**Summary Basis of Regulatory Action (SBRA)**

**Date:** December 2, 2015

**From:** Laurence Landow MD

**BLA/ STN#:** 125077/332

**Applicant Name:** Instituto Grifols, S.A.

**Date of Submission:** March 11, 2015

**PDUFA Goal Date:** January 9, 2016

**Proprietary Name/ Established Name:** IGIV3I Grifols 10% / Flebogamma 10% DIF

**Indication:** Chronic immune thrombocytopenic purpura (ITP) in adults and children aged ≥ 2 years

**Recommended Action:** Approval for the chronic ITP indication

**Signatory Authorities Action:**

**Offices Signatory Authority:**
Paul D. Mintz, MD, Director
Division of Hematology Clinical Review, Office of Blood Research and Review

**□ I concur with the summary review.**

**□ I concur with the summary review and include a separate review to add further analysis.**

**□ I do not concur with the summary review and include a separate review.**

| **Material Reviewed/ Consulted Reviewer Name – Document(s) Date** | **Specific documentation used in developing the SBRA** |
|---|---|
| Clinical Review | Laurence Landow, M.D. |
| Clinical Pharmacology Review | N/A |
| Statistical Review | Boris Zaslavsky, Ph.D., Dr. Sc. |
| CMC Review | N/A |
| Pharmacology/ Toxicology Review | N/A |
| Bioresearch Monitoring Review | Erin McDowell |
| Establishment Inspection Report | N/A |
| Advisory Committee Transcript | N/A |
| Epidemiology | Maria Said, M.D., MHS |

## 1. Introduction

STN 125077/332 is intended to support the use of Grifols' Flebogamma 10% DIF[1] (IGIV3I Grifols 10%) in the treatment of chronic immune thrombocytopenia (ITP) in adults and children aged ≥2 years. Idiopathic (immune) thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by platelet destruction and thrombocytopenia (peripheral blood platelet count $<150 \times 10^9$/L). It is due to autoantibody binding to platelet antigens and premature destruction by reticuloendothelial cells, in particular those of the spleen. Recent evidence suggests that platelet production also is impaired in ITP subjects. The diagnosis remains one of exclusion. Clinical features are highly variable and range from asymptomatic presentation to mild bruising and mucosal bleeding. Frank hemorrhage is uncommon unless ITP is severe (platelet count $<30 \times 10^9$/L).

Flebogamma 5% was approved for treatment of primary immunodeficiency (PI) in adults on December 15, 2003. Flebogamma 5% DIF, which added nanofiltration to its manufacturing process, was approved on December 21, 2006. An efficacy supplement was submitted in 2013 and after review by FDA, a labeling update was approved on August 19, 2014 to include use in patients aged ≥2 years. On July 27, 2010, Flebogamma 10% DIF was approved for treatment of PI.

To support the chronic ITP indication, Grifols has submitted safety and efficacy data from a phase 3 efficacy study, IG0601 (N=58; adults: N=46; children: N=12), and a supportive study, IG202 (N=18). Both were designed as prospective, multicenter, open-label, single-arm studies in chronic ITP subjects with platelet counts $\leq 20 \times 10^9$/L. Chronic ITP was defined as lack of complete remission (platelet count $\geq 150 \times 10^9$/L) at 6 months after diagnosis of ITP. Flebogamma 10% DIF was administered in divided doses over (a) 2 consecutive days (IG0601) or (b) 2 or 5 consecutive days (IG202). Primary and secondary endpoints were similar. Both studies met their primary endpoint.

## 2. Background

The primary goal in treating patients with chronic ITP is to maintain the platelet count at hemostatic levels. Medical management includes use of intravenous immune globulin (IGIV), Rho(D) and glucocorticoids. Surgical management, i.e., splenectomy, also is an option.

## 3. Chemistry Manufacturing and Controls (CMC)

No new CMC information was submitted and information provided in prior submissions adequately supports this submission.

## 4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted and information provided in prior submissions adequately supports this submission.

## 5. Clinical Pharmacology

No new clinical pharmacology information was submitted.

