent (i.e. had a CD4+ T cell count  $\geq 400/\mu\text{l}$ ) at the time of enrollment. A summary of the demographic characteristics of the pediatric subjects is presented in Table 4.

Patient No	Age at inclusion (years)	Race	Gender	Factor IX <sup>a</sup> (%)	Severity of Hemophilia B <sup>b</sup>	Status
0102	2	Caucasian	Male	2	Moderate	Treated / Evaluated
0104	11	Caucasian	Male	1	Moderate	Treated / Evaluated
0105	17	Caucasian	Male	4	Moderate	Treated / Evaluated
0106	15	Caucasian	Male	3	Moderate	Non Treated
0201	3	Caucasian	Male	2	Moderate	Treated / Evaluated
0202	14	Caucasian	Male	<1	Severe	Treated / Evaluated
0203	14	Caucasian	Male	1	Moderate	Treated
0301	4	Caucasian	Male	<1	Severe	Treated / Evaluated
0401	4	Caucasian	Male	2	Moderate	Treated / Evaluated
0501	3	Caucasian	Male	<1	Severe	Treated / Evaluated
3101	10	Caucasian	Male	2	Moderate	Treated / Evaluated
3102	4	Caucasian	Male	2	Moderate	Treated / Evaluated
3103	13	Caucasian	Male	<1	Severe	Treated / Evaluated
3104	15	Caucasian	Male	10	Mild	Treated / Evaluated
3105	6	Caucasian	Male	<1	Severe	Treated / Evaluated
3106	10	Caucasian	Male	4	Moderate	Treated / Evaluated
3107	12	Caucasian	Male	17	Mild	Treated / Evaluated
3108	3	Caucasian	Male	<1	Severe	Treated / Evaluated
3109	9	Caucasian	Male	2	Moderate	Treated / Evaluated
3110	12	Caucasian	Male	2	Moderate	Treated / Evaluated
3111	16	Caucasian	Male	<1	Severe	Treated / Evaluated
3112	17	Caucasian	Male	3	Moderate	Treated / Evaluated

<sup>a</sup> Lowest Factor IX level recorded for patient at any visit

<sup>b</sup> Severity of hemophilia B is defined according to the following FIX level criteria: <1 = severe, 1-5 = Moderate, >5 = Mild

**Table 4: Demographic characteristics of pediatric patients in ACT 96-04**

- **Treatments**  
All patients were to receive AlphaNine as their sole treatment for hemophilia B during the course of two-year study with a minimum of 50 cumulative exposure days (CEDs), unless: a) they developed inhibitors equal to or greater to 10 BU, b) treatment became ineffective even with inhibitors levels less than 10 BU, or c) they developed severe or serious adverse events which prevented completion of participation in the study.
- **Outcomes/endpoints**  
Efficacy: no endpoints  
Safety:
  - viral safety as evidenced by changes in serologic status, ALT levels, and PCR testing
  - the incidence of FIX inhibitor development
  - the incidence of adverse events including thrombogenicity
- **Statistical Methods**
  - viral safety: instances of new infection with Hepatitis A, B or C or with HIV-1 and 2 at any time point during the study were tabulated. Post-infusion values of serum ALT were compared to baseline values.
  - inhibitors: the incidence of inhibitors to FIX was reported descriptively
  - adverse events: were reported descriptively. Adverse events were tabulated by severity and probable relationship to study drug. Serious adverse events were tabulated and described separately.

## Results and conclusions

- **Efficacy results**  
The study was not designed to evaluate efficacy of AlphaNine SD

- Safety results

From the 30 patients initially planned, 42 patients were enrolled of which 40 were treated with AlphaNine. One (1) patient received AlphaNine once and had no further follow-up clinical observations or laboratory data. Therefore, a total of 39 patients were evaluable for the safety analysis. Twenty-two (22) of the 42 enrolled subjects were pediatric patients of which 21 were treated with AlphaNine and 20 were considered evaluable for safety.

The mean number of infusions per patient was  $47.3 \pm 49.5$  (median 25, range 1-181). Regarding the pediatric age group the mean number of infusions per patient was  $45.7 \pm 52.1$  (median 19, range 1-172). In total, the study participants received 1893 infusions of which 959 of those infusions were administered to pediatric subjects (50.7 %).

No cases of Hepatitis A or B infection were documented among the 39 evaluable patients treated with AlphaNine for periods up to 20 months. However, the number of individuals who were HAV or HBV seronegative at baseline was small (5 for HAV and 2 for HBV). Of those 5 HAV seronegative at baseline, 4 of them were from pediatric age group: 0201 and 0301 received HAV vaccination during the study; 0501 was the only participant who was anti-HAV negative at baseline, with no history of prior HAV vaccination, and neither received HAV vaccination during the study; and 3109 was anti-HAV negative despite having a history of prior HAV vaccination. On the other hand, 2 pediatric patients were HBsAg negative at baseline: 0501 received HBV vaccination prior to the study and 0301 had no history of prior HBV vaccination.

None of the 21 patients who were anti-HCV seronegative and none of the 38 patients who were anti-HIV seronegative at baseline/enrollment seroconverted. Considering the pediatric age group, 17 patients were anti-HCV seronegative and 20 patients were anti-HIV seronegative at baseline and none of them seroconverted.

All patients who had baseline measurements were found to be seropositive for Parvovirus B19 and therefore it was not possible to assess Parvo B19 seroconversion.

None (0) of the 39 (20 pediatric) evaluable patients treated with AlphaNine for periods of up to 20 months exhibited any evidence of inhibitor formation.

Overall, 117 AEs were reported in 27 (67.5%) of the 40 subjects treated with AlphaNine. Eight AEs were considered to be related to study drug. Of the 117 AEs, 101 (86%) were considered to be mild or moderate and 16 (14%) were considered to be severe or of unknown severity. Twenty-three (23) serious AEs were observed in 11 (27.5%) of the 40 treated patients. None of the serious AEs was deemed related to treatment.

Regarding the pediatric age group, 11 (52.4%) of the 21 pediatric patients treated under the study experienced 48 AEs, of which 3 were considered to be related to study drug. Of the 48 AEs summarized in Table 5, 45 (93.8%) were considered to be mild or moderate and 3 (6.3%) were considered severe or of unknown severity. Ten (10) serious AEs were observed in 5 (25%) of the 21 pediatric treated patients. None of the serious AEs was deemed related to treatment.



Patient No	Associated with infusion?	Description of AE	Severity	Seriousness	Relation to test drug	Outcome	Action taken
0301	Yes # 6	Temperature of 102°F (38.9°C)	Moderate	None Serious	Not related	Resolved, NRE	Med req
0301	NO	Bilat ear infect	Mild	None Serious	Not related	Resolved NRE	Med req
0301	NO	Growing pain	Mild	None Serious	Not related	Resolved NRE	Med req
0301	NO	Necrotic skin over port	Moderate	SERIOUS	Not related	Resolved RE	Other
0301	NO	Head injury	Moderate	SERIOUS	Not related	Resolved NRE	Hosp req
0301	NO	Broken humerus	Moderate	SERIOUS	Not related	Resolved NRE	Other
3101	NO	Headache	Mild	None Serious	Not related	Resolved NRE	Med req
3101	NO	Common cold / Headache	Mild	None Serious	Not related	Resolved NRE	Med req
3101	NO	Common cold / chest cough / tracheitis	Moderate	None Serious	Not related	Resolved NRE	Med req
3101	NO	Neck muscle spasm	Mild	None Serious	Not related	Resolved NRE	Med req
3102	NO	Tonsillitis	Moderate	None Serious	Not related	Continued	Med req
3102	NO	Temperature	Unknown	None Serious	Probably Not	Resolved NRE	Med req
3103	Yes #1	Shakes	Mild	None Serious	Definitely related	Resolved NRE	Other

