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Safety and efficacy of intravenous immunoglobulin (Flebogamma® 10% DIF) in patients with immune thrombocytopenic purpura

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Aim: To evaluate the safety and efficacy of 10% intravenous immunoglobulin (IVIg; Flebogamma® 10% DIF) in individuals with chronic immune thrombocytopenic purpura (ITP). **Patients & methods:** Patients aged 3–70 years, diagnosed with chronic ITP, received 1 g/kg IVIg over two consecutive days. **Results:** 64 evaluable patients (51 adults, 13 children) with chronic ITP received IVIg. The primary efficacy end point (increased platelet counts from $\leq 20 \times 10^9/l$ to $\geq 50 \times 10^9/l$ by day 8) was achieved by 81.3% of patients; mean time to response was 1.7 days (all responders). Adverse events, mostly mild or moderate, were reported in 59 patients (92.2%). **Conclusion:** Flebogamma® 10% DIF administered over two consecutive days was safe and effective in adults and children with chronic ITP.

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Primary immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by isolated thrombocytopenia, defined by a peripheral blood platelet count $< 100 \times 10^9/l$, and in the absence of other known causes or disorders that may result in thrombocytopenia [1]. Historically, ITP was used as the abbreviation for idiopathic thrombocytopenic purpura, but a suggested nomenclature revision to 'immune thrombocytopenia' by the International ITP Working Group (IWG) [1] reflects the immune-mediated nature of the disease [2].

The pathophysiology of ITP is complex and variable. In 60–70% of patients, platelets are destroyed in the spleen following their coating with antibodies, predominantly against the platelet glycoproteins GPIIb/IIIa and GPIb/IX [3–5]. In other individuals, platelet destruction is caused by abnormal T cells, autoantibody production resulting from T-cell dysregulation, or impaired megakaryocytopoiesis [5].

The diagnosis of ITP is one of exclusion [2,6]. Although minor differences exist between guidelines published by the IWG [2] and the American Society of Hematology (ASH) [7], diagnosis of ITP is generally made following patient history review, physical examination, evaluation of peripheral blood count and evaluation of peripheral blood smear [5]. In children, ITP is typically acute, with purpura and bruising appearing during a 24–48 h period

and resolving within the first 3–6 months of illness. However, chronic ITP is more common in children aged >10 years. In adults, ITP is typically a chronic disease, the signs and symptoms of which are highly variable ranging from asymptomatic patients with mild bruising or mucosal bleeding to life-threatening hemorrhage. However, besides severe ITP (platelet count $<30 \times 10^9/l$), bleeding is uncommon [6].

First-line treatment options for adult ITP patients include corticosteroids, intravenous (iv.) anti-D (Rh) and intravenous immunoglobulin (IVIG) [2,7]. In children, first-line treatment options include IVIG and corticosteroids [2,7], with iv. anti-D only recommended by IWG guidelines [2]. However, there are few large clinical trials testing IVIG in chronic ITP patients, particularly pediatric patients.

Flebogamma® 10% DIF (Grifols, Barcelona, Spain) is a high-purity human IVIG which has been shown to be well tolerated and effective in treating adult patients with chronic ITP [8]. The objective of this study was to evaluate the safety and efficacy of Flebogamma® 10% DIF in adults and children with chronic ITP. Interim data from this study were published previously, with data from a separate European study of Flebogamma® 10% DIF in adults with chronic ITP [9].

Materials & methods

This was a multicenter, prospective, open-label, Phase III clinical trial conducted at 44 medical centers in India, USA and Canada from 19 May 2008 to 8 April 2014 (ClinicalTrials.gov Identifier: NCT00511147). Overall, 26 sites in India (8), USA (17) and Canada (1) screened at least one patient.

Patients

A total of 75 patients were planned for enrolment in this study. Enrolment of children was set to a maximum of 25% (18 patients) of the total number of patients planned for enrolment. ITP was defined as ITP with no other clinically apparent associated condition or factors known to cause thrombocytopenia, diagnosed according to American Society of Hematology ITP guidelines [7]. Chronic ITP was defined as the lack of complete remission from 6 months postdiagnosis.

All subjects who received at least one infusion (at any dose) of Flebogamma® 10% DIF were included in the modified intent-to-treat (mITT) analysis population.