[1] DIF: dual inactivation filtration

## 6. Clinical/Statistical

a) Clinical Program

- **Study IG0601: "A multicenter, prospective, open label, clinical study to assess the safety and the efficacy of a new intravenous immune globulin (IGIV3I Grifols 10%) in subjects with idiopathic (immune) thrombocytopenia purpura"**

IG0601 was conducted in adult (N=46) and pediatric (N=12) subjects (N=58) with chronic ITP in the United States, Canada, India, and Puerto Rico (no subjects from Puerto Rico were included in this submission). It was designed to evaluate the efficacy of Flebogamma 10% DIF in raising platelet count to hemostatic levels in subjects aged 3 to 70 years.

Dosing: a dose of 1 g/kg/day was infused for 2 consecutive days starting on Day 1 according to a prespecified infusion rate titration schedule.

Endpoints: the primary endpoint was response rate, defined as the proportion of subjects whose platelet count increased from $\leq 20 \times 10^9$/L on Day 1 to $\geq 50 \times 10^9$/L by Day 8 (± 1).

Secondary efficacy endpoints included:

(a) Time to platelet count recovery, as determined by the number of days elapsed from Day 1 to the day on which the platelet count was first found to be $\geq 50 \times 10^9$/L during scheduled follow-up visits (final visit: Day 30 ±1)

(b) Duration of response, as determined by the number of consecutive days that the platelet count remained $\geq 50 \times 10^9$/L (Day 30 ± 1)

(c) Maximum platelet count

(d) Regression of hemorrhage/bleeding, as determined by the proportion of treated subjects with hemorrhage/bleeding on Day 1 whose diathesis improved using a categorized rating scale.

- **Study IG202: "A multicenter, prospective, open label, clinical study to assess the safety and the efficacy of a new intravenous immune globulin (IGIV3I Grifols 10%) in subjects with immune thrombocytopenia purpura"**

IG202 enrolled adult subjects (N=18) with chronic ITP and was conducted in Russia, Spain, and the United Kingdom. It was designed to assess the safety and efficacy of Flebogamma 10% DIF in subjects with platelet counts $\leq 20 \times 10^9$/L.

Dosing: each subject received a total dose of 2 g/kg/day intravenously either (a) 1 g/kg/day for 2 consecutive days identical to dosing in Study IG0601 above or (b) 400 mg/kg over 5 consecutive days, depending on the dose the subject was currently receiving or the dose to which the subject had been responsive.

Endpoints: the primary endpoint was response to therapy, defined as a platelet count $\geq 50 \times 10^9$/L at any time during the study period.

Secondary endpoints included:
(a) Time for platelet count to reach ≥50 x $10^9$/L
(b) Duration of response
(c) Maximum platelet count reached during the follow-up period
(d) Regression of hemorrhage/bleeding during the first 10 days of observation ranked according to a prespecified scoring system

**Demographic characteristics**

- Table 1 presents demographic characteristics of the IG0601 population, which included 19 male and 39 female subjects. Adult subjects were predominately female, but the number of male and female pediatric subjects was identical. Overall, 31 subjects were Asian (53.4%), 21 subjects White (36.2%), 4 subjects Hispanic/ Latino (6.9%), and 2 subjects Black/African American (3.4%). Most of the pediatric subjects were White.

- Table 2 presents demographic characteristics of the IG202 population, which consisted of male (N=6) and female (N=12) adult White subjects.

- Efficacy related to demographics could not be assessed due to limited sample size.