Patient No	Associated with infusion?	Description of AE	Severity	Seriousness	Relation to test drug	Outcome	Action taken
3103	Yes # 1	Abdominal pain	Mild	None Serious	Definitely related	Resolved NRE	Other
3103	NO	Viral infection in throat and chest	Moderate	None Serious	Not related	Resolved NRE	Med req
3103	NO	Head knock	Mild	None Serious	Not related	Resolved NRE	Other
3103	NO	Bruised head	Mild	None Serious	Not related	Resolved NRE	Other
3103	NO	Nausea	Mild	None Serious	Not related	Resolved NRE	Other
3104	NO	Dry skin	Mild	None Serious	Not related	Resolved NRE	Med req
3105	NO	Cough	Mild	None Serious	Not related	Resolved NRE	Med req
3105	NO	Sore throat	Mild	None Serious	Not related	Resolved NRE	Med req
3105	NO	Flu	Mild	None Serious	Not related	Resolved NRE	Med req
3105	NO	Tooth decay	Mild	SERIOUS	Not related	Resolved NRE	Hosp req
3105	NO	Nausea	Mild	None Serious	Not related	Resolved NRE	Med req
3105	NO	Sore mouth	Mild	None Serious	Not related	Resolved RE	Med req
3106	NO	Orthodontic tx	Mild	SERIOUS	Not related	Continued	Hosp req
3106	Yes #4	Post operative vomiting	Mild	None Serious	Not related	Resolved NRE	None
3106	Yes #4	Fainted	Mild	None Serious	Possibly related	Resolved NRE	None
3106	NO	Superficial laceration right thigh	Moderate	None Serious	Not related	Resolved NRE	Other
3106	NO	Head injury	Mild	SERIOUS	Not related	Resolved RE	Hosp req
3107	NO	Swollen right hypotenar eminence	Moderate	None Serious	Not related	Continued	None
3107	NO	Greenstick fracture right 5 <sup>th</sup> metacarpal	Mild	None Serious	Not related	Continued	None
3107	NO	Fracture to base 5 <sup>th</sup> left metatarsal	Moderate	None Serious	Not related	Resolved RE	None
3107	NO	Tonsillitis	Moderate	None Serious	Not related	Resolved RE	Med req
3107	NO	Acute tonsillitis haemorrhage	Severe	SERIOUS	Not related	Resolved RE	Hosp req
3107	NO	Vomiting	Moderate	None Serious	Not related	Resolved NRE	Med req
3107	NO	Severe headache	Severe	None Serious	Not related	Resolved NRE	Med req
3108	NO	Swollen right forearm	Moderate	SERIOUS	Not related	Resolved NRE	Other
3108	NO	Greenstick fracture right forearm	Moderate	SERIOUS	Not related	Continued	Other
3108	NO	Dental caries	Moderate	SERIOUS	Not related	Resolved RE	Hosp req
3108	NO	Post operative vomiting	Mild	None Serious	Not related	Resolved NRE	None
3109	Yes not available	Cough and cold	Mild	None Serious	Not related	Resolved NRE	Med req
3109	Yes not available	Cellulitis	Moderate	None Serious	Not related	Resolved NRE	Med req
3109	Yes . . .	Right eye pus in AM	Mild	None Serious	Not related	Resolved NRE	Other

Patient No	Associated with infusion?	Description of AE	Severity	Seriousness	Relation to test drug	Outcome	Action taken
3112	NO	Head injury	Mild	None Serious	Not related	Resolved NRE	Med req

NRE = Non residual effects; RE = Residual effects

**Table 5: Adverse events in pediatric patients in ACT 96-04**

**Assessor's comment:**

*Based on the provided demographic data, eight subjects younger than 6 years have been included in this study.*

*As with the previous study, this study has not been design to evaluate efficacy of AlphaNine. Therefore no conclusions on the efficacy in this pediatric subgroup can be made.*

*No new safety signals have been observed during this study.*

*As with the previous study, the assessor is of the opinion that the statement in the current SmPC of AlphaNine "there are insufficient data to recommend the use of AlphaNine in children less than 6 years of age" is adequate and no new efficacy and safety recommendations can be derived from the study ACT 96-04.*

**IG104:****Efficacy and Safety of Factor IX (FIX) Contained in FIX-Grifols in Patients with Severe Hereditary Haemophilia B.**Methods

- Objective
  - To compare FIX-Grifols pharmacokinetics to currently available preparations with respect to in vivo recovery and half-life in at least 15 severe haemophilia B patients.
  - To demonstrate efficacy of FIX-Grifols by comparison of the first FIX-Grifols pharmacokinetics with a second assessment after 3-6 months of treatment.
  - To determine clinical efficacy of FIX-Grifols exhibits with respect to:
    - Treatment of bleedings severe enough to be treated in the haemophilia centre in at least 15 patients during at least 6 months of follow-up.
    - Prophylaxis for surgical interventions in at least 5 patients submitted to at least 10 surgical procedures.
    - Long-term clinical efficacy for prophylaxis or treatment of bleedings in at least 15 patients receiving FIX-Grifols on demand at home for at least 6 months of followup.
  - To determine safety of FIX-Grifols with respect to:
    - Incidence of inhibitors to FIX in at least 20 PTPs after at least 50 exposure days, or at least 6 months of follow-up and more than 10 exposure days.
    - Nature, severity and frequency of adverse reactions during and after infusions and clinically relevant changes in the vital signs after the infusions of the pharmacokinetic assessments.
    - Thrombogenic effects detected by relevant changes in activation coagulation markers after the infusions of the pharmacokinetic assessments and clinical evaluation in surgical procedures.
    - Transmission of viruses (HIV and HCV) on patients treated with the product in the clinical trial.
- Study design

This study was a multicentre, open-label, single-arm, non-randomized study to evaluate the efficacy and safety of Factor IX Grifols in 25 patients with severe hemophilia B, performed in 5 hospitals in Poland and Bulgaria. The study was set to first compare the pharmacokinetic (PK) profile of Factor IX Grifols the subject's previously dosed FIX preparation (bioequivalence to previously used FIX) and secondly to determine the PK profile of Factor IX Grifols as assessed twice, at baseline and after a six month follow-up



period. In addition, clinical safety and efficacy were measured during a follow-up of 52 weeks (12 months).