Inclusion criteria

Patients were male or female, aged from 3 to 70 years, and diagnosed with chronic ITP with a platelet count $\leq 20 \times 10^9/l$. Informed consent was obtained from all individual participants included in the study. Adults (≥ 18 years old) provided written informed consent, or, for subjects not qualified to give legal consent, written consent was obtained from the patient's parent or legal guardian (irrespective of age). Additionally, an age-appropriate assent form was obtained from children (<18 years old).

Patients who had received corticosteroids, azathioprine, danazol or vinca alkaloids before the screening visit, had to receive a stable dose and schedule of each treatment for at least 3 weeks, 3 months, 8 weeks and 2 weeks, respectively, prior to the screening visit.

Exclusion criteria

Patients were excluded if they had a history or clinical evidence of medical conditions (other than ITP) considered to be the underlying cause of the thrombocytopenia; had a diagnosis of secondary immune thrombocytopenia; had a history of severe (e.g., anaphylactic) reactions to blood or any blood-derived product, or intolerance to any component of the investigational product, such as sorbitol; had a documented history of thrombotic complications to polyclonal IVIG therapy; had immunoglobulin A (IgA) deficiency; were suffering from serious and/or life-threatening hemorrhage/bleeding (e.g., intracranial or central nervous system bleeding); were pregnant or nursing females; had a recent history (within 12 months) of abuse of alcohol, opiates or psychotropic agents; had unstable angina, congestive heart failure (New York Heart Association Classification Class III/IV), uncontrolled arterial hypertension (diastolic blood pressure [DBP] >95 mmHg), anemia (hemoglobin <9 g/dl), renal impairment (serum creatinine >1.5 -times upper normal limit) or documented history of acute renal failure; had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >2.5 -times upper normal limit; were hepatitis C virus (HCV) or human immunodeficiency virus type 1 and 2 (HIV 1/2) positive; had a splenectomy within 8 weeks prior to screening; or had received an immune serum globulin (ISG) product, any alkylating agent (e.g., cyclophosphamide) or rituximab within 3 weeks, 4 weeks and 3 months, respectively, prior to screening.

Administration & dosage

Flebogamma® 10% DIF was infused iv. at 1 g/kg body weight per day over 2 consecutive days, to give a total dose of 2 g/kg. Routine pre-infusion medication (e.g., acetylsalicylic acid, nonsteroidal anti-inflammatory drugs or corticosteroids) was not allowed. Other medications (e.g., antihistamines or acetaminophen) were allowed pre-infusion, if considered necessary by the investigator.

Clinical evaluation

Each patient was evaluated clinically, including monitoring of platelet counts, which was performed centrally for standardization, at a screening visit, two infusion visits (on days 1 and 2), and at follow-up visits (day 3, day 5 ± 1, day 8 ± 1, day 15 ± 1, day 22 ± 1 and day 30 ± 1). Additional platelet monitoring was performed daily from days 4 to 8, or until counts were $\geq 50 \times 10^9/l$, and then every 3 to 5 days until day 22 ± 1. Signs of bleeding/hemorrhage and safety assessments were also performed throughout the study. Any adverse events (AEs) that occurred at any time between signing the informed consent form and day 30 ± 1 were reported on the appropriate case report form. Summary tables for AEs only include AEs that occurred between the start of study drug infusion and the final visit.

Efficacy end points

The primary end point was response rate, defined as the proportion of treated patients whose platelet counts increased from $\leq 20 \times 10^9/l$ to $\geq 50 \times 10^9/l$ by day 8 ± 1 in the mITT population. The response rate was also determined in a per-protocol (PP) population, consisting of the mITT population but excluding patients with major protocol violations (n = 11).

Secondary efficacy end points were: the time to platelet count recovery, determined by the number of days elapsed from day 1 to the day when the platelet count was first found to be $\geq 50 \times 10^9/l$ during the clinical follow-up period which ended on day 30 ± 1; duration of response, determined by the number of consecutive days in which the platelet count remained $\geq 50 \times 10^9/l$ during the 30 day clinical follow-up period; and regression of hemorrhage/bleeding, determined by the proportion of treated patients with hemorrhage/bleeding on day 1 who improved their diathesis. This was assessed by the treating physician using a categorized rating scale during the clinical follow-up period ending on day 15 ± 1.

