OPTIMAL USE OF COAGULATION FACTORS & IMMUNOGLOBULINS MEETING

(Kreuth III)

26-27 April 2013

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Clinical Safety Benefits

**in terms of thromboembolic effect**

**Thromboembolic effects (TEE) with Tegeline®**
- From 2001 to 2011: a very infrequent AE

**Thromboembolic effects (TEE) with ClairYg®**
- In 2010 and 2011: a very infrequent AE

**in terms of haemolysis**

**Haemolysis with Tegeline® per 1000 exposed subjects:**
- A very infrequent AE

**Haemolysis with ClairYg®:**
- A very infrequent AE

**Conclusion**

Due to the complex method of production and various processes used by different manufacturers, different IVIG preparations may exhibit meaningful differences in terms of safety.

Mastering critical steps in the process leads to improved clinical safety for the patients.

Systematically applying the most predictive and reproducible in-vitro tests is recommended (e.g. Flow cytometry for anti-A/B HA, TGA for procoagulant fractions)

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**Procoagulant activity**

- **FXI and FXII quantification in five liquid IVIg products** by Elisa assay

**Analytical results**

- **TGA: undetectable for Tegeline® and ClairYg®**
- **Anti-A & anti-B haemagglutinins detection**
- **Specific lysis (OD) of red blood cells from A, B, AB and O Rh(D) negative groups induced by five liquid IVIg products**

**Anti-A and anti-B haemagglutinin detection**

**Flow cytometry for anti-A & anti-B**

- Specific lysis of red blood cells from A, B, AB and O Rh(D) negative groups induced by five liquid IVIg products

**Direct haemagglutination EP assay:**
- **significant variability**

International Collaborative Study to evaluate candidate reference reagents for standard haemagglutination testing for anti-A and anti-B in IVIG products Vox Sang. 2009 Apr 27, Thorpe S. J. et al.

This study demonstrates up to 16-fold variability in haemagglutination titre between laboratories.

Appropriate reference reagents for anti-A and anti-B in IVIG are needed, first, to control testing methodology; second, to define limits where these are applicable; and third, to facilitate the identification of higher titre batches

**Need for selection and harmonisation among fractionaters on technical assays**

**Assay reproducibility for anti-A anti-B haemagglutin**

**Detection with Flow cytometry**
Clinical trial evaluating the pharmacokinetics, efficacy and safety of a new human plasma-derived polyvalent intravenous immunoglobulin product (NewGam 10%) in patients with new primary immunodeficiency disease (PID)

Introduction

NewGam 100 mg IgG (10%) is the development name of a new human normal immunoglobulin (IVIG) product from Octapharma. This novel high-purity glycine-stabilised IVIG is manufactured using various precipitation and chromatography techniques for the harvesting and purification of IgG, and the process comprises two dedicated steps: for pathogen safeguarding (solvent/detergent treatment) and small-particle nanofiltration at extreme pH.

The clinical development of this product follows the relevant guidelines issued by the European Medicines Agency [EMA/CHMP/543/2003 Rev.2. Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). 22 July 2010.], and we hereby present the key findings from the first clinical trial in patients suffering from PID. The study was conducted in accordance with the ‘International Conference on Harmonisation – Good Clinical Practice’, and the primary objective of this prospective, open-label, non-controlled, non-randomised, multicentre phase III study was to assess the efficacy of NewGam in preventing serious bacterial infections (SBIs). A determination of the pharmacokinetic (PK) profile and an evaluation of NewGam’s safety profile were among the secondary objectives.

Results

One child each was excluded from the PK and efficacy analyses. Thus, the per-protocol population in both cases comprised 50 patients. The results from the PK evaluation in these 50 subjects can be seen in Figure 1 and Table 1. The detailed IgG3 total Cmin, Cmax, and half-life (t1/2) values for the adult patient portfolio (n=20) can be seen in Table 2, and the plasma IgG total trough level by infusion through the study for all subjects (n=50) is shown in Figure 2. It is clear from these results that there is a trend towards a shorter t1/2 for the subcu subjects (IgG), and than the ones demonstrated for the other two subcutanea busscas, but all the results were in the expected range and in line with the figures reported for other new IgGXs launched during the last decade (data not shown).

Patient and infusion details

The full-analysis population comprised 51 previously immunoglobulin treated patients with either common variable immunodeficiency (n=26, 51.0%), or X-linked agammaglobulinaemia (n=15, 71.4%), and it was enrolled by four European and seven US centres. The study included 33 (64.7%) men and 18 (35.3%) women. Thirteen (25.5%) of the subjects were children in the age range 3-11 years, 12 (23.5%) were adolescents (12-15 years) and 26 (51.0%) were adults (16-75 years). The median age was 17 years (range: 2-65), and the median body weight of the patients was 65 kg (range: 13-141). The corresponding numbers for height and body mass index were 163 cm (range: 90-191) and 22 kg/m² (range: 15-52), respectively.

Table 1. Median half-lives for total per-protocol population (n=50)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG total</td>
<td>39.7 (1.4)</td>
</tr>
<tr>
<td>IgG1</td>
<td>38.6 (0.5-4.7)</td>
</tr>
<tr>
<td>IgG2</td>
<td>38.0 (3.7-4.5)</td>
</tr>
<tr>
<td>IgG3</td>
<td>28.2 (3.7-4.5)</td>
</tr>
</tbody>
</table>

Table 2. Pharmacokinetic details for adult full-analysis population (n=50)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± standard deviation Median (range) (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG total</td>
<td>3.13 ± 1.7 2.4 (1.0-7.0)</td>
</tr>
<tr>
<td>IgG1</td>
<td>3.13 ± 1.7 2.4 (1.0-7.0)</td>
</tr>
<tr>
<td>IgG2</td>
<td>3.13 ± 1.7 2.4 (1.0-7.0)</td>
</tr>
<tr>
<td>IgG3</td>
<td>3.13 ± 1.7 2.4 (1.0-7.0)</td>
</tr>
</tbody>
</table>

Figure 1. Average plasma IgG total trough level for full-analysis population (n=50)

Figure 2. Average plasma IgG total trough level for full-analysis population (n=50)

Table 3. Efficacy for per-protocol population (n=50)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>50</td>
</tr>
<tr>
<td>Patient exposure</td>
<td>49.2</td>
</tr>
<tr>
<td>Patients with serious bacterial infections</td>
<td>3</td>
</tr>
<tr>
<td>Patients with serious bacterial infections/patient exposure year</td>
<td>0.06 (0.01-0.62)</td>
</tr>
</tbody>
</table>

Table 4. Adverse events (AEs) occurring in >5% of the patients during infusion or within 72 hours after the end of infusion of NewGam