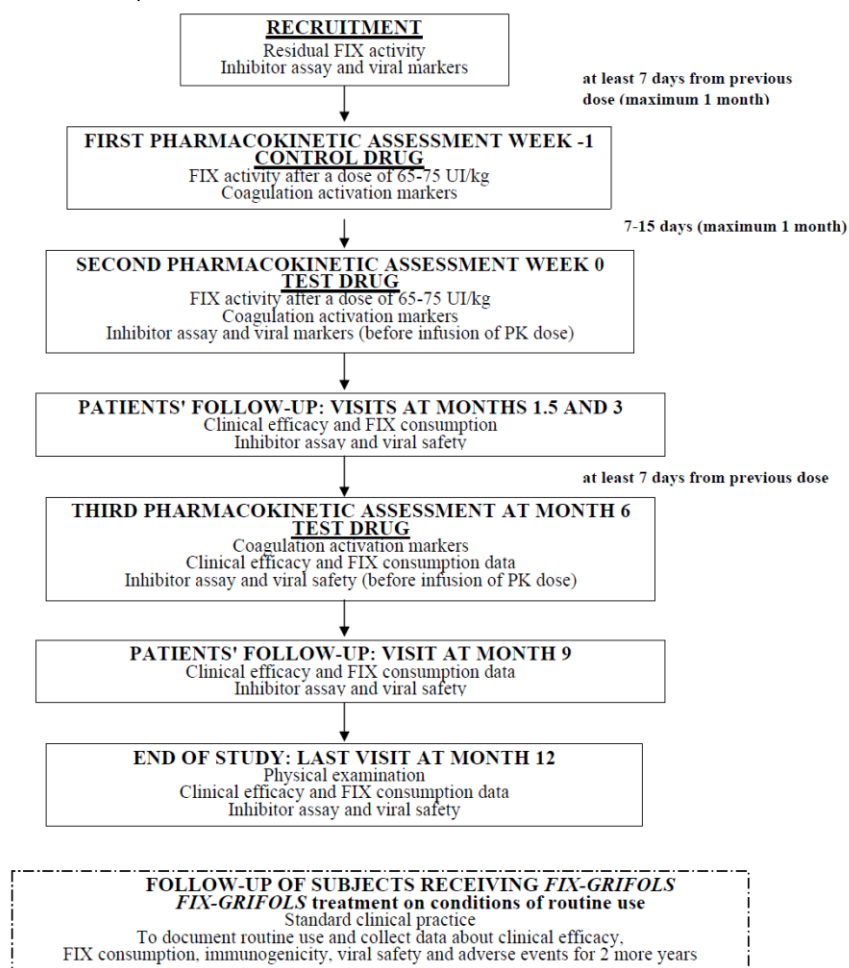


Figure 2: Summary of the safety and efficacy study plan

- Study population /Sample size

25 patients were planned and analysed.

Eligible participants were at least 12 years of age, diagnosed with moderate to severe haemophilia B (FIX residual activity <2 %), who had received previous treatment with FIX replacement products (≥150 exposure days). Subjects with evidence of FIX inhibitor levels >0.5 Bethesda units (BU) or with history of clinically relevant inhibitors in the past (>5 BU) were excluded.

All 25 participating subjects were male Caucasians of which 10 (age range: 12-17 years) were less than 18 years of age (Table 6).

Patient No	Date of the examination (dd/mm/yy)	Sex	Date of birth (dd/mm/yy)	Age (years)	Height (cm)	Weight (kg)	Ethnic group
1106	25-Nov-02	male	16-Jun-86	16	171	70	caucasian
1202	11-Feb-03	male	29-Aug-87	15	149	44	caucasian
1203	18-Feb-03	male	18-May-88	14	160	60	caucasian
1302	19-Feb-03	male	28-Feb-90	12	155	36	others
3102	27-Jan-03	male	17-Jul-85	17	177	97	caucasian
3201	04-Oct-02	male	31-Mar-88	14	169	63	caucasian
3202	14-Oct-02	male	19-Feb-90	12	159	43.1	caucasian
3203	21-Oct-02	male	12-Feb-86	16	176	59.5	caucasian
3204	25-Nov-02	male	30-Nov-85	17	177	74	caucasian
3205	27-Jan-03	male	01-May-99	12	162	52.5	caucasian

**Table 6: Demography of Pediatric Subjects in IG104**

- **Treatments**

Test product: FIX-Grifols, a dual-inactivated, high-purity FIX concentrate. A single dose of 65-75 IU/kg was administered for each pharmacokinetic study. This dose should have been administered at least 7 days after the previous infusion of FIX.

At least three different batches were used. Patients received treatment according to their requirements during 12 months.

Reference therapy: Previous FIX concentrate (Immunine and Octanine). Dosage as test product.

- **Outcomes/endpoints**

Efficacy:

- Pharmacokinetic variables - The plasma activity of FIX was measured at baseline (prior to the infusion), and at 15 and 30 (in children 45) minutes, 1, 3, 6, 9, 24, 48, 50 (optional), 72 and 74 hours after the end of the infusion.
- 
- Clinical efficacy in major bleedings - type, location, duration and severity of the bleeding; number of doses and total amount of FIX required
- 
- Clinical efficacy in surgery
- 
- Long term clinical efficacy - The long-term clinical efficacy will be evaluated by calculating the consumption of FIX, expressed as number of infusions and IU/kg per month, as well as number of events (prophylaxis, on-demand and surgery) per month and IU/kg per event.

Safety:

- Immunogenicity, clinical safety (thrombogenicity and tolerance to infusion), viral safety (HIV, HCV).

- **Statistical Methods**

Data from the pharmacokinetic study were evaluated by model-independent and two-compartment methods. In vivo recovery was estimated as:

$$([FIX \text{ max (IU/dl)}] - [FIX \text{ pre-inf. (IU/dl)}]) / FIX \text{ administered (IU)} / \text{Body weight (kg)}$$

To compare pharmacokinetic parameters between control and investigational drug at the two first pharmacokinetic assessments, a paired Student-t test and a non-parametric Wilcoxon signed rank test were performed for each parameter.

The Shapiro-Wilk test for normality was also applied to enable the choice between the result of the t-test and that of Wilcoxon's signed rank test.

All the statistical tests were two-sided. No adjustment for multiplicity was made. Analysis of the kinetic data was done by Topfit 2.0 and SAS version 6.12 (univariate and means procedure). Clinical efficacy in major bleedings, surgery, and long term clinical efficacy are evaluated descriptively.

## Results

- **Recruitment/ Number analysed**  
All 25 participating subjects were male Caucasians of which 10 (age range: 12-17 years) were less than 18 years of age.
- **Efficacy results**  
Factor IX Grifols presented a similar pharmacokinetic profile to other plasma-derived FIX concentrates as no clinically relevant differences were found in the comparative pharmacokinetic assessment with the subject's previously product used as controls.  
In addition, after 6 months of treatment with Factor IX Grifols, the product presented a similar pharmacokinetic profile and no differences between the two Factor IX Grifols PK analyses were found in terms of half-life, clearance, mean residence time and area under the curve.  
  
In addition to the two infusions of 65-75 IU kg<sup>-1</sup> scheduled for the PK analysis, the median number of infusions per month per patient during the 12 month follow-up was 3.3 (range: 1.2– 7.3). In the pediatric cohort the median number of infusions per month per patient was 4.7 (range: 2.6-7.3).  
During the 12 month follow-up a total of 961 infusions we administered for various reasons. Overall, 95.9% of all specified efficacy assessments were rated as excellent or good, 3.5% as moderate and 0.2% as not observed. Five hundred and forty-one (541) of the total infusions were administered to pediatric patients and 96.7% were rated as excellent or good, 2.2% as moderate and 1.1% were not rated.
- **Safety results**  
Overall, 25 AEs were reported in 8 patients none of which were considered related to the study medication. These AEs were attributed to either the underlying disease, a concomitant disease in connection with the blood system or by infections not related to the product and in some cases the origin was unspecified. None of the events was considered serious.  
Three (3) of these 8 subjects with adverse events were in the pediatric age group, and their 13 adverse events are summarized in Table 8.

Patient No	Description of AE	Severity	Seriousness	Relation to test drug	Outcome	Action taken
1202	Hypochromic anaemia	mild	None serious	Not related	Recovered	None
1202	Tonsilopharyngitis	mild	None serious	Not related	Recovered	Treatment required
1202	Tonsilopharyngitis	mild	None serious	Not related	Recovered	Treatment required
1202	Flu	mild	None serious	Not related	Recovered	Treatment required
1202	Haemorrhagia cutis (right thigh)	mild	None serious	Not related	Not yet recovered	Treatment required
1202	Massive oedema (left knee)	moderate	None serious	Not related	Recovered with sequel	Treatment required
1202	Massive oedema (left elbow)	moderate	None serious	Not related	Recovered with sequel	Treatment required
1202	Massive oedema (left knee)	moderate	None serious	Not related	Recovered with sequel	Treatment required
1202	Massive oedema (right elbow)	moderate	None serious	Not related	Recovered with sequel	Treatment required
1202	Mild hypochromic anaemia	mild	None serious	Not related	Recovered	None
1203	Mild anaemia	mild	None serious	Not related	Recovered	None
1203	Flu	mild	None serious	Not related	Recovered	Treatment required
1302	Flu	mild	None serious	Not related	Recovered	None

Table 7: Display of Adverse Events in Pediatric Patients

### Conclusion

FIX-Grifols has a similar pharmacokinetic profile to the control products and to other highly purified plasma-derived FIX concentrates, which is maintained after routine treatment. Clinical efficacy was considered excellent or good in 95.9% of the infusions. In addition FIX-Grifols is a FIX concentrate well tolerated which presents a safe profile in terms of thrombogenicity, immunogenicity and viral safety. Therefore, it can be concluded that FIX-Grifols is an effective and safe plasma-derived concentrate that can be used as replacement therapy for haemophilia B patients.