Safety

AEs, physical assessments, vital signs and laboratory parameters were collected and monitored. The nature, severity and frequency of AEs and serious AEs (SAEs) were analyzed using the Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class (SOC) and Preferred Term (PT) descriptors. At every study visit, the occurrence of AEs was assessed by study staff, and reported on the appropriate case report form. AEs were elicited by asking the subject a nonleading question such as 'Do you feel different in any way since the last assessment?'. Investigators were required to assess the relationship of all AEs to the investigational product, to determine potential treatment-related AEs.

Statistical methods

The primary efficacy end point, response rate, was the basis for calculating the sample size, using nQuery Advisor v5 (Statistical Solutions Ltd, Cork, Ireland) software. Using a threshold of 50% of patients who achieved the response rate, with a 0.05 one-sided significance level and 80% power, it was estimated that at least 67 evaluable patients would be required. Thus, the aim was to enroll 75 patients to achieve this number, considering a 10% attrition rate. The descriptive analysis of categorical variables comprised the calculation of simple and relative frequencies. Numeric variables are reported as the mean ± SD, minimum and maximum. Categorical data were compared using χ -squared or Fisher's exact tests.

Results

Efficacy

A total of 64 evaluable patients (51 adults and 13 children) with chronic ITP were treated with Flebogamma® 10% DIF and included in the mITT population. Most patients were female (67.2%) with the predominant ethnic origins being Asian (50%) and White (37.5%) (Table 1).

Table 1. Demographic parameters of patients in the modified intention-to-treat population.

Parameter	Adults (n = 51)	Children (n = 13)	All patients (n = 64)
Age (years), mean $\pm$ SD	39.1 $\pm$ 16.38	11.3 $\pm$ 3.75	33.4 $\pm$ 18.50
Male: female, n (%)	15 (29.4): 36 (70.6)	6 (46.2): 7 (53.8)	21 (32.8): 43 (67.2)
Ethnic origin, n (%)			
Asian	32 (62.7)	0	32 (50.0)
White	15 (29.4)	9 (69.2)	24 (37.5)
Hispanic/Latino	3 (5.9)	3 (23.1)	6 (9.4)
Black/African-American	1 (2.0)	1 (7.7)	2 (3.1)

Table 2. Efficacy outcomes in the modified intention-to-treat and per-protocol populations.

Parameter	Adults	Children	All patients
mITT population, n	51	13	64
Responders, n (%) [95% CI]	39 (76.5) [62.5–87.2]	13 (100) [75.3–100]	52 (81.3) [69.5–89.9]
PP population, n	41	12	53
Responders, n (%) [95% CI]	37 (90.2) [76.9–97.3]	12 (100) [75.3–100]	49 (92.5) [82.5–97.2]
Responders, mITT population:			
Time to response (days), mean $\pm$ SD	1.8 $\pm$ 0.9	1.4 $\pm$ 0.5	1.7 $\pm$ 0.9
Duration of response (days), mean $\pm$ SD	9.7 $\pm$ 7.5	14.0 $\pm$ 7.7	10.8 $\pm$ 7.7
Maximum platelet count ($\times 10^9$ /l), mean $\pm$ SD	196.0 $\pm$ 141.6	331.2 $\pm$ 190.5	229.8 $\pm$ 164.2
Maximum increase in platelet count ($\times 10^9$ /l), mean $\pm$ SD	183.2 $\pm$ 140.5	318.5 $\pm$ 188.3	217.0 $\pm$ 163.0
Time to maximum platelet count (days), mean $\pm$ SD	4.6 $\pm$ 1.8	5.4 $\pm$ 1.3	4.8 $\pm$ 1.7

mITT: Modified intention-to-treat; PP: Per-protocol; SD: Standard deviation.

The primary efficacy end point, increased platelet counts from $\leq 20 \times 10^9$ /l to $\geq 50 \times 10^9$ /l by day 8 $\pm$ 1, was achieved in 52 of 64 patients (81.3%; 95% CI: 69.5–89.9) in the mITT population. The proportion of responding adults and children was 76.5% (39/51) and 100% (13/13), respectively (Table 2).