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of patients with AEs (%) of patients (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>9 (17.6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7 (13.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (5.9)</td>
</tr>
</tbody>
</table>

Figure 3. Average (range) AE ratio by patient for eight FDA US licensed IgG5s® vs. NewGam, representing the value 1.0

Figure 4. Average (range) AE ratio by infusion for FDA US licensed IgG5s® vs. NewGam, representing the value 1.0

Conclusions

NewGam has demonstrated a PK profile, as well as an efficacy performance, equivalent to other IgGs developed and commercialised during the last 10 years. With only a few AEs revealed both per patient and infusion, NewGam may display a very positive safety feature over some of the currently marketed IgGs.
Introduction

Von Willebrand factor (VWF) is a multimeric adhesive glycoprotein, with a dual function in hemostasis. It mediates platelet adhesion at sites of vascular injury, which is necessary for primary hemostasis, and stabilizes factor VIII (FVIII) in the circulation. The pathophysiological significance of the different biological functions of this protein is demonstrated by von Willebrand’s disease (VWD), the most common hemorrhagic disorder, affecting 1% of the population. Approximately 1% of patients with VWD have severe VWF deficiency resulting in defective platelet adhesion, secondary FVIII deficiency, and a prolonged bleeding time. These patients can only be treated effectively with VWF concentrates. A variety of plasma-derived concentrates (with or without FVIII) are available, and used for the treatment of VWD. The development of a recombinant VWF (rVWF), manufactured and formulated in the absence of animal or human plasma proteins, may increase the safety of the treatment of von Willebrand’s disease in the management of bleeding episodes, surgery and prophylaxis.

Production of rVWF

Recombinant VWF is co-expressed with recombinant FVIII in CHO cells. The fermentation line for rVWF-PFM (ADVATE®) manufacturing process can be used for the manufacture of rVWF. The column flow-through of the FVIII capture step, containing pro-VWF, is processed by the FVIII-VWF co-expression process to produce rVWF. After DNA removal, rVWF is solvent-detergent (SD) treated and purified by two further chromatography steps to a purity of more than 95%. Fermentation for rVWF and recombinant FVIII in CHO cells is performed under serum-free conditions. The starting material for rVWF is an intermediate of the commercial rFVIII product ADVATE®. The column flow-through of the FVIII capture step, containing pro-VWF, is further treated to produce rVWF.

Structural and Functional Characterization

Key Product Characteristics

An intermediate from the rFVIII-PFM (ADVATE®) manufacturing process can be used as a source material for a rVWF product.

- Functional activity of rVWF shown by the binding capacity for FVIII and VWF:RCo activity were similar to or higher than the in-house purified or commercial pdVWF products.
- rVWF has an intact multimer pattern.
- High-resolution multimer analysis demonstrated the lack of satellite bands, similar to plasma-derived human VWF.
- These satellite bands are formed simultaneously with the disappearance of high molecular-weight multimers upon incubation with ADAMTS13.
- The carbohydrate pattern of rVWF was similar to that of plasma-derived VWF with respect to terminal siacid, indicating an intact glycosylation.

BAX 111 Clinical Study

Phases 1 and 2: (ClinicalTrials.gov Identifier: NCT00816660)
- Multicenter, controlled, randomized 3-step dose escalation study
- Evaluation of pharmacokinetics, tolerability and safety in 32 VWD patients
- Study successfully completed

Phases 3 and 4: (ClinicalTrials.gov Identifier: NCT01410227)
- Treatment of bleeding episodes for 6M (rVWF 50IU/kg)
- Evaluation of pharmacokinetics, tolerability and safety
- Study planned to be completed 2013
BAX 326, a recombinant human factor IX drug candidate
Baxter BioScience, Vienna, Austria

Introduction
Human coagulation factor IX (FIX) is a vitamin-K-dependent coagulation factor whose absence or dysfunction causes hemophilia B. Treatment of hemophilia B is based on replacement therapy using highly purified FIX concentrates. Baxter has developed BAX 326, a recombinant factor IX drug candidate for treating hemophilia B patients that is produced in a CHO cell-line using a serum- and protein-free fermentation technology. The purification process avoids the use of immune-affinity chromatography and includes two viral reduction steps. The final drug product is formulated in the absence of proteins of animal or human origin. BAX 326 resembles commercially available rFIX in most characteristics with the exception of a significantly lower FIXa content, which might improve standardization compared with commercial rFIX products.

Goal and current status
- Development of a recombinant FIX molecule for treatment and prevention of bleeding in patients with hemophilia B
- Expression in CHO cells
- Plasma-albumin free manufacturing process
- Pre-clinical and toxicological studies established that BAX 326 demonstrates comparability with licensed rFIX product
- A pivotal global phase 1/3 clinical trial proceeds to evaluate the pharmacokinetics, efficacy, safety and immunogenicity of BAX 326
- Biologicals License Application (BLA) under review by regulatory authorities

Key Product Characteristics
- Full functionality in hemostasis could be shown for BAX 326 for:
  - affinity of FIX to phospholipids - assembly of the tenase complex on a negatively charged surface
  - the rate of FXa and FVIIa-mediated FIX activation - initiation and amplification of the coagulation cascade
  - TGA - assessment of the overall hemostatic potency
- Very low levels of pre-activated FIX found in BAX 326
- Similar glycosylation pattern of BAX 326 and comparator product
- Activation kinetics and affinity to phospholipid of BAX 326 were similar to those of commercial rFIX
- Thrombin generating capacity similar to that of comparator FIX products

Determination of FIXa content in BAX 326
- Pre-activation of FIX may occur during the purification process
- The amount of pre-activated FIX in FIX end-product needs to be tightly controlled

Detection of FIXa in FIX products with a FIXa chromogenic assay

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>FIX Activity (clotting assay) (IU/mL)</th>
<th>FIXa Activity (chromogenic assay) (IU/mL)</th>
<th>FIX pre-activation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of 100 lots (preclinical production, n=10)</td>
<td>0.88</td>
<td>0.88</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean of 10 lots (clinical production, n=10)</td>
<td>0.97</td>
<td>0.97</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean of 200 determinations (n=200)</td>
<td>0.25</td>
<td>0.25</td>
<td>0.05</td>
</tr>
</tbody>
</table>

- The level of pre-activated FIX as shown as % of FIX activity was consistent in all BAX 326 lots tested
- Very low levels of FIXa are not likely to induce adverse events in clinical settings

Detection of FIXa in FIX products with a sensitive FIXa generation assay
- FIXa levels were measurable in the licensed rFIX product, and to a lesser extent in a commercially available pdFIX, but FIXa was undetectable in BAX 326 lots