**Table 1: Subject Demographics, Study IG0601**

| **Demographic Parameters** | | **Adults (N=46)** | **Pediatrics (N=12)** | **All Subjects (N=58)** |
|---|---|---|---|---|
| Age (years) | Mean ± SD | 38.9 ± 16.7 | 11.5 ± 3.9 | 33.2 ± 18.7 |
| | Median (min, max) | 34 (18, 70) | 13 (3, 16) | 28 (3, 70) |
| Gender, n (%) | Male | 13 (28.3) | 6 (50.0) | 19 (32.8) |
| | Female | 33 (71.7) | 6 (50.0) | 39 (67.2) |
| Race, n (%) | Asian | 31 (67.4) | 0 | 31 (53.4) |
| | Black/African American | 1 (2.2) | 1 (8.3) | 2 (3.4) |
| | Hispanic/Latino | 2 (4.3) | 2 (16.7) | 4 (6.9) |
| | White | 12 (26.1) | 9 (75.0) | 21 (36.2) |

*Source:* Table 16.2.4.1, CSR

**Table 2: Subject Demographics, Study IG202**

| **Demographic Parameters** | | **ITT Population (N=18)** |
|---|---|---|
| Age (years) | Mean ± SD | 43.7 ± 19.1 |
| | Median (min, max) | 43 (20, 77) |
| Gender, n (%) | Male | 6 (33.3) |
| | Female | 12 (66.7) |
| Race, n (%) | Asian | 0 |
| | Black/African American | 0 |
| | Hispanic/Latino | 0 |
| | White | 18 (100.0) |

*Source:* Table 16.2.4.1, CSR

**Disposition of Subjects**

IG0601: 58 male and female subjects, ages 3 to 70 years of age, diagnosed with chronic ITP, were enrolled. Seven subjects discontinued, leaving 40 adults and 11 children who completed the study. One child withdrew because of disease progression. Of the remaining 6 adults, one withdrew consent, four experienced disease progression and one needed a platelet transfusion.

IG202: 18 male and female subjects aged ≥18 years completed the study. No subject withdrew prematurely.

## Efficacy

Primary Endpoint

IG0601: Table 3 shows that 47/58 subjects (81% responders) met the primary efficacy endpoint. The lower bound of the 95% confidence interval exceeded the prespecified value of ≤50% and the null hypothesis was rejected.

**Table 3: IG0601 Response Rates (mITT, PP Populations)**

| | **mITT Population* (N=58)** | | |
|---|---|---|---|
| | **Adults (N=46)** | **Pediatrics (N=12)** | **All Subjects (N=58)** |
| **Responders, N (%) (95% CI)** | 35 (76.1) (63.5, 86.0) | 12 (100) (77.9, 100.0) | 47 (81.0) (70.6, 89.0) |
| | **PP Population† (N=51)** | | |
| | **Adults (N=37)** | **Pediatrics (N=11)** | **All Subjects (N=48)** |
| **Responders, N (%) (95% CI)** | 33 (89.2) (76.9, 96.2) | 11 (100.0) (76.2, 100.0) | 44 (91.7) (81.9, 97.1) |

*Adapted from* Tables 14.2.1 and 14.2.2, CSR IG0601, 25 Jun 2013, pages 75 and 76 of 408

*****mITT: subjects who received ≥1 infusion (at any dose) of Flebogamma 10% DIF

†Per Protocol: subjects in the mITT population who completed the planned dosing schedule without major protocol violations

IG0202: Table 4 shows that 13/18 subjects (72.2% responders) met the primary efficacy endpoint. The lower bound of the 95% confidence interval exceeded the prespecified value of ≤50% and the null hypothesis was rejected.

**Table 4: IG202 Response Rates to Flebogamma 10% DIF**

| **Responders** | **ITT Population (N=18)** | **PP Population (N=14)** |
|---|---|---|
| Number of responders | 13 | 9 |
| % of responses | 72.2 | 64.3 |
| 95% CI | 50.2, 88.4 | 39.0, 84.7 |

*Adapted from* Table 14.2.1, CSR IG202, 10 Dec 2013, pages 81 and 82 of 305

Secondary Endpoints

IG0601

- Mean time to platelet response (defined by the number of days elapsed from Day 1 to the day when the platelet count was first known to be $\geq 50 \times 10^9$/L): ≤ 1.7 days: ≤ 1.8 days in adult responders and ≤ 1.4 days in pediatric responders
- Median time to response: ≤ 2 days for all responders and adult responders, and ≤ 1 day for pediatric responders
- Mean duration of response (defined as the number of consecutive days platelet count remained $\geq 50 \times 10^9$/L during study): ≥ 10.8 days in all responders, ≥ 9.6 days in adult responders, and ≥ 14.3 days in pediatric responders

