Safety and tolerability of subcutaneous immunoglobulin 20% in primary immunodeficiency diseases from two continents

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Aim: This pooled analysis evaluated the safety and tolerability of the subcutaneous immunoglobulin 20% product, Ig20Gly, in primary immunodeficiency diseases using data from two Phase II/III studies conducted in North America and Europe. **Patients & materials/methods:** Patients received Ig20Gly (volumes, ≤ 60 ml/site; rates, ≤ 60 ml/h/site). Adverse events (AEs), tolerability and infusion parameters were assessed. **Results:** Patients (2–83 years; N = 122) received 6676 Ig20Gly infusions. No causally related serious or severe AEs were reported. Thirty-five patients (28.7%) reported 232 causally related local AEs. Twenty-seven patients (22.1%) reported 165 causally related systemic AEs. There was no association between the infusion volume or rate and causally related local AEs. **Conclusion:** Ig20Gly was well tolerated in a broad population of patients with primary immunodeficiency diseases.

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There are more than 300 distinct primary immunodeficiency diseases (PID) resulting from more than 320 different gene mutations [1]. Many of these conditions are associated with defective production or low levels of immunoglobulin (Ig) that make patients more susceptible to bacterial and viral infections. Ig replacement therapy is indicated for the treatment of PID with defective antibody production and has been shown to reduce the frequency and severity of infections [2].

Immunoglobulin replacement therapy may be administered by intravenous (IV) or subcutaneous (SC) infusions [2,3], with the clinical response as the primary driver of dosing decisions. IV administration of IG (IVIG) requires monthly doses of 300–800 mg/kg body weight and is typically administered every 3–4 weeks over 2–4 h. IVIG is delivered rapidly into the systemic circulation, which leads to peaks of serum Ig levels that are thought to be associated with an increased incidence of systemic adverse reactions [3]. In contrast, SC infusion of IG (SCIG) allows

slow diffusion of IG from the SC tissue into systemic circulation, smoothing significant serum level variations and leading to stable IgG levels and lower rates of systemic adverse events (AEs) compared with IV administration [3]. In addition, SCIG infusion offers the convenience of self-administration at home [4,5]. Drawbacks of SCIG therapy compared with IVIG include a higher incidence of local adverse reactions and a need for more frequent infusions and multiple infusion sites due to the limited volume that can be infused into each site [3,6].

The development of more highly concentrated SCIG products allows for the infusion of the same dose in smaller volumes compared with less concentrated products permitting fewer infusion sites and possibly reducing the frequency of infusions [6]. One such preparation, Ig20Gly (CUVITRU, immune globulin subcutaneous [human] 20% solution; Baxalta US, Inc., a member of the Takeda group of companies, CA, USA), is a ready-for-use human IgG preparation produced with a manufacturing process similar to the IVIG 10% solution (GAMMAGARD LIQUID/Kiovig, Baxalta US, Inc., a member of the Takeda group of companies), except for an additional step of ultra-/diafiltration resulting in a final protein concentration of 20% (weight/volume). Ig20Gly can be infused at up to 60 ml/h per site and has been shown to be efficacious and well tolerated in two Phase II/III clinical studies conducted in Europe [7] and North America [8]. The safety and tolerability of Ig20Gly were assessed in both trials in a consistent manner facilitating a pooled analysis of AEs and tolerability data from these two studies.

Patients & methods

Study design

This is a pooled analysis of two prospective, open-label clinical trials in Europe (ClinicalTrials.gov NCT01412385) [7] and North America (ClinicalTrials.gov NCT01218438) [8]. Both studies were performed in accordance with the Declaration of Helsinki and the international standards of Good Clinical Practice. Patients were enrolled at 15 sites in the USA and Canada for the North American study, and at 16 sites in seven countries (Germany, Austria, Sweden, The Netherlands, Great Britain, Belgium and Hungary) for the European study. Written informed consent was obtained from all patients before undergoing any study procedure. Details of the inclusion and exclusion criteria and study design have been published previously [7,8]. In brief, patients were eligible for study inclusion if they were aged ≥ 2 years with a documented diagnosis of humoral immunodeficiency for which they had been receiving a stable monthly equivalent dose of IG (IV or SC) at an average dose of 300–1000 mg/kg body weight every 4 weeks for ≥ 3 months before enrollment and had a serum IgG trough level of >500 mg/dl at screening [7,8].