Seven patients discontinued the study early due to withdrawal of informed consent (one adult), disease progression (four adults and one child) and other reasons (one adult) (Figure 1). Overall, 15 infusions in ten patients (three children) had to be stopped, interrupted or slowed down due to dosage error (n = 5), AEs (n = 4), pump malfunction (n = 3), nurse error (n = 2) and unreported reason (n = 1). A total of four patients (three adults, one child) received less than 80% of the planned dose which excluded them from the PP population. These protocol violations in adults comprised an infusion pump malfunction on day 1 (although infusion on day 2 was completed); an AE (infusion-related reaction) on day 1 (infusion on day 2 was not performed); an AE (headache) during infusion on day 1 (although infusion on day 2 was completed); in the pediatric case, infusion was interrupted on day 2 because of AEs (chills and hypotension). Repeating the primary analysis in the PP population produced a response rate of 92.5% (49/53) (Table 2).

The pediatric population responded earlier and had a longer duration of response than the adult population (Table 2). Median time to response was ≤ 2 days for all responders and adult responders, and ≤ 1 day for pediatric responders. The median duration of response was 10 (range 1–29) days in all responders (7 [1–29] and 13 [3–29] days in adults and children, respectively).

Most adults (31/51, 60.8%) and all children (13/13, 100%) presented with signs of hemorrhage/bleeding on day 1 before the first infusion of IVIG. The majority of these patients (40/44, 90.9%), experienced improvement in bleeding symptoms during the follow-up period ending on day 15, irrespective of their classification as responders or nonresponders (based on their increase in platelet count). Regression of hemorrhage/bleeding was achieved in 87.1 and 100% of adults and children, respectively (Table 3).

All responders had a mean maximum platelet count of 229.8×10^9 /l, with a mean time to maximum platelet count of 4.8 days. The mean maximum increase in platelet count in all responders was 217.0×10^9 /l (Table 2). All nonresponders were in the adult population (n = 12) with a mean increase of 25.1×10^9 /l.

Figure 1. Disposition of enrolled patients.

Modified intention-to-treat population: all subjects who received at least one infusion (at any dose) of Flebogamma® 10% DIF.

Table 3. Regression of hemorrhage/bleeding in the modified intention-to-treat population.

Parameter	Adults (n = 51)	Children (n = 13)	All patients (n = 64)
Patients with hemorrhage/bleeding at day 1, n (%)	31 (60.8)	13 (100)	44 (62.5)
Improvement in diathesis of patients with hemorrhage/bleeding at day 1, n (%)† [95% CI]	27 (87.1) [70.2–96.4]	13 (100) [75.3–100.0]	40 (90.9) [78.3–97.5]

† Expressed as a percentage of patients with bleeding at day 1.

Safety

Overall, 291 AEs (regardless of causality) were reported in 59 patients (92.2%) between the start of study drug infusion and the final study visit. By age group, 127 AEs were reported in 13 children (100%) and 164 AEs in 46 adult patients (90.2%), with five adults reporting no AEs. The most common AE (by Preferred Term) was headache (70 events in 41 patients [64.1%]), followed by nausea (15 events in 14 patients [21.9%]), pyrexia (17 events in 13 patients [20.3%]), chills (13 events in 12 patients [18.8%]), vomiting (nine events in nine patients [14.1%]), contusion (15 events in eight patients [12.5%]) and hypotension (ten events in six patients [9.4%]).

Most AEs were reported to be mild (32/64, 50%) or moderate (18/64, 28.1%) in severity, with AEs in nine patients (14.1%) reported as severe. These were headache, chills, infusion-related reaction, injection site pain, soft tissue inflammation and aseptic meningitis.

Some differences in patterns of AEs were observed between pediatric and adult patients, although the number of children (n = 13) was much smaller than the adult number (n = 51). Several AEs were much more frequent in children than adults: nausea (61.5 vs 11.8%), vomiting (38.5 vs 7.8%) and hypotension (38.5 vs 2.0%).

54 patients (84.8%) reported at least one AE that was not excluded for possible causality: 28 patients (43.8%) experienced at least one probable treatment-related AE; 23 patients (35.9%) at least one possible treatment-related AE; and three patients (4.7%) at least one AE unlikely to be treatment-related.

Table 4. Treatment-related adverse events occurring in >5% of patients by Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term in the modified intention-to-treat population.