- Regression of bleeding, observed pre-infusion (Day 1) in 27/46 adults (59%) and 12/12 children (100%), occurred in 24/46 adults and 12 children (12/12) by Day 15

IG202

- Mean time to platelet response (defined as the number of days elapsed from Day 1 to the day when platelet counts first reached $\geq 50x10^9$/L, and calculated as study day when platelet count reached $\geq 50x10^9$/L — 1st Infusion (Day 1)): ≤2.1 days after starting study treatment
- Duration of response: ≤13.5 days[2]
- Maximum platelet count: 204.5 ± 183.3 $x10^9$/L
- Regression of bleeding, observed pre-infusion (Day 1) in 15/18 subjects, occurred in all 15 adult subjects by Day 10

**Pediatrics**

The number of subjects enrolled in each subpopulation was as follows: >3 to <6 years: N=1; ≥6 to <12 years: N=2; ≥12 to <16: N=9. After consultation with the PeRC, a Waiver was granted for a phase 4 study in children aged 0 to ≤3 years because such a study would be unfeasible.

**Overall Comparability Assessment**

Previous clinical trials of other licensed IgG products, e.g., Privigen, Hizentra, and Gammagard liquid, have reported no differences in safety or efficacy between adult and pediatric subjects. Although efficacy was no different, the incidence of headache, nausea, and other safety events occurring in ≥10% of subjects who received Flebogamma 10% DIF was disproportionately higher in the pediatric cohort. These signals could be due to increased sensitivity of children to rapid infusion rates of hyperviscous protein solutions, random variation resulting from small sample size, and/or unknown reasons. The applicant has revised the Highlights and Sections 6.1, 8.4 and 14.2 of the PI to highlight a disproportionate increase in the incidence of TEAEs in children compared with adults. See Table 5 and corresponding text, below.

**7. Safety**

- Serious Adverse Events (SAE)

  A boxed warning for thrombosis, renal dysfunction and acute renal failure is included in the package inserts of all IGIV products. No case of death or renal impairment was reported in either study, but one IG202 subject experienced a thrombosis SAE (severe intensity). This subject was a 54 year old White male who was morbidly obese and led a sedentary lifestyle. He entered the study and received five daily infusions at 0.4 g/kg/day. One day after his last dose, the area around his right antecubital fossa became swollen. He was diagnosed with deep venous thrombosis of the right humeral vein and hospitalized. This was followed by recovery without sequelae. In the reviewer's opinion, the thrombosis was probably related to the product based on the temporal

[2] As time to response was only assessed at study visits, a response likely had already occurred. before the visit and therefore the symbol ≤ is used. The duration of response was also determined at the visit and not between two visits, so it is also likely that the response lasted beyond the visit. Therefore, the symbol ≥ is used for the duration of response.

sequence, presence of underlying risk factors favoring thrombosis, and infusion of a hyperviscous IGIV solution.

Other reported SAEs included the following:

*(a)* A 30 year old Asian IG0601 male experienced soft tissue inflammation in both legs accompanied by pain and swelling in both lower extremities on Day 29. He was admitted to hospital for medical management and the event resolved without sequelae the next day. Given its transient nature and absence of a plausible temporal relationship between the event and exposure to study drug, the reviewer considered this to be an unrelated event.

*(b)* A 35 year old Asian IG0601 female experienced an episode of severe headache after infusion on Day 2 and was admitted to the hospital for medical management. The SAE resolved without sequelae on Day 5. In the reviewer's opinion, this SAE was possibly related to study drug given the temporal sequence and the fact that headaches are the most frequent side-effect reported in clinical trials using IGIV.

*(c)* A 28 year old Asian IG0601 female experienced a severe headache seven hours after receiving her second infusion (Day 2). She was admitted to hospital for medical management and by Day 5, her headache had resolved without sequelae. This event was considered possibly related for the same reasons indicated in the prior subject.