#### **Assessor's comment:**

*In comparison with two previous studies, this study had also efficacy objectives. However, based on the provided demographic data, no subjects younger than 6 years have been included in this study. Therefore no conclusions on the efficacy in this pediatric subgroup can be made. No new safety signals have been observed during this study.*

### **IG404:**

### **Efficacy and Safety of Factor IX (FIX) Contained in AlphaNine in Patients with Severe Hereditary Haemophilia B**

### Methods

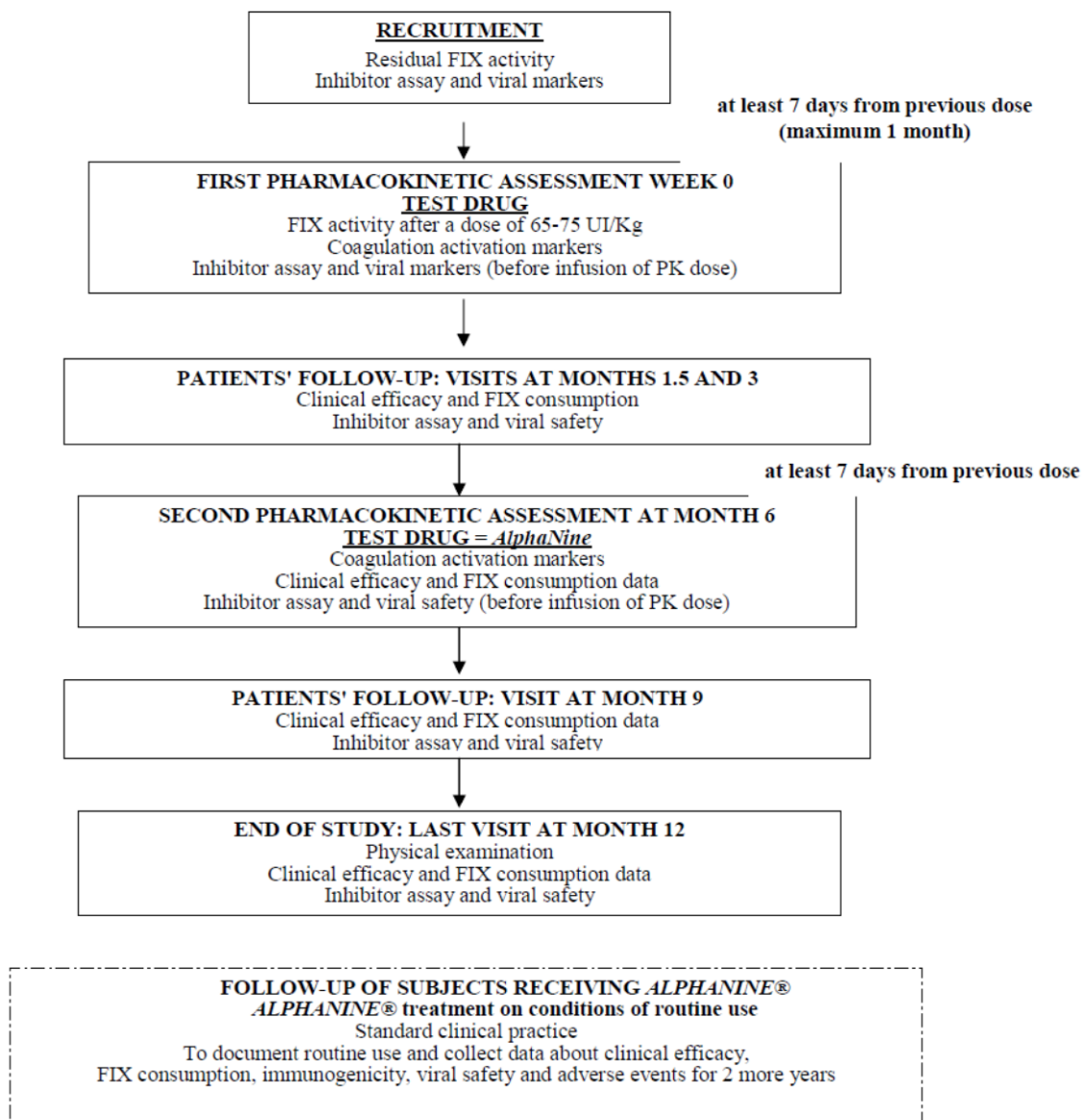
- Objectives
  - To determine the pharmacokinetic profile of AlphaNine with respect to in vivo recovery and half-life in at least 15 severe haemophilia B patients.
  - To demonstrate the efficacy of AlphaNine by comparison of the first AlphaNine pharmacokinetics with a second assessment after 6 months of treatment.
  - To determine clinical efficacy of AlphaNine with respect to:
    - Treatment of bleedings severe enough to be treated at a haemophilia centre in at least 15 patients during at least 6 months of follow-up. Prophylaxis for any surgical intervention.
    - Long-term clinical efficacy for prophylaxis or treatment of bleedings in at least 15 patients receiving AlphaNine® on demand at home for at least 6 months of followup.
  - To determine safety of AlphaNine with respect to:
    - Incidence of inhibitors to FIX in at least 20 PTPs after at least 6 months of treatment with AlphaNine.
    - Nature, severity and frequency of adverse reactions during and after infusions and clinically relevant changes in the vital signs after the infusions of the pharmacokinetic assessments.
    - Thrombogenic effects detected by relevant changes in activation coagulation markers after the infusions of the pharmacokinetic assessments and clinical evaluation in surgical procedures.
    - Transmission of viruses (HIV and HCV) to patients treated with the product in the clinical trial.

- Study design

This study was designed as a non-randomised, multi-centre study. There was an initial determination of the pharmacokinetic parameters of AlphaNine.

Subsequently, all patients received 12 months of treatment with AlphaNine. During this treatment period a second pharmacokinetic study with AlphaNine was performed at month 6.

After finishing their participation in the study the sponsor started to provide the enrolled patients with AlphaNine required for their treatment for at least 2 more years, free of charge if legally permitted, on a name-patient basis. Patients were treated by their physicians following their standard clinical practice. However, the data obtained from routine medical treatment and examinations may be gathered by the sponsor in order to collect more information about the use of the product under routine conditions in the frame of a pharmacovigilance observational study.



**Figure 3: Summary of the safety and efficacy study plan**

- **Study population /Sample size**  
25 patients were planned and analysed.  
Subjects enrolled in the present study were the same that participated in a previous study named “Efficacy and safety of Factor IX (FIX) contained in FIX-GRIFOLS in patients with severe hereditary haemophilia B”.
- **Treatments**  
AlphaNine, a high-purity solvent detergent treated and nanofiltered preparation of Human Coagulation Factor IX, freeze dried, Ph. Eur. A single dose of 65-75 IU/kg was administered for each pharmacokinetic study. This dose should have been administered at least 7 days after the previous infusion of FIX. Three different batches with different starting plasma were used. Patients received treatment according to their requirements during 12 months.