System organ class/preferred term	Adults (n = 51)		Children (n = 13)		All patients (n = 64)	
	n (%)	AEs, n	n (%)	AEs, n	n (%)	AEs, n
Patients with at least one treatment-related AE	41 (80.4)	130	13 (100.0)	83	54 (84.4)	213
Nervous system disorders	27 (52.9)	44	12 (92.3)	23	39 (60.9)	67
Headache	26 (51.0)	40	12 (92.3)	21	38 (59.4)	61
Dizziness	4 (7.8)	4	1 (7.7)	1	5 (7.8)	5
General disorders and administration site conditions	18 (35.3)	26	6 (46.2)	14	24 (37.5)	40
Pyrexia	9 (17.6)	12	4 (30.8)	5	13 (20.3)	17
Chills	8 (15.7)	9	4 (30.8)	4	12 (18.8)	13
Gastrointestinal disorders	12 (23.5)	15	8 (61.5)	16	20 (31.3)	31
Nausea	4 (7.8)	4	8 (61.5)	9	12 (18.8)	13
Vomiting	4 (7.8)	4	5 (38.5)	5	9 (14.1)	9
Investigations	10 (19.6)	16	3 (23.1)	13	13 (20.3)	29
Body temperature increased	5 (9.8)	7	2 (15.4)	2	7 (10.9)	9
Musculoskeletal and connective tissue disorders	9 (17.6)	12	2 (15.4)	2	11 (17.2)	14
Back pain	4 (7.8)	4	2 (15.4)	2	6 (9.4)	6
Vascular disorders	5 (9.8)	5	3 (23.1)	5	8 (12.5)	10
Hypertension	3 (5.9)	3	1 (7.7)	1	4 (6.3)	4
Skin and subcutaneous tissue disorders[†]	3 (5.9)	3	3 (23.1)	3	6 (9.4)	6
Eye disorders [†]	1 (2.0)	1	3 (23.1)	3	4 (6.3)	4

[†]No AEs by PT with a frequency of ≥5% in patients.

Bold terms are general System Organ Class (SOC) headings/terms, and the terms below each bold term are Preferred Terms (PT).

AE: Adverse event; PT: Preferred term.

Of 213 treatment-related AEs (investigator-assessed), the most common was headache (61 events in 38 patients [59.4%]), followed by pyrexia (17 events in 13 patients [20.3%]), nausea (13 events in 12 patients [18.8%]), chills (12 events in 11 patients [18.8%]) and vomiting (nine events in nine patients [14.1%]) (Table 4).

In total, 38 bleeding/hemorrhagic AEs were reported in 20 patients (31.3%) between the start of study drug infusion and the final visit, and were mild or moderate in severity. Only 5/38 bleeding AEs were not excluded for possible causality to the study drug: hematemesis (probably related), contusion (possibly related), epistaxis, purpura and contusion which were all unlikely to be related to the study drug.

Fifty-three percent of patients (34/64) experienced at least one AE during infusion. After completion of study drug infusion, most AEs that occurred within the first 72 h after infusion were clustered within the first 24-h postinfusion period.

No deaths were reported in this study and no patients discontinued from the study due to AEs. There was no clinical evidence of hemolysis in any patient. There were no SAEs reported in children. Four SAEs that required hospitalization for medical management were reported in four adult patients: an event of soft tissue inflammation reported on day 30 in one patient which was severe and given the long lag in temporal association, not considered to be related to the study drug; episodes of headache, reported in two patients, were severe and possibly related to the study drug; and one event of aseptic meningitis after infusion on day 2 was reported in one patient, which was deemed severe and probably related to the study drug. All SAEs resolved without sequelae.

Discussion

This was a Phase III, prospective, multicenter study on chronic ITP (64 evaluable patients, including 13 children) treated with Flebogamma® 10% DIF for 2 days. Overall, the results demonstrated that Flebogamma® 10% DIF administered in two iv. infusions over two consecutive days was effective and safe in treating adults and children with chronic ITP.

With an overall response rate of 81.3% (76.5% of adults and 100% of children) in the mITT population, the predefined primary efficacy end point of >50% response rate was met, months before the predefined end date. This led to the early termination of the study without completing the planned enrolment specified in the protocol, as the efficacy objectives had already been met. Results were confirmed in the PP population. Comparable results were reported in a European trial of adults with ITP (n = 18) following administration of Flebogamma® 10% DIF for two consecutive days, with a response rate of 72.2% [9].

Median time to platelet response of ≤2 days for adult responders was better than the ≤2.5 days observed in a smaller study of chronic ITP adult patients (n = 20) by Julia and colleagues which used the same overall dose of IVIG using a 5% Flebogamma® DIF solution which was infused over 2–5 days [8]. Pediatric patients had a shorter median time to response (≤1 day) than adults. Patients treated with IVIG infusions (1 g/kg) commonly attain a platelet increase within 24 h. In contrast, the response times of other first-line therapies are slower; the response time of corticosteroid therapy is typically several days or weeks and that of iv. anti-D is 4–5 days [2].