BAX 326: Status of Clinical Development
- Immunine (pd FIX concentrate, Baxter) pre-treatment study: Completed, final study report in preparation (ClinicalTrials.gov Identifier: NCT01128881)
- Pivotal Phase 1/3 Study: PK, safety and efficacy evaluation in PTPs>12a: (ClinicalTrials.gov Identifier: NCT01174446)
  - Study completed
  - Data presented @ ASH 2012, abstracts accepted for ISTH 2013
- Continuation Study: safety, immunogenicity and hemostatic efficacy: (ClinicalTrials.gov Identifier: NCT01286779)
  - Ongoing until BAX326 is licensed in subject’s countries
  - > 70 subjects as of 10 April 2013
- Surgery Study: efficacy and safety in surgical settings (major and minor surgeries): (ClinicalTrials.gov Identifier: NCT01507896)
  - Interim report including 10 major surgeries completed, runs parallel to Continuation study, abstract accepted for ISTH 2013
- Pediatric Study: PK, safety and efficacy evaluation in PTPs<12a:
  - Ongoing (ClinicalTrials.gov Identifier: NCT01488994)

Presented at the EUROPEN SYMPOSIDUM: Optimal use of clotting factors and immunoglobulins
26-27 April 2013, Wildbad Kreuth, Germany
Introduction

Human coagulation factor VII (FVII) is a vitamin-K-dependent protein with a molecular weight of 50 kDa. Activation of FVII occurs by a single cleavage resulting in two disulfide-linked peptide chains. The therapeutic utility of rFVIIa is based on its capacity to trigger hemostasis independently from factor VIII and factor IX even in the presence of inhibitors against these proteins. Baxter has developed BAX 817 a recombinant FVIIa (rFVIIa) that is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line. No materials of human or animal origin are employed in the manufacture, purification, or formulation of the final product, thus reducing the risk of transmission of adventitious agents. The growth medium is a chemically defined medium, and the downstream process does not use monoclonal antibodies for the purification of rFVIIa.

Key Product Characteristics

- Biochemical features were similar in all test systems between BAX 817 and the comparator product
  - Overall hemostatic potency of rFVIIa
    - Thrombelastography
    - Thrombin generation assay
  - TF-binding capacity of rFVIIa
    - TF-bearing cell line
    - Dual activated platelets
  - Susceptibility of rFVIIa to inhibition by TFPI (data not shown)
  - Reproducibility shown within preclinical and clinical lots

Baxter’s Development Program for BAX 817

Scope:
Development of a recombinant FVIIa produced by a high yield CHO expression system with an animal-component free manufacturing process

Target indication:
Treatment of bleeding in Hemophilia A and B patients with inhibitors

Thrombelastography and thrombin generation assay as parameter for overall hemostatic potency

Thrombin (nM) vs FVIIa [ng/mL]

- No significant differences between the preclinical and clinical lots in the three TEG parameters R, K, and angle were observed.
- The preclinical and clinical lots were not significantly different to the comparator lots.
- No statistically significant difference in dose-response of rFVIIa-mediated thrombin generation in the FVIII inhibitor plasma between the preclinical, clinical and comparator lots.

BAX 817: Status of Clinical Development

Phase 1 Study: (WHO: CTRI Main ID: CTRI/2011/06/001798)
- Cross-over with commercial rFVIIa at 90 µg/kg per dose
- Dose levels: 45, 90, 180 and 270 µg/kg per dose
- Results: A single infusion of rFVIIa was well tolerated at all dose levels. PK/PD data demonstrated that BAX 817 has a similar profile to commercial rFVIIa
- Completed (43 subjects)

Phase 3 Pivotal Study: (ClinicalTrials.gov Identifier: NCT01757405)
- Evaluate the safety and efficacy of BAX 817 in the treatment of bleeding episodes by an on-demand regimen in hemophilia A or B patients with FVII or FIX inhibitors.
- Parallel 2 Arm: 3x90 or 1x270 µg/kg treatment regimen per bleed with a 6 month treatment period per subject (home treatment)
- Outcomes measured per bleeding episode through 24 hours: # doses needed, pain, mobility, subject efficacy assessments (4 point scale)
- Other outcomes: Quality of Life, antibodies to FVII (binding and/or inhibitory)
- Study started Q2/2013 (34-40 subjects planned)

Presented at The EUROPEAN SYMPOSIUM, Optimal use of clotting factors and immunoglobulins 26-27 April 2013, Wildbad Kreuth, Germany
BAX 855, a PEGylated rFVIII product with prolonged half-life

Baxter BioScience, Vienna, Austria

Introduction

Baxter Innovations GmbH (Vienna, Austria) and Nektar Therapeutics (Huntsville AL) have developed BAX 855, a PEGylated form of Baxter’s recombinant FVIII (rFVIII) with prolonged half-life. Recombinant FVIII is expressed in Chinese hamster ovary cells by a plasma-albumin-free cell culture method and is the active substance in Baxter’s licensed product ADVATE™. The conjugation process for preparing BAX 855 uses proprietary stable PEGylation developed by Nektar Therapeutics. Similar technology has been successfully used for licensed and marketed PEGylated drug products including proteins and peptides in clinical use. After PEGylation the product is purified by use of a procedure that is based on the manufacturing process for ADVATE™.

PEGylation chemistry

- BAX 855 is a PEGylated recombinant full-length human rFVIII for the treatment of hemophilia A
- BAX 855 is derived from the parent, licensed rFVIII product, ADVATE™
  - ADVATE™ protein is PEGylated with a 20-kDa branched PEG polymer
  - Amine coupling chemistry is used for PEGylation of rFVIII in BAX 855
    - Standard reaction in protein chemistry
    - Results in specific modification

Manufacturing process of BAX 855

The BAX 855 manufacturing process consists of an ion exchange chromatography step for changing the product matrix and increasing the protein con-centration of full-length rFVIII. The rebuffered rFVIII is used for the chemical reaction with the PEG reagent. The protein conjugate is purified by another ion exchange chromatography, followed by an ultra/filtration step. The BAX 855 final drug product is formulated by lyophilization of the BDS supplemented with formulation components without any additives of animal origin. The lyophilized product contains only rFVIII protein coupled to PEG for reconstitution with sterile Water for Injection prior to intravenous infusion.

Key Product Characteristics

- BAX 855 is a PEGylated derivative of ADVATE™
- BAX 855 can be manufactured in industrial scale, with a good batch to batch consistency
- BAX 855 retained the specific activity of FVIII, indicating that PEGylation does not have an impact on the hemostatic function of rFVIII

Large scale manufacturing of BAX 855 (BDS data)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (n=5)</td>
<td>6039</td>
<td>91</td>
<td>2.2</td>
</tr>
<tr>
<td>SD</td>
<td>831</td>
<td>11</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Specific activities (ratio FVIII act./total protein) were determined by a FVIII chromogenic assay and a protein fluorescence assay in comparison with rebuffered rFVIII starting material.