- Outcomes/endpoints

Efficacy:

- Pharmacokinetic variables – the plasma activity of FIX was measured at baseline (prior to the infusion), and at 15 and 30 (in children 45) minutes, 1, 3, 6, 9, 24, 48, 50 (optional), 72 and 74 hours after the end of the infusion.
- Clinical efficacy in patients treated for major bleedings or submitted to a surgical procedure - type, location, duration and severity of the bleeding; number of doses and total amount of FIX required.
- Long-term efficacy in patients treated on demand - long-term clinical efficacy was evaluated by calculating the consumption of FIX
- expressed as the number of infusions and IU/kg per month, as well as the number of events (prophylaxis, on-demand and surgery) per month and IU/kg per event.

Safety:

Immunogenicity, clinical safety (thrombogenicity and tolerance to infusion), and viral safety (HIV, HCV).

- Statistical Methods

Data from the pharmacokinetic study were evaluated by modelling dependent methods. In vivo recovery was estimated as:

$$([FIX \text{ max (IU/dl)}] - [FIX \text{ pre-inf. (IU/dl)}]) / FIX \text{ administered (IU)} / \text{Body weight (kg)}$$

To compare logarithmic pharmacokinetic parameters (half-life and in vivo recovery) between the first pharmacokinetic study and the second one (at 3-6 months), a paired Student-t test or the non-parametric Wilcoxon W test, as necessary, were used. In case of quantitative variables, mean, standard deviation (SD) and confidence intervals were assessed. The normality of the distribution of the quantitative variables will be assessed by Shapiro-Wilks test.

All the statistical tests were two-sided. No adjustment for multiplicity was made. Analysis of the kinetic data was done by Topfit 2.0 and SAS version 6.12 (univariate and means procedure).

Clinical efficacy in major bleedings, surgery, and long term clinical efficacy are evaluated descriptively.

## Results

- Recruitment/ Number analysed

All 25 participating subjects were male caucasians of which 6 (age range: 15-17 years) were less than 18 years of age (Table 8).



Patient No	Date of the examination (dd/mm/yy)	Sex	Date of birth (dd/mm/yy)	Age (years)	Height (cm)	Weight (kg)	Ethnic group
1202	22-Aug-05	m	29-Aug-87	17	171	57	caucasian
1203	24-Aug-05	m	18-May-88	17	180	90	caucasian
1302	29-Sep-05	m	28-Feb-90	15	170	55	caucasian
3201	26-Sep-05	m	31-Mar-88	17	184	64	caucasian
3202	26-Sep-05	m	01-May-90	15	182	67	caucasian
3205	17-Aug-05	m	19-Feb-90	15	186	58	caucasian

**Table 8: Demography of PediatricSubjects in IG104**

- **Efficacy results**

The mean FIX activity - time curves drawn from both PK assessments exhibited almost perfectly overlapping biphasic decay profiles that could be wellfitted into a bi-exponential formula and were comparable to other analogous products. No significant differences were found between the two applications of the investigational product in any analyzed PK parameter demonstrating the high stability of AlphaNine's PK parameters over time.

In addition to the two infusions of 65-75 IU kg<sup>-1</sup> scheduled for the PK analysis, the median number of infusions per month per patient during the 12 month follow-up was 3.2 (range: 1.1– 5.7). In the pediatric cohort the median number of infusions per month per patient was 5.2 (range: 2.7-5.6).

- **Safety results**

During the 12 month follow-up a total of 889 infusions we administered for various reasons. Overall, 93.0% of all specified efficacy assessments were rated as excellent or good, 5.9% as moderate and 0.8% as none (7 out of 889, in four severe and 3 mild/moderate bleeding episodes). Two hundred and ninety-eight (298) of the total infusions were administered to pediatric patients and 91.6% were rated as excellent or good, 8.1% as moderate and 1 infusion (0.3%) was not rated.

Twenty-one (21) AEs were reported in 8 patients none of which were considered related to the study medication. These AEs were attributed to either the underlying disease, a concomitant disease in connection with the blood system or by infections not related to the product. The causality of two AEs, an elevated ALT and an abdominal discomfort were classified as unspecific. Only one event, a hospitalization due to tooth extraction, was considered as serious.

Three (3) of these 8 subjects with adverse events were in the pediatric age group, and their 11 adverse events are summarized in Table 9. None of the latter was considered to be serious and all events resolved completely.



Patient No	Description of AE	Severity	Seriousness	Relation to test drug	Outcome	Action taken
1202	flu	mild	Non serious	Not related	Recovered	Treatment required
1202	flu	mild	Non serious	Not related	Recovered	Treatment required
1202	tonsillitis	mild	Non serious	Not related	Recovered	Treatment required
1202	edema in left knee	moderate	Non serious	Not related	Recovered	None
1202	pain in left knee	mild	Non serious	Not related	Recovered	Treatment required
1203	pain in both ankles	mild	Non serious	Not related	Recovered	None
1203	pain in both ankles	mild	Non serious	Not related	Recovered	None
1203	injury of left thumb	mild	Non serious	Not related	Recovered	None
1302	abdominal discomfort	mild	Non serious	Not related	Recovered	Treatment required
1302	flu	mild	Non serious	Not related	Recovered	None
1302	anaemia	mild	Non serious	Not related	Recovered	Treatment required

**Table 7: Display of adverse events in pediatric patients**

After extensive exposure to AlphaNine during the 12 month follow-up, there was no evidence of inhibitor formation in any of the treated subjects. No clinical or laboratory evidence showed the occurrence of neither allergic reactions nor thrombotic events in the patients receiving AlphaNine throughout the entire study period. Regarding viral safety, HIV 1-2 IgG and HCV IgG status did not change during the observation time and thus, the cumulative incidence of seroconversion was 0.

**Assessor's comment:**

*Subjects enrolled in this study were the same that participated in a previous study (IG 104). No subjects younger than 6 years have been included in this study. Therefore no conclusions on the efficacy in this pediatric subgroup can be made.*

*No new safety signals have been observed during this study.*

**MAH's conclusion on paediatric data**

A total of fifty-nine (59) subjects (23 aged less than 6 years) have received Alphanine or FIX Grifols/Novix in clinical studies over a 17-year period (Table 11) for the treatment of haemophilia B. In the clinical studies, the safety profile of Alphanine and FIX Grifols/Novix was favorable in pediatric subjects. Approximately 0.68% of the total of infusions were associated with any adverse event and fewer than 0.097% of the infusions were associated with the occurrence of an adverse event potentially related to the product.

Study Identifier	Pediatric Subjects	Number of infusions	Subjects with Adverse Events	Infusions with Adverse Events <sup>a</sup>
ACT 91-11	21	350	2	2
ACT 96-04	22	1893	11	8
IG104	10	541	3	5
IG404	6	298	3	6

<sup>a</sup>Defined as infusions with any adverse event(s), regardless of relationship, that occurred during an infusion or within 72 hours after the end of the infusion.

**Table 10: Summary of Pediatric Information from Clinical Studies**

**Assessor's overall comment on studies conducted with AlphaNine/FIX Grifols/Novix:**

*In total, four studies have been submitted of which two studies (ACT 91-11 and ACT 96-04) included subjects younger than 6 years (total of eighteen subjects in study ACT 91-11 and eight subjects in study ACT 96-04). As both of these studies have not been designed to explore efficacy of Alphanine, no conclusion on the efficacy in this pediatric subgroup can be made.*

*As regards to safety, no new safety signals have been observed during the four studies submitted.*

*The assessor is of the opinion that the statement in the current SmPC of AlphaNine "there are insufficient data to recommend the use of AlphaNine in children less than 6 years of age" is adequate and no new efficacy and safety recommendations can be derived from the submitted studies.*

#### **IV.4.3 Studies conducted with Octanine-F**

The company (Octapharma Pharmazeutika) has provided study reports of following trials with paediatric subjects:

#### **YNE-203: Efficacy and safety in children with Haemophilia B treated with OCTANINE F**

##### Methods

This was a phase III, prospective, open-label, uncontrolled clinical, non-randomised, single arm study.