The North American trial consisted of four study periods. During period 1, all patients received IVIG 10% for 13 weeks to determine the area under the curve for IgG after IVIG treatment. During periods 2–4, patients received Ig20Gly. In period 2, Ig20Gly was administered in some patients at a dose adjusted to 145% of the IVIG dose for approximately 12–16 weeks to assess bioequivalence; in period 3, all patients received the same adjusted dose for 12 weeks. Patients received Ig20Gly at individually adapted doses during period 4 (40 weeks) [8].

The European trial consisted of two periods. During period 1, patients received IVIG 10% for 13 weeks or SCIG 16% for 12 weeks to attain a stable baseline serum IgG before starting Ig20Gly treatment. Patients were treated with Ig20Gly for 52 weeks during period 2 [7].

Patients had the choice to infuse Ig20Gly into one site or multiple sites simultaneously using a T34L electromechanical syringe driver (Caesarea Medical Electronics, Caesarea, Israel) and a high-flow 24-gauge needle set (MarCal Medical, MD, USA) ranging in length from 6–12 mm, at the discretion of the investigator [7,8]. Infusion sites were rotated to avoid repeated use of the same site within a short period. Infusion rates were increased incrementally. The first two infusions were initiated at a rate of 10 ml/h per site and could be increased to a maximum of 20 ml/h per site. Subsequent infusions could be infused at a maximum rate of 60 ml/h per site as tolerated. Infusion volumes up to 60 ml per site were permitted in patients with body weight ≥ 40 kg as tolerated or according to patient preference and physician discretion. For patients weighing <40 kg, the infusion volume was ≤ 20 ml per site for the initial two infusions and then increased up to 60 ml per site as tolerated. Home infusion was allowed with the assistance of a healthcare professional or by the patient or a caregiver after adequate training [7,8].

Safety assessments

Safety was assessed by clinical and laboratory assessments throughout the two studies [7,8]. AEs occurring during infusions conducted at the study site (the first three infusions, and subsequently every 8–12 weeks) were recorded by the investigator. Investigators were trained on the assessment of potential AEs. Investigators also provided guidance to the patient or caregiver regarding the identification and documentation of local and systemic AEs in the event

Table 1. Patient demographics.

Demographic	Age group (years)					All patients (N = 122)
	< 6 (n = 6)	6–11 (n = 22)	12–15 (n = 11)	16–64 (n = 71)	≥ 65 (n = 12)	
Sex, n (%)						
– Male	5 (83.3)	19 (86.4)	9 (81.8)	34 (47.9)	1 (8.3)	68 (55.7)
– Female	1 (16.7)	3 (13.6)	2 (18.2)	37 (52.1)	11 (91.7)	54 (44.3)
Median (range) age, years	4 (2–5)	8 (6–11)	13 (12–13)	39 (16–63)	67 (65–83)	32 (2–83)
Median (range) weight, kg	15.9 (13–39)	29.1 (19–56)	50.8 (30–82)	76.2 (48–162)	67.4 (48–113)	66.8 (13–162)
Mean (SD) Ig20Gly dose, g/kg/week	0.17 (0.05)	0.18 (0.05)	0.19 (0.10)	0.19 (0.08)	0.21 (0.06)	0.19 (0.08)

Ig20Gly: Immune globulin subcutaneous [human] 20% solution; CUVITRU, Baxalta US, Inc.

that an AE were to occur at home. Patients were instructed to inform the investigator or site immediately if an AE occurred. Patients were also contacted by the investigator within 3–5 days of each infusion either at the study site or at home as follow-up to ensure appropriate AE documentation. Patients used an eDiary tablet to continuously record home treatments, AEs and additional information. Investigators reviewed patients' eDiary entries at every site visit. All AEs were assessed by the investigator for seriousness, severity, temporal association (occurring within 72 h of the infusion) and possible causal relatedness to Ig20Gly.