Data show that BAX 855 can be prepared in industrial scale
- PEGylation is specific and highly reproducible
- BAX 855 has a specific activity similar to that of rFVIII in ADVATE™
- PEGylation degrees are in the narrow range of 2 to 3 mols PEG / mol rFVIII

Characterization of BAX 855

Functional characterization

- BAX 855 fully retained its hemostatic potency compared with ADVATE™

Pharmacology & Toxicology

- Macaques: generally well tolerated; no adverse test-item related findings
- Rabbits: thrombogenicity as low as ADVATE
- Escalating dose toxicity in macaques: no observed adverse effect level (NOAEL) 1500 IU/kg (single dose)
- Repeated dose toxicity in rats and macaques: NOAEL 700 IU/kg
  - Large safety margin

Immunogenicity

- Comparative immunogenicity studies in mice and macaques revealed a similar immunogenicity profile compared to ADVATE

Pharmacokinetics & Pharmacodynamics

- > 1.5x prolonged MRT (Mean Residence Time) in hemophilic mice and macaques compared to ADVATE
- Primary pharmacodynamics (efficacy)
  - Clinically relevant prolonged (1.5x) efficacy shown in 2 hemophilia A mouse models in comparison to ADVATE

BAX 855 Clinical Study

Phase 1 Study Design: (ClinicalTrials.gov Identifier: NCT01599819)

BAX 855 (PEGylated Recombinant Factor VIII): A phase 1, prospective, open label, cross-over, dose-escalation study in previously treated patients with severe (FVIII < 1%) hemophilia A

- Assess tolerability and safety post single dose treatments of BAX 855 in PTPs with severe hemophilia A
- Determine the pharmacokinetic (PK) parameters of BAX 855 compared in crossover with ADVATE at the same single dose level
- Evaluate the impact of anti-PEG antibodies on PK parameters
- Estimate the dose necessary to maintain a factor VIII (FVIII) level of ≥ 1% for at least 5 days
- Phase 1 completed

Presented at the EUROPEAN SYMPOSIUM, Optimal use of clotting factors and immunoglobulins
28-27 April 2013, Wildbad Kreuth, Germany
Clinical Development Program for BAY 94-9027, a Long-Acting PEGylated B-Domain–Deleted Recombinant Factor VIII for Patients With Hemophilia A

Susan Radke,1 René Walsch,2 Benedikt Kerschgens,3 Mel Lederman,3 Dawn Deism,3 Bitak Bassiri,3 Anita Shah,3 Lisa A. Michaels3
1Bayer Pharma AG, Berlin, Germany; 2Bayer Pharma AG, Leverkusen, Germany; 3Bayer HealthCare Pharmaceuticals, Montville, NJ, USA

INTRODUCTION

• Factor VIII (FVIII) prophylaxis reduces bleeding frequency and joint damage in children and adolescents with hemophilia A.7
  – Prophylaxis is the standard of care for children and adolescents with severe hemophilia.1
  – Adoption of and adherence with prophylaxis is suboptimal because of challenges such as various access issues in children, the time-consuming nature of prophylaxis, and a requirement for frequent infusions.1
  – A longer-acting FVIII product may help overcome barriers associated with prophylaxis.

• BAY 94-9027, a B-domain–deleted recombinant FVIII (rFVIII) that has undergone site-directed modification with a 45- to 60-kDa polyethylene glycol (PEG) molecule (Figure 1), was designed as a long-acting FVIII product for prophylaxis and on-demand treatment of bleeds in patients with hemophilia A.
  – BAY 94-9027 demonstrated a prolonged half-life (t½) of 20 days and a prolonged efficacy of 36 weeks (Figure 2).
  – No FVIII inhibitors, anti-PEG antibodies, or anti-BAY 94-9027 antibodies were observed during the study.

• A phase 2/3 study of BAY 94-9027 in adults and adolescents is ongoing, and phase 3 studies in previously treated and previously untreated children with severe hemophilia A are forthcoming.
  – The BAY 94-9027 clinical development program will determine whether the longer t½ of BAY 94-9027 will allow for less frequent dosing.

METHODS

Study Design

• This was a multicenter, nonrandomized, open-label, parallel-group study in which BAY 94-9027 was administered to 2 cohorts of patients over 8 weeks (Figure 2).

Phase 1 Study

• This was a multicenter, nonrandomized, open-label, parallel-group study in which BAY 94-9027 was administered to 2 cohorts of patients over 8 weeks (Figure 2).

Phase 2 Study

• This was a multicenter, partially randomized, open-label, parallel-group study being conducted in North and South America, Europe, the Middle East, and Asia.

• This study has 2 parts:
  – Part A: on-demand and prophylactic treatment with BAY 94-9027 in 3 different dosing intervals (2 infusions per week, 1 infusion every 5 days, or 1 infusion every 7 days) for ≥50 EDs and ≥6 months; prophylaxis will be administered in 3 different dosing regimens (Table 1).
  – Part B: optional open-label, noncontrolled, single-arm study of safety and efficacy of BAY 94-9027 in major surgery.
  – Patients requiring major surgery who enrolled in part A and other patients meeting inclusion/exclusion criteria for part A will be included.

• A longer-acting FVIII product may help overcome barriers associated with prophylaxis.

• BAY 94-9027 demonstrated a prolonged half-life (t½) of 20 days and a prolonged efficacy of 36 weeks (Figure 2).

Outcomes

• Key efficacy and safety outcome measures are shown in Table 2.

RESULTS

Phase 1 Study

Patients

• 14 patients were enrolled and completed the protocol (7 per cohort).
  – The mean age was 36 years (range, 21–58 years).

Clinical Pharmacology

• BAY 94-9027 had an elimination t½ of approximately 18 hours after single and multiple dosing (rFVIII t½, approximately 15 hours).
  – Pharmacokinetic parameters with BAY 94-9027 were similar after single and multiple doses.
  – Dose proportional increases were observed in plasma concentrations of BAY 94-9027 at doses of 35 and 62.5 IU/kg.

Safety

• Treatment with BAY 94-9027 was well tolerated.
  – No FVIII inhibitors, anti-PEG antibodies, or anti-BAY 94-9027 antibodies were observed at the end of the 8-week dosing.
  – There were no serious adverse events (SAEs) related to the study drug, and there were no serious AEs related to BAY 94-9027.

CONCLUSIONS

• Phase 1 data showed that BAY 94-9027 was well tolerated and had an extended elimination t½ in patients with severe hemophilia A.