- Objectives
  - Primary
    - The primary objective of this clinical study was to assess the immunogenicity of OCTANINE F by monitoring the levels of inhibitor (one-stage method, modified Bethesda Nijmegen).
  - Secondary
    - to assess the viral safety by monitoring viral markers (HIV, HAV, HBV, HCV, parvovirus B19) at baseline and every 3-6 months during treatment with OCTANINE F.

- to assess recovery/24 hour survival of FIX.
  - to assess the efficacy of OCTANINE F for prevention and/or treatment of bleeding episodes and in surgical procedures.
  - to assess the tolerability of OCTANINE F by monitoring the occurrence of adverse events.
- Study population /Sample size  
More than twenty subjects were planned and twenty-six subjects successfully completed the study and were analysed.

#### Inclusion criteria

Moderate (FIX:C < 2-5%) to severe haemophilia B (FVIII:C < 2%); age < 6 years; previously treated and previously untreated patients; regular treatment at the corresponding, participating centre; freely given fully informed written consent obtained (parents/guardians).

#### Exclusion criteria

Patients with severe liver or kidney disease; patients with allergic thrombocytopenia, DIC, hyperfibrinolysis or thrombosis; patients where immunogenicity is not evaluable (past or present inhibitor activity, CD4 counts below 400/μl, interferon therapy; participation in another clinical study currently or during the past four weeks.

- Treatments  
OCTANINE F, lyophilised powder and water for injection.

A dose of >25 IU/kg BW was given intravenously for recovery investigations. During a 12-24 month substitution therapy OCTANINE F was given prophylactically, on demand and during surgical procedures according to the clinical needs of the patients and the recommendations of the investigator.

Route of administration: Intravenous as an injection or as continuous infusion (surgical interventions).

Duration of treatment: 12-24 months substitution treatment with at least 50 exposure days.

- Outcomes/endpoints  
Efficacy: Prevention and treatment of bleeding episodes; recovery of FIX during the first 3 months of treatment and at the end of treatment.  
Safety: Immunogenicity (development of inhibitors) investigated at baseline, during the treatment period (frequency dependent on previous FIX treatment status) and at the end of treatment; viral safety testing (HIV, HAV, HBV, HCV, parvovirus B19) at baseline and every 3-6 months of treatment (for negative results at baseline only); determination of ALAT; adverse event monitoring;
- Statistical Methods  
In general, continuous variables were described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. Frequency (absolute and relative counts) tables for qualitative data were provided.

All tables and listings were presented separately by centre as well as for the total study population.

If recovery was assessed, an analysis of variance (ANOVA) and its nonparametric equivalent was performed to test the stability of recovery over time.

The frequency of inhibitor development was to be given within these groups if applicable. An estimate for the incidence rate as well as the p-value for the binomial test was to be given if applicable.

Adverse events were grouped by MedDRA (Version 7) primary system organ class (SOC) and preferred term.

Data on the surgical procedures were only listed and presented in the appendix of this report.

## Results and conclusions

- Recruitment/ Number analysed

Twenty-six (26) eligible Caucasian male patients were enrolled into the study. Two (2) patients dropped out prematurely at their own request. 6 patients were previously untreated (PUPs). 14 patients had less than 50 previous exposure days, 6 patients had more than 50 previous exposure days. 20 patients suffering from severe and 4 patients suffering from moderate haemophilia B completed the study in accordance with the study protocol.

Parameter	Total (N=26)
Age (Months)	37.4 ± 23.5 (5.0 – 70.0)
Height (Cm)	95.2 ± 15.8 (66.0 – 120.0)
Weight (Kg)	14.8 ± 4.4 (7.3 – 21.5)

Table 11: Baseline characteristics of Safety Population

- Efficacy results

The patients received OCTANINE F during 12-24 months for prophylaxis, for bleeds and/or for surgical interventions.

From 1,668 exposure days recorded during the study, 1,065 were for prophylactic reasons and study related, 601 days were for treatment of bleeds and 2 for perioperative treatment.

On average the patients received 39.7 IU OCTANINE F/kg BW/exposure day. This average dose is considered to be within the range of an adequately efficacious FIX product. During the study period the patients needed on average 0.81 exposure days to OCTANINE F/week, again pointing to the efficacy of the investigational product.

From a total of 1684 injections 1631 were rated as excellent, 51 were rated as good and only 2 as moderate in terms of efficacy. Comparative results for the tolerability assessment were 1630 excellent ratings and 54 good ratings.

The efficacy of OCTANINE F during 499 treatment days to stop bleeds which occurred during the study was adequately shown. For 499 bleeds recorded the efficacy was rated

as "very good" in 481 occasions and as "good" in 14 cases (for the remaining 4 cases no information is available).

The severity of 67.3%, 29.8% or 2.8% was graded "minor", "moderate" or "severe", respectively.

On average, a daily dose of 40.27 IU OCTANINE F /kg BW was adequate to stop the bleed on average within 1.28 days. Except in 4 occasions, bleeds needed treatment for not more than 3 days.

The recovery after administration of > 25 IU OCTANINE F/kg BW was investigated during the first 3 months of treatment and at the end of the treatment period (12-24 months). The incremental recovery (geometric mean  $\pm$  s.d., one-stage assay, actual potency) was calculated to  $0.83 \pm 1.38$  and  $0.94 \pm 1.30$  %/IU/kg at the 1st and the 2nd assessment, respectively. These results indicate that, over the period studied, the incremental recovery remains stable in the population studied. The recovery is lower than expected from previous findings in adults. Whether this is a difference in the pharmacokinetic response, a consequence of the different body surface/body weight ratio in children when compared to adults or a consequence of the sparse blood sampling introduced to reduce the burden for the patients remains to be established.

Treatment with OCTANINE F during 7 dental surgeries was assessed as effective in terms of haemostasis and was well tolerated.

Parameter	N	Mean	sd	Min	Median	Max
Average No. of Treatment Days/Bleeding Episode	25	1.28	0.37	0.73	1.15	2.33
Average Dose/Exposure Day (IU)	25	698.26	229.10	500.00	600.00	1250.00
Average Dose/Kg Bw/Exposure Day (IU)	25	40.27	9.98	26.23	39.01	58.10
Average Loading Dose/Kg Bw/Exposure Day (IU)	25	41.14	11.46	26.27	41.03	65.22
Av. Maintenance Dose/Kg Bw/Exposure Day (IU)	22	40.65	12.47	25.45	35.10	76.92

Table 12: Descriptive statistics of treatment days ad dosages in bleeding episodes

- Safety results

In total, twenty-five (25) patients were exposed to OCTANINE F; all 26 patients were included into the safety analysis.

As primary variable for this study the assessment of the immunogenicity of treatment with OCTANINE F was chosen. All patients were tested negative (< 0.4 BU) at study entry and all patients remained negative during the whole study period. This result is especially important for six previously untreated patients enrolled with the highest risk of developing inhibitors.

Ninety-seven (97) adverse events affecting thirteen (13) patients were recorded during the study period. For ninety-four (94) adverse events a causal relationship to the treatment with OCTANINE F was excluded.

The remaining three (3) -seroconversions for parvovirus B19- were rated as unlikely(1) or possibly (2) related to the treatment.

Ten (10) serious adverse events were recorded during the study. For seven (7) of them a causal relationship to the treatment with OCTANINE F was ruled out. The remaining three (3) were the above mentioned seroconversions which are "serious adverse events" per definition in the protocol.

Most importantly, the three (3) patients affected completed the study according to protocol without documented clinical symptoms.

It should be emphasised that 14 of 26 patients were positive for parvovirus B19 at baseline; hence infection with parvovirus B19 can obviously occur independently from the treatment with blood/blood derived products. It should also be mentioned that several patients receiving the same batches of OCTANINE F as those 3 patients showing a seroconversion remained negative throughout the whole study period.