*(d)* A 75 year old Asian IG202 male experienced leukopenia (moderate) and hemolysis (moderate) that self-corrected without sequelae. Both events have been reported in prior clinical trials using IGIV products. In the reviewer's opinion, they were possibly related to the product.

- Treatment Emergent Adverse Events (TEAE)

  No subject discontinued either study due to a TEAE. The most frequent TEAEs in study IG0601 were headache, pyrexia, nausea, chills, contusion, hypotension, and vomiting. The most frequent TEAEs in study IG202 were petechiae, ecchymosis, headache and pyrexia; all events were of mild or moderate intensity. These events have been reported at comparable rates in clinical trials of other IgG products and thus, were expected.

  Table 5 presents the incidence of headache, nausea, and other events occurring in ≥10% of subjects who received Flebogamma 10% DIF. As noted above (Pediatrics), the rate of these events was disproportionately higher in the IG0601 pediatric cohort. .

**Table 5: TEAEs Occurring in ≥10% of IG0601 Subjects**

| **Preferred Term** | **Adults (N=46)** | | **Pediatrics (N=12)** | | **All Subjects** | |
|---|---|---|---|---|---|---|
| | N (%) | n | N (%) | n | N (%) | n |
| Headache | 27 (58.7) | 42 | 11 (91.7) | 20 | 38 (65.6) | 52 |
| Nausea | 6 (13.0) | 6 | 8 (66.7) | 9 | 14 (24.1) | 15 |
| Pyrexia | 8 (17.4) | 11 | 4 (33.3) | 5 | 12 (20.7) | 16 |
| Chills | 7 (15.2) | 8 | 4 (33.3) | 4 | 11(19.0) | 12 |
| Vomiting | 4 (8.7) | 4 | 5 (41.7) | 5 | 9 (15.5) | 9 |
| Hypotension | 1 (2.2) | 1 | 5 (41.7) | 9 | 6 (10.3) | 10 |
| Contusion | 3 (6.5) | 4 | 2 (16.7) | 8 | 5 (8.6) | 12 |

*Adapted from* Table 14.3.1.2, CSR IG0601, 25 Jun 2013, page 107 of 408

N=number of subjects
n=number of AEs

- Viral markers: No seroconversion in viral markers was seen in any subject.

**8. Advisory Committee Meeting**

There were no issues for the Blood Products Advisory Committee to address.

**9. Other Relevant Regulatory Issues**

No substantive problems that could impact the data were found in Bioresearch Monitoring (BIMO) inspections of two foreign and two domestic clinical investigators for this supplement.

No new safety concerns have been identified in the latest postmarketing surveillance report. FDA's Division of Epidemiology in the Office of Biostatistics and Epidemiology is in agreement with the applicant's plan for ongoing routine surveillance. Available safety data do not substantiate a need for a postmarketing requirement study or a Risk Evaluation and Mitigation Strategy.

**10. Labeling**

The Advertising and Promotional Labeling Branch (APLB) was consulted and provided input with respect to physician labeling, as well as carton/container labeling. All issues raised by the APLB reviewer and the clinical reviewer were addressed by the applicant.

**11. Recommendations and Risk/ Benefit Assessment**

**a) Recommended Regulatory Action**

Approval of STN125077/332 for treatment of ITP in adults and pediatric patients ≥2 years.

**b) Risk/ Benefit Assessment**

Flebogamma 10% DIF raised the platelet count to $\geq 50 \times 10^9$/L within 1-2 days in subjects with chronic ITP. The therapeutic effect lasted for 10 days (mean). Among the clinically significant risks labeled for this and other IGIV products, only single cases of thrombosis and hemolysis were reported in supportive study IG202. Pediatric subjects appear to be at greater risk of TEAEs compared with adult subjects.

**c) Recommendation for Postmarketing Risk Management Activities**

Aside from ongoing collection of pharmacovigilance data, no other postmarketing actions are recommended.

**d) Recommendation for Postmarketing Activities**

The applicant's plan for ongoing surveillance is sufficient.