• A phase 2/3 study of BAY 94-9027 in adults and adolescents is ongoing, and phase 3 studies in previously treated and previously untreated children with severe hemophilia A are forthcoming.

• The BAY 94-9027 clinical development program will determine whether the longer t½ of BAY 94-9027 will allow for less frequent dosing.

REFERENCES


DISCLOSURES

SR, RW, and BK are employees of Bayer Pharma AG. ML, DD, BB, AS, and UM are employees of Bayer HealthCare Pharmaceuticals.

ACKNOWLEDGMENTS

Study funding provided by Bayer Pharma AG (Leverkusen, Germany). We would like to thank. Jane A. Phillips, PhD, from Complete Healthcare Communications, Inc., for medical writing assistance, which was fully funded by Bayer HealthCare Pharmaceuticals.
Introduction

FACTOR X is a high purity factor X concentrate developed for the treatment of hereditary factor X deficiency. FACTOR X for the treatment of this very rare disease has received Orphan Drug Designation in EU and USA.

Clinical Study Design

January 2008: parallel scientific advice was requested from EMA and FDA to inform the FACTOR X clinical development programme. The resulting advice from the two agencies was constructive, but differed with regard to patient numbers and follow-up required to secure marketing authorization.

As the clinical development for orphan drug products cannot sustain individual trials for licensing in different territories, a consolidated protocol was developed. This provided for interim and final analyses of data to satisfy the requirements of different regulatory agencies.

Two clinical trials were planned to collect the data required by the two agencies:

- A pharmacokinetic, safety & efficacy study in 16 patients with severe or moderate FX deficiency (basal FX:C <5 IU/dL).
- A surgery study in 10 procedures in 5 patients with severe to mild FX deficiency (basal FX:C <20 IU/dL).

Results to date from the pharmacokinetic, safety & efficacy study and surgery study are presented here. Collection of further data is ongoing.

Efficacy of FACTOR X in Treating Bleeds

Methods

Recommended dose for replacement therapy was 25 IU/kg FACTOR X, to be repeated as necessary to achieve haemostasis. Efficacy was defined according to the number and timing of doses, depending on whether it was an overt, covert or menorrhagia bleed.

Results

To date >180 bleeds in 15 subjects have been treated with FACTOR X. Of 96 bleeds included in the interim analysis, the majority required a single infusion of FACTOR X (Figure 1). In an interim analysis on the first 50 assessable bleeds to be analysed, FACTOR X was rated as ‘excellent’ or ‘good’ in treating 96% of bleeds (Figure 2). Analysis of the remaining bleeds is ongoing and will be reported in the final analysis.

Figure 1 Number of infusions of FACTOR X given to treat a bleed

Figure 2 Assessment of efficacy of FACTOR X in treating a bleed

Safety of FACTOR X in Factor X Deficiency

Adverse events: 6 adverse events were considered possibly related to FACTOR X:
- Infusion site erythema (2 cases), fatigue (2 cases), infusion site pain, back pain. None were severe or serious.
- >50 post-dose inhibitor tests in 15 subjects have been negative for the FX inhibitor screening and FX Nijmegen-Bethesda inhibitor assay.

Serology: No seroconversions for HAV, HBV, HCV, HIV or Parvovirus B19 in seven subjects tested at end of study.

Thrombogenicity: Significant inter-patient variability for TAT, D-dimer and F1+2, which are known to be sensitive to blood draw and sample handling technique. There was no consistent pattern to the results, and no clinical signs or symptoms of a thrombogenic response to FACTOR X was observed.

Considerations from our experience

Several challenges can delay access to orphan drug products by patients with rare diseases:

- Clinical Trial Protocol Development
  - Parallel scientific advice by EMA and FDA may differ, requiring lengthy iterations of a consolidated protocol to address all expectations.
  - Any remaining requirement for an extended data set from a small patient group may still delay drug availability in one territory compared to another.

- Investigator Participation
  - The sparse patient population needs investigators at diverse sites, many enrolling only one patient.
  - The logistical and bureaucratic burden for such a small study could discourage investigators, given its duration and follow-up requirements.

Patient Recruitment

- Market research did not fully reflect patients’ treatment regimens, so many potential subjects were not eligible, or were unwilling to interrupt their existing treatment patterns.
- Some patients withstood consent, due to the clinical and domestic impact of the study.

Efficacy Data Acquisition

- Efficacy data are dependent on unpredictably, sporadic events (treatment of bleeding episodes and surgical interventions with product) which significantly extends the study duration.
- Surgery data requires the prospective set-up of investigation sites, anticipating where patients may need eligible procedures (different bleeding patterns in factor X deficiency reduces reliance on elective orthopedic surgeries which are common to surgery studies in hemophilia A or B).
- Eligible procedures can be lost if contracts are incomplete, while maintaining other costly sites where no patient presents for surgery.

Conclusions

- FACTOR X was efficacious in treatment of 50 bleeding episodes
- FACTOR X was efficacious in the control of blood loss during and after major and minor surgical procedures.
- FACTOR X pharmacokinetics matched published data.
- FACTOR X was well-tolerated in 15 patients.
- Development and licensing of products such as FACTOR X for the treatment of very rare diseases requires the active co-operation of sponsor, regulators, investigators and patients.

Pharmacokinetics of FACTOR X in Factor X Deficiency

Methods

25 IU/kg FACTOR X was administered to subjects at baseline and a repeat PK assessment. Plasma samples were assayed for FX:C using the one-stage clotting assay at a central laboratory.

Results

Figure 3 Mean pre-dose-adjusted plasma concentrations of FX:C at baseline and repeat PK assessment

<table>
<thead>
<tr>
<th>Time post-dose (hour)</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>96</th>
<th>120</th>
<th>144</th>
</tr>
</thead>
<tbody>
<tr>
<td>FX:C (IU/mL)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 1 Pharmacokinetic Parameters of FACTOR X

<table>
<thead>
<tr>
<th>Parameters</th>
<th>geometric mean</th>
<th>CV (%)</th>
<th>median</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>13</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Incremental recovery</td>
<td>2.22</td>
<td>2.21</td>
<td>2.32</td>
</tr>
<tr>
<td>Half-life</td>
<td>50.9</td>
<td>24.8</td>
<td>50.0</td>
</tr>
</tbody>
</table>

* All values are presented here. Collected further data is ongoing.

FACTOR X and Historical Data: Use of Factor X in-health volunteers.

Safety Data: C. Ostermann et al. (2007) Pharmacokinetic and efficacy study and surgery study are presented here.

Figure 4 Inclusion of further data is ongoing.