Centre/ Patient	MedDRA Preferred Term	Reason for Serious- ness *	Outcome**	Causality
1/9	Parvovirus B19 Serology Positive	according to protocol	NR/NR	possible
	Enterocolitis	HOSP REQ/PROL	R/R	not related
2/3	Periodontitis	HOSP REQ/PROL	R/R	not related
2/5	Parvovirus B19 Serology Positive	according to protocol	NR/NR	unlikely
2/6	Ketosis	HOSP REQ/PROL	R/R	not related
2/7	Renal Haemorrhage	HOSP REQ/PROL	R/R	not related
2/8	Asthma	HOSP REQ/PROL	R/R	not related
	Periodontitis	HOSP REQ/PROL	R/R	not related
2/9	Parvovirus B19 Serology Positive	according to protocol	NR/NR	possible

2/10	Yersinia Infection	HOSP REQ/PROL	R/R	not related
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\* HOSP REQ/PROL hospitalisation required/prolong; HOSP & LIFE THREAT hospitalisation and life threatening;

\*\* R/R recovered/resolved; NR/NR not recovered/not resolved;

Table 13: Display of Serious Adverse Events

No other safety related findings were observed from the laboratory evaluation.

#### **Assessor's comment:**

*Based on the provided data, children as young as 5 months of age have been included in the study and on average the patients received 39.7 IU OCTANINE F/kg BW/exposure. This dose is basically in line with the recommendation provided in the current SmPC of Octanine-F (...In the study conducted in 25 children under 6 years of age, the median dose administered per exposure day was similar for prophylaxis and treatment of bleeding, i.e. 35 to 40 IU/kg BW....)*

*As regards to safety, in total three serious adverse events possibly related to the treatment (parvovirus B19 serology positive) have been observed. However this is recognised risk and caveat is already stated in section 4.4 of the SmPC.*

*Therefore the assessor is of the opinion that no new efficacy and safety recommendations can be derived from the study YNE-203.*



## **YNE-204: Evaluation of immunogenicity, tolerability and viral safety in haemophilia B patients under therapy with Octanine F**

### **Assessor's comment:**

*According to the clinical overview this was a post-marketing study. Unfortunately, report body has not been found in the submitted dossier. Within the document named "report-body" submitted in Module 5.3.6, only some sections of the study report have been found (specifically only section 14). The MAH is invited to submit full report body document.*

## **V. POST-MARKETING EXPERIENCE**

According to the MAH Octapharma Pharmazeutika All, corresponding PSURs have already been submitted within the MRP (DE/H/0213/01-02); respectively the latest PSUR was submitted within the single PSUR assessment procedure (PSUSA/000/617/201307) therefore no assessment is deemed necessary.

Grifols has commented on the postmarketing surveillance data covering the period from 07th June 1996 to 31<sup>st</sup> October 2013:

### **AlphaNine**

Since the product was first launched in 07 June 1996 to 31 October 2013, a total of 791,776,802 IU AlphaNine have been distributed world-wide. Although the dose should be adjusted according to the patient's individual needs, the number of doses could be calculated assuming an average dose of 40 IU/kg of body weight.

This average takes into account the prophylactic treatment dose which varies from 20 to 40 IU/kg, the treatment for acute haemorrhages which varies from 16-32 IU/kg for minor haemorrhages and between 48-80 IU/kg for life threatening haemorrhages. It has been considered 50 kg as the average body weight, slightly lower than actual adult weight to account for children. Thus, the total number of doses has been estimated using the following equation:

$$\text{No of doses} = \text{IU sold} / (40 \text{ IU/kg} * 50 \text{ kg}) = \text{IU sold} / 2,000$$

Considering this equation and the IU of AlphaNine sold, it can be stated that 395,888 infusions have been performed with the product. A total of 18 patients and 23 infusions associated with suspected adverse reactions have been reported to the manufacturer since the product was first distributed. Therefore, the estimated overall frequency of reported adverse reactions of 1 in 17,212 infusions (0.006%). In the reports of adverse events, there were 5 pediatric patients with a range of age between 1 to 10 years old; 2 adult patients and 11 patients which the age range is unknown. This pattern suggests that there is clinical use of AlphaNine in children of these age groups, in countries where the product is currently licensed. Per age, the distribution of the use of AlphaNine has been estimated in the last PSUR (July 2013) as 20% in patients of 0-14 years; 14% in patients 15-24 years; 40% in patients 25-54 years; 12% in patients 55-64 years and 14% in patients ≥65 years.

<b>System Organ Class*</b>	<b>Pediatric Subjects</b>	<b>Adult Subjects</b>	<b>Unknown Subjects</b>	<b>Age % Pediatric Subjects</b>
<b>Blood and lymphatic system Disorders</b>				
Factor IX inhibition	2	0	0	100
<b>Cardiac Disorders</b>				
Chest discomfort	0	1	0	0
Chest pain	0	0	1	
<b>Gastrointestinal Disorders</b>				
Gastrointestinal haemorrhage	0	0	1	0
<b>General Disorders and administration site conditions</b>				
Drug ineffective	0	0	2	
Influenza like illness	0	0	1	0
Pyrexia	0	0	1	
<b>Immune System Disorder</b>				
Anaphylactic Reaction	1	0	0	
Hypersensitivity	1	0	0	50
Urticaria	0	1	1	
<b>Infections and infestations</b>				
Bacterial sepsis	0	0	1	0
<b>Investigations</b>				
Hepatitis B core antibody positive	0	0	1	0
<b>Nervous system disorders</b>				
Headache	0	0	1	0
VII <sup>th</sup> nerve paralysis	0	0	1	
<b>Renal and urinary Disorders</b>				
Nephrotic syndrome	1	0	0	100
<b>TOTAL</b>	<b>5</b>	<b>2</b>	<b>11</b>	<b>18</b>

\* Terms have been classified under the most relevant SOC considering the coding at case-level, which is not necessary the same as the primary SOC for each event.

**Table 14: Suspected Adverse Events from Spontaneous Reports**

### **Novix/Factor IX Grifols**

Since the product was first launched in 17 February 2004 to 12 July 2013 (the data lock point of the last PSUR), a total of 50,297,000 IU of FIX Grifols/Novix have been distributed world-wide. Although the dose should be adjusted according to the patient's individual needs, the number of doses could be calculated assuming an average dose of 40 IU/kg of body weight. This average takes into account the prophylactic treatment dose which varies from 20 to 40 IU/kg, the treatment for acute haemorrhages which varies from 16-32 IU/kg for minor haemorrhages and between 48-80 IU/kg for life threatening haemorrhages. It has been considered 50 kg as the average body weight, slightly lower than actual adult weight to account for children. Thus, the total number of doses has been estimated using the following equation:

$$\text{No of doses} = \text{IU sold} / (40 \text{ IU/kg} * 50 \text{ kg}) = \text{IU sold} / 2,000$$

Considering this equation and the IU of FIX Grifols/Novix sold, it can be stated that 25,149 infusions have been performed with the product. A total of 1 patients and 1 infusions associated with suspected adverse reactions (ADR) have been reported to the manufacturer since the



product was first distributed, giving the estimated overall frequency of reported adverse reactions of 1 in 25,149 infusions (0.004%). This report corresponded to a patient of 12 years old with infusion site pain (SOC: General Disorders and administration site conditions) and no reports of ADRs coming from adult population were received by the manufacturer. Due to the low number of ADRs received is impossible to conclude a different pattern of tolerance between pediatric and adult population. However considering that the only report of ADR was related to a pediatric patient it can be thought that the product is normally used in children in countries where the product is currently licensed. Per age, the distribution of the use of FIX Grifols/Novix has been estimated in the last PSURs (July 2013) as 15% in patients of 0-14 years; 10% in patients 15-24 years; 46% in patients 25-54 years; 11% in patients 55-64 years and 17% in patients ≥65 years.