In the current study, the median duration of response in adults and children was 7 and 13 days, respectively, which is in agreement with the value of ≥7 days in adults reported by Julia and colleagues [8]. Results from our study are also comparable with those reported by Kovaleva *et al.* for two trials of adult ITP patients treated with Flebogamma® 10% DIF for 2–5 days in which the time and duration of response were approximately 2 and 10 days, respectively [9].

In the present study, prior to the first IVIG infusion, most adults (60.8%) and all children presented with signs of hemorrhage/bleeding. Regression of hemorrhage/bleeding was achieved in most patients during follow-up, irrespective of their classification as responders/nonresponders in terms of platelet count, with all children and 87.1% of adults improving their diathesis. These results are consistent with improvement of bleeding diathesis reported in the previous studies by Julia *et al.* (90%) and Kovaleva *et al.* (83%) [8,9].

The most common treatment-related AEs were headache and pyrexia reported in 59.4 and 20.3% of patients, respectively. Four SAEs were reported in four adult patients, which were resolved without sequelae. These included an episode of severe headache in two patients which were considered to be possibly related to the study drug, as expected for IVIG treatment. A surveillance study on the tolerability and safety of Flebogamma® DIF (10 and 5% IVIG) in adult and pediatric patients found that the most frequent treatment-related AEs were headache and pyrexia [10]. However, serious headaches requiring hospitalization are uncommon [11]. Overall, the surveillance study reported that the products were safe and well tolerated [10]. In the present study, no new safety concerns were identified, and the safety profile remained consistent with the known adverse effects of IVIG treatment.

While the current study reports data for patients, including children, with chronic ITP, a large, pivotal Phase III multicenter, randomized, prospective study (“Treatment with or without IVIg for Kids with ITP [TIKI]”) has recently provided valuable evidence regarding the role of IVIG in children with newly diagnosed ITP [12]. While IVIG did not appear to influence the development of chronic ITP compared with careful observation (the current standard of care in children without major bleeding), IVIG recipients had higher early complete response rates and fewer severe bleeding events than patients who underwent careful observation. Moreover, the presence of *FCGR2B* polymorphism had a significant influence on the outcome of pediatric ITP in untreated patients as well as response to IVIG therapy. Thus, the findings from the TIKI study provide valuable insights into the use of IVIG and the potential for individualized treatment in children with ITP at diagnosis [12].

The current study has some limitations. Of the 64 evaluable patients, only 13 were children, potentially limiting the strength of the study findings. However, the predefined primary efficacy end point (>50% response rate) was met well in advance of the predefined end date. This led to the early termination of the study without completing the planned enrolment specified in the protocol, as the efficacy objectives had already been achieved. Other limitations include the open-label, nonrandomized design of the study; moreover, the study design does not allow the results to be generalized beyond chronic ITP, or in other clinical settings.

In conclusion, in the current study, Flebogamma® 10% DIF administered in two intravenous infusions over consecutive days was confirmed to be safe and effective in treating adults and children with chronic ITP.

Summary points

- Previous studies have shown that intravenous immunoglobulin (IVIG) 2 g/kg infused over 2–5 days is safe and efficacious for children and adults with immune thrombocytopenic purpura (ITP).
- In this multicenter, prospective, open-label, Phase III clinical trial, 64 patients aged 3–70 years (51 adults, 13 children), diagnosed with chronic ITP, received 1 g/kg IVIG (Flebogamma® 10% DIF) over 2 consecutive days.
- The primary efficacy end point (increased platelet counts from $\leq 20 \times 10^9/l$ to $\geq 50 \times 10^9/l$ by day 8) was achieved by 81.3% of patients; mean time to response was 1.7 days (all responders).
- Adverse events, mostly mild or moderate, were reported in 59 patients (92.2%). No deaths were reported and no patients withdrew from the study due to AEs.
- Flebogamma® 10% DIF was safe and effective for the treatment of patients with chronic with ITP.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Data sharing statement

The authors certify that this manuscript reports original clinical trial data. The data reported in this manuscript are available within the article. The study results are available at ClinicalTrials.gov (NCT00511147).

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