Clinical Experience with New Orphan Factor X

P. Feldman1, I. Lloyd1, M. Norton1, S. MacDonald2, T. Aldwickle1 and the FACTOR X investigator group1

1 Bio Products Laboratory Ltd., Elstree, UK; 2 Department of Haematology, Addenbrooke’s Hospital, Hills Road, Cambridge, UK
Clinical studies with Nanogam (50 mg/ml intravenous immunoglobulin product)

Karin Velthove PharmD PhD1, Ilona Kleine Budde PhD1, Rachel van Beem PhD1, Paul Strengers MD1

1 Sanquin Blood Supply Foundation, Division Plasma Products, Medical Department, Amsterdam, The Netherlands

Sanquin Blood Supply Foundation, Amsterdam, The Netherlands collects blood and plasma, and provides blood components, cellular products, plasma derived medicinal products, and reagents. It promotes all aspects of transfusion medicine. Sanquin also performs basic and translational research in immunology, hematology, inflammation, virology and coagulation, offers specialised diagnostic services, and provides education and training.

IgG Subclass study - ongoing

Treatment in patients with recurrent infections and IgG subclass deficiency, and/or deficient anti-polysaccharide antibody response

Primary objective: To assess the effectiveness of Nanogam in comparison with the prophylactic use of oral antibiotics

Population: adults and children ≥ 5 years with IgG subclass deficiency and/or anti-polysaccharide antibody deficiency and with recurrent respiratory infections; n ≥ 40 patients

Design: Randomized, open label cross-over study; treatment period 2x12 months, in between 3 months wash-out.


Inclusion closed: November 2012

Investigators: members of the Dutch Inter-university Working Party for Immune Deficiencies

Sponsor: Sanquin

Parvo B19 study - ongoing

IVIG in idiopathic cardiomyopathy and endomyocardial Parvovirus B19 persistence

Primary objective: To investigate whether IVlg therapy on top of conventional heart failure may improve cardiac systolic function as assessed by quantitative echocardiography (LVEF, LVEDD, LVESD).

Population: patients with chronic "idiopathic" cardiomyopathy despite optimal standard heart failure treatment and a significant PVB19 viral load in their hearts; n=50

Design: Single-centre double-blind, randomized placebo-controlled clinical trial (6 month follow-up)


January 2013: 26 patients included

Investigators: Department of Cardiology, Academic Hospital Maastricht

Sponsor: Sanquin

SID-GBS study - ongoing

Second IVIG Dose in Guillain Barré Syndrome patients with poor prognosis

Primary objective: To determine whether a second IVIg dosage in GBS patients with a poor prognosis improves functional outcome after 4 weeks.

Population: GBS patients ≥12 years with indication for IVIg treatment. Randomization patients with poor prognosis: second IVIg course (Nanogam) or placebo (Albuman 4%). N=174 (N =88 with poor diagnosis)

Design: Multicentre double-blind, randomized, placebo-controlled trial (6 month follow-up)


January 2013: 33 poor diagnosis and randomized

Investigators/sponsor: Department of Neurology, Erasmus MC, Rotterdam

In cooperation with: Sanquin

TIKI study - ongoing

Treatment with or without IVIG in Kats with acute ITP

Primary objective: To measure the extent to which treatment with IVIG early in the disease reduces the risk of development of chronic disease in children with newly diagnosed acute ITP (estimate reduction in developing chronic disease from 25% to about 10%)

Population: Children aged 3 months -16 years, with acute ITP presented to a pediatrician in one of the Dutch study centers; n=200 (6 month follow-up)

Design: Multi-centre randomized open-label controlled study


January 2013: 130 patients included

Investigators/sponsor: Wilhelmina Children's Hospital Utrecht

In cooperation with: Sanquin

ALL-11 IVIG study - ongoing

Treatment study protocol of the Dutch Childhood Oncology Group for children and adolescents (1-19 year) with newly diagnosed acute lymphoblastic leukemia

Primary objective: Does prophylactic administration of IVIG reduce the number of infections during the intensive treatment?

Population: Children with secondary immune deficiency in newly diagnosed Acute Lymphoblastic Leukemia (ALL); inclusion 226 children with ALL; 140 pt with medium risk continue after week 14 for 2 years

Design: Multicentre randomized controlled trial, 50% prophylactic IVIG, 50% on demand IVIG

First Patient In: November 2012; Last Patient Out: 2017

March 2013: 11 patients

Investigators: 5 Departments of Pediatric Oncology/Hematology

Sponsor: DCOG (Dutch Childhood Oncology Group) (=SKION)

In cooperation with: Sanquin

IVIG in transplant glomerulopathy study – in preparation

A randomized controlled trial on the efficacy of IVIG in transplant glomerulopathy

Primary objective: To assess the effectiveness of IVIG in transplant glomerulopathy (TGP)

Population: 34 patients (adults) with histologically proven TGP in the absence of acute humoral rejection or other glomerular pathology

Investigators/sponsor: Department of Transplantation, Erasmus MC, Rotterdam

In cooperation with: Sanquin

The Medical Department is, in its applied research activities, responsible for the design and conduct of clinical trials with (recently developed) plasma products. The Medical Department cooperates with clinical investigators in the Netherlands e.g. the Netherlands Inter-University Working Party on the Study of Immune Deficiencies and the Dutch Haemophilia Treatment Centers, and with investigators abroad.
Successful immune tolerance induction in patients with hemophilia A and inhibitors treated with a plasma-derived FVIII product containing von Willebrand factor: a large international, multicenter, retrospective study

Johannes Oldenburg¹, Elena Santagostino², Victor Jiménez Yuste³, Margaret Heisel Kurth⁴ and the Investigator Participants of the ITI Study

1 Institut für Experimentelle Hämatologie und Transfusionsmedizin, Bonn, Germany; 2 IRCCS - Ospedale Maggiore Policlinico, Milan, Italy; 3 Hospital La Paz, Madrid, Spain; 4 Children’s Hospitals and Clinics of Minnesota, Minneapolis, MN, USA

Background

Immune tolerance induction (ITI) is the treatment of choice to resolve inhibitors against FVIII in hemophilia A patients. ITI eradicates the inhibitors and subsequently induces tolerance with recovery of FVIII to normal levels in these patients. Some small studies suggest that VWF-containing plasma-derived FVIII products (VWF/pd-FVIII) are more successful for ITI than those lacking VWF [1].

Objective

To describe the ITI outcomes in moderate to severe HA patients with inhibitors who have been treated with a single factor VIII/VWF concentrate as part of either a primary or rescue ITI protocol.

Methods

Data from HA patients (FVIII <2 IU/dL) with inhibitors, from 35 centers in Spain, Italy, Germany and the USA, who completed primary or rescue ITI with Fanhdi®/Alphanate® (Grifols, Barcelona Spain/LA, CA, US), were collected retrospectively and evaluated. Outcome was assessed using the criteria for complete/partial success and failure based on the 2006 International ITI Workshop Consensus [2] (Table 1).