## **VI. DISCUSSION ON CLINICAL ASPECTS AND CONCLUSION**

In total, seven MAHs have been requested for submission of paediatric studies; however only two of these submissions were relevant for this pdWS. Non-submission of respective data by other MAHs is understandable and acceptable.

Two MAHs have submitted paediatric data for coagulation factor IX in accordance with Article 45 of the Paediatric Regulation: Grifols and Octapharma Pharmazeutika.

Submitted data from Grifols have not been previously submitted to the regulatory agencies. Submitted studies by Octapharma Pharmazeutika (YNE – 203 and YNE – 204) have been previously submitted within the MRP Re-Baselining DE/H/0213/01-02/IA/036. Submitted on February 28, 2012 and approved on March 14, 2012. Though, no clinical assessment has been done yet.

Assessment has been done separately for each MAH, when in total four studies have been submitted by Grifols whereas Octapharma Pharmazeutika submitted two studies.

As the current SmPC of AlphaNine states that there are insufficient data to recommend the use of AlphaNine in children less than 6 years of age, the main interest during this pdWS would be studies conducted with AlphaNine in children below 6 years. Two (ACT 91-11 and ACT 96-04) out of four studies submitted by Grifols included subjects younger than 6 years (total of eighteen subjects in study ACT 91-11 and eight subjects in study ACT 96-04). As both of these studies have not been designed to explore efficacy of Alphanine, no conclusion on the efficacy in this pediatric subgroup can be made.

As regards to safety, no new safety signals have been observed during the four studies submitted.

The assessor is of the opinion that the statement in the current SmPC of AlphaNine “there are insufficient data to recommend the use of AlphaNine in children less than 6 years of age” is adequate and as no new efficacy and safety recommendations can be derived from the submitted studies no further action is required.

The current SmPC of Octanine F does already provide recommendation for prophylaxis and treatment dosing in children below 6 years of age (*...“In the study conducted in 25 children under 6 years of age, the median dose administered per exposure day was similar for prophylaxis and treatment of bleeding, i.e. 35 to 40 IU/kg BW.”...*). The MAH has provided a discussion concerning data from two studies (YNE-203 and YNE-204).

Concerning the study YNE-203, the assessor is of the opinion that no new efficacy and safety recommendations can be derived from this study. Based on the provided data, children as

young as 5 months of age have been included in the study and on average the patients received 39.7 IU OCTANINE F/kg BW/exposure. This dose is basically in line with the recommendation provided in the current SmPC of Octanine-F (...In the study conducted in 25 children under 6 years of age, the median dose administered per exposure day was similar for prophylaxis and treatment of bleeding, i.e. 35 to 40 IU/kg BW....)

As regards to safety, in total three serious adverse events connected to the treatment (parvovirus B19 serology positive) have been observed in study YNE-203. However this is recognised risk and caveat is already stated in section 4.4 of the SmPC.

Unfortunately, report body of the study YNE-204 has not been found in the submitted dossier. Within the document named “report-body” submitted in Module 5.3.6, only some sections of the study report have been found (specifically only section 14). The MAH is therefore invited to submit full report body document.

Due to the missing data, no final recommendation can be given for the medicinal product Octanine F.

### **Recommendation**

No further action is deemed necessary for the medicinal products AlphaNine/ Novix/ Factor IX Grifols (MAH Grifols).

The MA holder Octapharma Pharmazeutika is invited to submit full report body for study YNE-204, as it has not been found in the submitted dossier and within the document named “report-body” submitted in Module 5.3.6, only some sections of the study report have been found (specifically only section 14). Furthermore, the authorship of the submitted clinical overview should be clarified by the MAH.

## **VII. LIST OF QUESTIONS AS PROPOSED BY THE RAPPORTEUR ON DAY 70 (REQUEST FOR SUPPLEMENTARY INFORMATION) AND COMMENTS RECEIVED FROM OTHER MSs ON DAY 85**

### **Ad Grifols**

N/A

### **Ad Octapharma Pharmazeutika**

The MA holder Octapharma Pharmazeutika is invited to submit full report body for study YNE-204, as it has not been found in the submitted dossier and within the document named “report-body” submitted in Module 5.3.6, only some sections of the study report have been found (specifically only section 14). Furthermore, the authorship of the submitted clinical overview should be clarified by the MAH.

Supportive comments have been received from UK, HU, FR and DE.

## **VIII. ASSESSMENT OF MAH’S RESPONSE**

The Applicant’s response was as follows:

Referring to the Preliminary Paediatric assessment report of Human coagulation factor IX (Octanine) dated January 8, 2015, mistakenly within the document named “report-body” in Module 5.3.6 for YNE-204 only section 14 has been included.

Please find attached the full study report for study YNE-204 (without appendices which have already been submitted) as well as the CV of the author of the submitted clinical overview Dr. Wolfgang Frenzel (Module 2.5).

***Assessment of MAH’s response:***

*The Applicant has clarified the authorship of the clinical overview and has also submitted full study report of study YNE-204.*

*Study YNE-204 was a post-marketing study evaluating Immunogenicity, Tolerability and Viral Safety in Haemophilia B Patients under Therapy with OCTANINE F. This was a multicentre study conducted in four centres in Germany.*

*The primary objective of the study was to assess the immunogenicity of OCTANINE F by monitoring the levels of inhibitor against FIX (modified Bethesda assay) and incremental recovery over time.*

*The secondary objectives of the study were: to survey the viral safety of OCTANINE F in patients by monitoring HIV, HBV, HCV, HAV, parvovirus B19 and ALAT; to assess the efficacy of OCTANINE F for prevention and/or treatment of bleeding episodes and in surgical procedures; and to assess the tolerability of OCTANINE F by monitoring the occurrence of any adverse events.*

*In total, ten patients were enrolled. The observation period for nine patients ranged from 23 to 31 months. One patient was only treated for a surgery – as mild haemophiliac he had usually no need for clotting factor concentrates. two patients have had no previous exposure days before study entry. Seven patients were paediatric patients below 12 years of age.*

*Forty-nine (49) bleeding episodes were treated on 94 exposure days (average treatment duration for haemorrhage: 1.9 days) with a mean dose of 43.5 IU/kg body weight. Three surgeries were performed in 3 patients with an uneventful course. 87 % of all exposure days (945) were prophylactic exposures. 100 % of all injections assessed for efficacy were rated with “excellent” or “good” efficacy.*

*There were two adverse events in one patient. This patient had an ear disorder and bronchitis, both of which were mild in intensity and judged not to be related to OCTANINE F. The ear disorder was serious, as hospitalisation was required.*

*100 % of all injections assessed for tolerability were rated with “very good” or “good” tolerability.*

*No inhibitor was detected. Recovery over time could not be evaluated, as data were not available for 8 of the 10 patients. No drug-induced sero-conversions occurred. All positive post-baseline results were caused by vaccination.*

*Subjective assessments of efficacy indicated that it is efficacious in prophylaxis, surgery and bleeding episodes. There were no hypersensitivity or allergic reactions, no inhibitor development and no thrombotic events. Viral surveillance also did not raise any concerns.*

*It is agreed with the Applicant that the results of this post-marketing study further confirmed that OCTANINE F is efficacious and safe in adult and paediatric patients with Haemophilia B. No new efficacy and/or safety recommendations can be derived from the study YNE-204.*

## **IX. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION**

### **Overall conclusion**

The MAH (Octapharma Pharmazeutika) has adequately addressed the questions raised by the Rapporteur on Day 70. There are hence no remaining issues.

Based on the review of the submitted data, the Rapporteur agrees with the MAHs that no further action is deemed necessary for the medicinal products AlphaNine/ Novix/ Factor IX Grifols (MAH: Grifols) and Octanine F (MAH: Octapharma Pharmazeutika).

### **Recommendation**

No further action required.