Routine hematology screening was performed to monitor for hemolysis. In the event of a ≥ 2 g/dl decrease in hemoglobin, assessments for hemolysis were to be performed within 48–72 h of receipt of the hemoglobin value. Hemolysis assessments included a direct antiglobulin (Coombs) test, plasma-free hemoglobin level, reticulocyte count, lactate dehydrogenase, serum haptoglobin and urine hemosiderin [7,8].

Results

A total of 122 patients aged 2–83 years received Ig20Gly for a median (range) of 365 (30–629) days in the two clinical trials (Table 1). Overall, 68 male and 54 female patients were enrolled; however, the male to female ratio varied with age. Most patients aged ≤ 15 years were male (33/39, 84.6%), whereas more patients aged ≥ 16 years were female (48/83, 57.8%). A total of 6676 Ig20Gly infusions were administered to the 122 patients enrolled in the two trials.

In the pooled population, 112 patients (91.8%) completed the planned duration of treatment. In the North American trial, 74 patients received Ig20Gly. Of these, seven patients discontinued: five patients withdrew consent for reasons unrelated to AEs, one patient discontinued owing to an AE unrelated to Ig20Gly and one patient discontinued owing to poor adherence to the study protocol. In the European study, 48 patients received Ig20Gly. Of these, three patients discontinued during Ig20Gly treatment: one patient reported pain during and after administration of Ig20Gly and chose to stop participation, and two patients withdrew consent for reasons unrelated to an AE.

Adverse events

There were no serious or severe AEs related to Ig20Gly treatment reported in either study. Overall, 397 nonserious AEs that were considered to be causally related to Ig20Gly (frequency rates of 0.059 per infusion) were reported in 48 of 122 patients (39.3%) enrolled in the two trials.

Thirty-five patients (28.7%) reported a total of 232 causally related local AEs in 2.7% of infusions with frequency rates of 0.035 per infusion (Table 2). All Ig20Gly causally related local AEs were considered to be mild (226 AEs; 0.034/infusion) or moderate (6 AEs; <0.001 /infusion) in severity. The most common local reactions were infusion site erythema (0.012/infusion), infusion site pain (0.009/infusion), and infusion site swelling (0.007/infusion). Of note, 34.1% (79/232) of the local AEs deemed causally related to Ig20Gly were reported by the parent of one patient; all 79 AEs were mild. This patient/parent completed the study and expressed preference for Ig20Gly over other IgG treatment options at the end of the study.

A total of 27 of 122 patients (22.1%) reported 165 systemic AEs that were deemed causally related to Ig20Gly, with frequency rates of 0.025 per infusion (Table 3). All Ig20Gly causally related systemic AEs were considered to be mild (101 AEs; 0.015/infusion) or moderate (64 AEs; 0.010/infusion) in severity. The most frequently reported causally related systemic AEs were headache (0.010/infusion), diarrhea (0.007/infusion) and fatigue

Table 2. Causally related[†] local adverse events (excluding infections) occurring in $\geq 1\%$ of patients.

Adverse event	AEs, n	Affected patients, n (%) n = 122	Affected infusions, n (%) n = 6676	AEs/patient	AEs/infusion
Total local AEs [‡]	232	35 (28.7)	181 (2.711)	1.902	0.035
Infusion/injection site erythema	77	18 (14.8)	76 (1.138)	0.631	0.012
Infusion/injection site pain or discomfort	57	18 (14.8)	55 (0.824)	0.467	0.009
Infusion site swelling	46	4 (3.3)	46 (0.689)	0.377	0.007
Infusion/injection site pruritus	34	10 (8.2)	34 (0.509)	0.279	0.005
Infusion site urticaria	8	3 (2.5)	8 (0.120)	0.066	0.001
Infusion/injection site reaction	3	2 (1.6)	3 (0.045)	0.025	<0.001

[†]As assessed by the investigator.[‡]Includes 79 local AEs, all mild, reported by 1 patient (deemed to be related to treatment).