Table 1. Criteria for ITI Outcome Assessment

<table>
<thead>
<tr>
<th>Titer ITI</th>
<th>ITI regimen</th>
<th>Success</th>
<th>Partial Success</th>
<th>Failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 BU</td>
<td>Primary</td>
<td>19 (73%)</td>
<td>5 (19%)</td>
<td>2 (8%)</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Rescue</td>
<td>6 (75%)</td>
<td>0 (0%)</td>
<td>2 (25%)</td>
<td>8</td>
</tr>
<tr>
<td>50-200 BU</td>
<td>Primary</td>
<td>6 (50%)</td>
<td>5 (42%)</td>
<td>1 (8%)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Rescue</td>
<td>5 (36%)</td>
<td>5 (36%)</td>
<td>4 (28%)</td>
<td>14</td>
</tr>
<tr>
<td>≥200 BU</td>
<td>Primary</td>
<td>4 (40%)</td>
<td>3 (30%)</td>
<td>3 (30%)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Rescue</td>
<td>3 (14%)</td>
<td>7 (32%)</td>
<td>12 (54%)</td>
<td>22</td>
</tr>
</tbody>
</table>

Results

1. Patient characteristics

- Ninety-five patients were evaluated (Spain: 26, Italy: 19, Germany: 17 and USA: 33) who followed ITI protocols using Fanhdi® (62 patients) or Alphanate® (33 patients). Lost to follow up: 2 patients.
- Seventeen patients (17.9%) were not Caucasian (10 Hispanic/Latino, 3 African-American, 1 Native American, 2 Asian and 1 Arabic).

Table 2. Patient characteristics (median and range)

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Age (years)</th>
<th>Inhibitor peak (BU)</th>
<th>Titer at start of ITI (BU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary ITI (n=48)</td>
<td>3.3 (0.1-13.2)</td>
<td>38 (1-684)</td>
<td>7.1 (0-831)</td>
</tr>
<tr>
<td>Rescue ITI (n=45)</td>
<td>5.4 (0.9-24.9)</td>
<td>185 (8-4505)</td>
<td>18.2 (0-848)</td>
</tr>
</tbody>
</table>

2. Treatment

- A wide variation in treatment dose was observed (3x47 IU/kg/week - 2x300 IU/kg/day) but most patients were treated with a dose ≥100 IU/kg (Table 3). A dose-outcome relationship could not be established in either primary or rescue ITI.

Table 3. Dose at the start of ITI and frequency of treatment in patients

<table>
<thead>
<tr>
<th>Frequency / Dose</th>
<th>Primary ITI</th>
<th>Rescue ITI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 IU/kg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥100 IU/kg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt;100 IU/kg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥100 IU/kg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3/day</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2/day</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>1/day</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>3/week</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Total patients</td>
<td>48</td>
<td>43*</td>
</tr>
</tbody>
</table>

3. Outcome

- Most patients achieved success, complete or partial: 41/48 (85%) in primary ITI and 27/45 (60%) in rescue ITI (Table 4).
- Outcome according to inhibitor peak and titer at start of ITI is shown in Table 5 and 6 respectively.

Table 4. ITI outcomes in primary and rescue ITI

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Success</th>
<th>Partial Success</th>
<th>Failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>29 (60%)</td>
<td>12 (25%)</td>
<td>7 (15%)</td>
<td>48</td>
</tr>
<tr>
<td>Rescue</td>
<td>15 (33%)</td>
<td>12 (27%)</td>
<td>18 (40%)</td>
<td>45</td>
</tr>
</tbody>
</table>

Table 5. Outcome according to inhibitor peak

<table>
<thead>
<tr>
<th>Titer ITI</th>
<th>ITI regimen</th>
<th>Success</th>
<th>Partial Success</th>
<th>Failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 BU</td>
<td>Primary</td>
<td>19 (73%)</td>
<td>5 (19%)</td>
<td>2 (8%)</td>
<td>26</td>
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<tr>
<td></td>
<td>Rescue</td>
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<td>2 (25%)</td>
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</tr>
<tr>
<td>50-200 BU</td>
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<tr>
<td></td>
<td>Rescue</td>
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<td>Rescue</td>
<td>3 (14%)</td>
<td>7 (32%)</td>
<td>12 (54%)</td>
<td>22</td>
</tr>
</tbody>
</table>

4. Time to success and partial success

- Median time to complete tolerization was 16 months (range: 3-56) (Figure 1) and to partial tolerization was 23 months (range: 7-52).

Figure 1. Time to ITI success (complete and partial)

Conclusions

The high success rate reported in this large study, even in patients with poor prognosis, supports the effectiveness of Fanhdi® and Alphanate® in both primary and rescue ITI, and should encourage physicians and patients to consider VWF/pd-FVIII for these patients.

References


Acknowledgements: The authors thank Dr. Roser Peiró, Grifols S.A., for her support in data assessment and poster preparation.
Open prospective trial investigating pharmacokinetics, tolerability and safety of a new 10% human immunoglobulin for intravenous infusion (IVlg) in patients with primary immunodeficiency disease (PID)

G. Kriván (1), Ch. Königs (2), E. Betmatschicka (3), L. Marodi (4), A. Salama (5), R. Lind (2)

1) Dept. of Pediatric Hematology and Stem Cell Transplantation, United St. Island and St. Lazar Médical Hospital, Budapest; 2) Department of Pediatrics, Hemostasis and Immunodeficiency, Johann-Wolfgang-Goethe University, Frankfurt/Main; 3) Dept. of Immunology, Children’s Memorial Health Institute, Warsaw; 4) Dept. of Infectology and Pediatric Immunology, Medical and Health Science Center University of Debrecen; 5) Institute for Transfusion medicine. Charité Universitätsmedizin, Berlin.

Background

Intravenous immunoglobulins are well-established therapies in patients with primary or secondary immunodeficiencies and recurrent infections. BT090 is a highly purified 10% human IVlg (10 g human plasma protein per 100 mL of solution) with a IgG subclass distribution similar to that in normal serum. Its manufacturing is in general identical to the well-established process of Intratect® 50 g/L including 4 virus inactivation steps. The higher concentration offers the advantage of less volume and therefore shorter infusion times.

Objectives:

Pharmacokinetics (PK) and safety of a 10% solution of Intratect BT090 (Part A) and tolerability of escalating infusion rates (Part B).

Study Design/Methodology:

European multicenter trial with overall 30 PID patients (mainly with CVID), thereof 7 below 18 years.

Part A:

PID patients received 3 infusions of BT090 at 3- or 4-week intervals, with gradual increase of infusion rates at initially 30-minute intervals (from 0.3 to 1.4 to 2.0 mL/kg/h); dosing was consistent with the pre-trial standard IVlg treatment. Pharmacokinetic parameters were determined at 3rd infusion (Cmax, T1/2, AUC) for serum concentration of IgG and IgG subclasses 1 to 4 and maintenance of IgG trough levels 6-8 g/L. Patients without related adverse events proceeded with Part B.

Part B:

At the 4th infusion, the infusion rates were gradually increased at initially 30-minute intervals (from 0.3 to 1.4 to 4.0 to a maximum of 8.0 mL/kg/h) to determine safety and tolerability. Infusion rates and intervals were adjusted according to the discretion of the treating physician.

Results:

Table 1: Comparison of pharmacokinetics (total IgG, medians) of Intratect 100 g/L (BT090) with Intratect 50 g/L

<table>
<thead>
<tr>
<th>Parameter Study 981</th>
<th>Study 941</th>
<th>Study 957</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>17.7 g/L</td>
<td>16.2 g/L</td>
</tr>
<tr>
<td>T1/2</td>
<td>3.0 h</td>
<td>4.1 h</td>
</tr>
<tr>
<td>AUC0-1 last 285 day g/L</td>
<td>257 day g/L</td>
<td>261 day g/L</td>
</tr>
<tr>
<td>T1/2</td>
<td>34.1 days</td>
<td>26.9 days</td>
</tr>
</tbody>
</table>

Table 3: Frequently reported adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>URI</td>
<td>5 (0.0)</td>
</tr>
</tbody>
</table>

Overall Safety Profile of Intratect 100 g/L

Adverse events assessed as temporarily associated were reported in 4 of 105 infusions (24.2%) for overall study (Part A+B). No death and no serious related adverse event were reported during the study.

Table 3: Frequently reported adverse events in ≤3 patients (10%) Part A+B

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>URI</td>
<td>5 (0.0)</td>
</tr>
</tbody>
</table>

Table 4: Tolerability of increased infusion rate

<table>
<thead>
<tr>
<th>Infusion rate [mL/kg/h]</th>
<th>Patients tolerating infusion rate, n (%)</th>
<th>Number of patients with tolerable AE at infusion 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4</td>
<td>25 (100)</td>
<td>1</td>
</tr>
<tr>
<td>2.5</td>
<td>24 (96)</td>
<td>2</td>
</tr>
<tr>
<td>3.0-3.1</td>
<td>23 (92)</td>
<td>1</td>
</tr>
<tr>
<td>4.0</td>
<td>21 (84)</td>
<td>2</td>
</tr>
<tr>
<td>5.0</td>
<td>18 (72)</td>
<td>1</td>
</tr>
<tr>
<td>5.9-6.0</td>
<td>16 (64)</td>
<td>1</td>
</tr>
<tr>
<td>8.0</td>
<td>8 (32)</td>
<td>1</td>
</tr>
</tbody>
</table>

Conclusion

During treatment with Intratect 100 g/L (BT090) effective and reliable IgG serum levels are achieved which are consistent with those of other IVlgs and are also comparable to those of Intratect 50 g/L.

The safety profile of Intratect 10% is comparable to that of other 10% IVlgs.

Escalation of Intratect infusion rates was tolerated in most patients. Therefore, in PID patients an increased infusion rate that reduces the time required for administration can be considered. Every patient is supposed to have his own maximum tolerable infusion rate, which may differ between brands of IVlgs and may be also influenced on the other hand by the IVlg dose administered.

The physician should adjust the infusion speed for the individual patient taking into consideration the general condition (underlying disease, age, risk factors) as well as the condition at the day of infusion (e.g. indisposition, infection, stress).

References

**WHO 2nd Reference Standard**

**WILFACTIN® / WILFACT®** is a von Willebrand factor (VWF) product with a low FVIII content, labelled in VWF:F:RCo (10 IU mL⁻¹).

**Beneficial Clinical Experience**

- **21 years of beneficial clinical experience**
- **XXIX International Congress of the International Society on Thrombosis and Haemostasis** - Munich, Germany.
- **WHH** - 2012 - Paris, France - July 8th to 12th.
- **ISTH** - 2011 - Munich, Germany.
- **BSHT** - Antwerp 2011.
- **GTH** - Munich 2011.
- **GTH** - St Gallen 2013.
- **ASH** - Atlanta 2013.
- **XVIII International Congress of the WHH** - Buenos Aires, Argentina.
- **SSC Annual Meeting, Kyoto, Japan - July 23-28, 2011.**
- **Focus on Long Term Prophylaxis in von Willebrand Disease: Data from a French Clinical Plasma Re Stewart et al.** - J Thromb Haemost, 2007, at the dosage chosen avoided the attainment and maintenance of very high FVIII levels while simultaneously keeping VWF:F:RCO within the normal range.

**NHLBI/NIH guidelines (Nichols et al, haemophilia 2008) recommend in order to decrease the risk of peroperative thrombosis, - VWF:RCO levels should not exceed 200 IU/dL, and FVIII activity should not exceed 250 IU/dL.**

**No product-linked risk of thrombosis**

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**Adapted Patient’s Replacement**

- **Elevated FVIII levels are a common finding in patients with VTE**
  - These findings have been consistently replicated across a series of independent case-control studies:
    - Kramer et al Lancet 1995
    - Kraupe et al 1998
    - Oger et al 2003
    - De Zwart et al 2011
    - Perin et al 2010
  - In vitro and in vivo evaluation of the effect of elevated FVIII on the thrombogenic process (Golder, Thromb Haemost 2010) substantial FVIII levels > 200 % can increase the thrombogenic risk.

- **High plasma FVIII-C levels constitute a dose-dependent risk factor for VTE**
  - The rate of recurrence is higher (p<0.05) 2011).

**TARGETING THE MISSING FACTOR**

- **No supra-physiological FVIII levels**
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**CONCLUSION**

- **Efficacy and Safety of a von Willebrand Factor with a Low Factor VIII Content (WILFACTIN®)**
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- **Majors B leeding E pisodes**
  - **Treatments of Severe von Willebrand Disease**
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  - **FVIII Priming Dose**
    - **M anagement of Peri- and Post-O perative H aem ostasis**
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**PERUSSION PROCESS**

- **Low FVIII-content**
  - **W H O  2 nd IS** is intended to be used for the estimation of von Willebrand factor in therapeutic concentrates via the calibration of working standards, such as manufacturers’ “in house” standards. The W H O  2 nd IS has assigned values for (100 IU m L⁻¹);
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