AE: Adverse event.

Table 3. Causally related[†] systemic adverse events (excluding infections) occurring in $\geq 1\%$ of patients.

Adverse event	AEs, n	Affected patients, n (%)	Affected infusions, n (%)	AEs/patient	AEs/infusion
Total systemic AEs [‡]	165	27 (22.1)	145 (2.172)	1.352	0.025
Headache	70	11 (9.0)	65 (0.974)	0.574	0.010
Diarrhea [‡]	49	4 (3.3)	49 (0.734)	0.402	0.007
Fatigue	11	7 (5.7)	11 (0.165)	0.090	0.002
Nausea	9	5 (4.1)	9 (0.135)	0.074	0.001
Dizziness	6	2 (1.6)	6 (0.090)	0.049	<0.001
Myalgia	5	3 (2.5)	5 (0.075)	0.041	<0.001
Migraine	4	2 (1.6)	4 (0.060)	0.033	<0.001
Somnolence	3	2 (1.6)	3 (0.045)	0.025	<0.001

[†]As assessed by the investigator.[‡]46 AEs (diarrhea events) were reported by 1 patient with a history of recurrent diarrhea.

AE: Adverse event.

(0.002/infusion). Of note, one patient in the European study with a medical history of ongoing recurrent diarrhea reported 46/49 of the diarrhea events. For the most frequently reported causally related systemic AE (headache), the median (range) time between onset of the AE and start time of the preceding infusion was 8 (0–169) h and time between AE onset and its resolution was 25.2 (0–714) h.

Tolerability

Interruptions or reductions in the infusion rate due to tolerability or AEs were rarely required during treatment with Ig20Gly. Overall, 99.8% of infusions in both studies were administered without interruption or a reduction in the infusion rate. Moreover, there was no apparent association between infusion volumes and infusion rates per site and the rate of Ig20Gly causally related local AEs (Figures 1 & 2).

Administration characteristics

The median (range) number of sites per infusion was 2 (1–5), and the infusion volume was 30.3 (6.4–76.0) ml per site. The median (range) infusion duration was 0.95 (0.2–6.4) h, and the maximum infusion rate was 40 (2.5–180.0) ml/h per site (Table 4).

Discussion

Subcutaneous administration of Ig offers a treatment option for patients permitting self-administration at home with fewer systemic AEs than IV administration [6,9,10]. SC administration results in a more gradual absorption and lower peak levels of serum IgG, which likely accounts for the improved systemic tolerability [11]. However, SCIG formulations, in particular those with a low IgG concentration (e.g., 10 or 16%), have limitations in the volume that can be infused per site [9,10]. The development of more highly concentrated SCIG products allows for infusion of the same dose in smaller volumes, thus reducing the number of infusion sites and possibly the frequency of

Figure 1. Percentage of infusions with local adverse events by infusion volume (ml) per site for individual studies and pooled data. Portions of individual study data previously reported [7,8].
AE: Adverse event.

Table 4. Ig20Gly administration characteristics.

Characteristic	European study, n = 48		North American Study, n = 74		Pooled, N = 122	
	Infusions, n	Median, min–max	Infusions, n	Median, min–max	Infusions, n	Median, min–max
Duration of infusion, h	2335	0.95 (0.3–4.1)	4162	0.95 (0.2–6.4)	6497	0.95 (0.2–6.4)
Sites per infusion, n	2338	2.0 (1–5)	4326	2.0 (1–4)	6664	2.0 (1–5)
Infusion volume, ml/site	2338	16.6 (6.5–48.0)	4326	39.5 (6.4–76.0)	6664	30.25 (6.4–76.0)
Maximum infusion rate, ml/h/site	2338	20.0 (2.5–60.0)	4314	60.0 (4.4–180.0)	6652	40.0 (2.5–180.0)

Ig20Gly: Immune globulin subcutaneous [human] 20% solution; CUVITRU, Baxalta US Inc.
Individual study data previously reported [7,8].

infusions compared with less concentrated SCIG preparations [6]. The 20% IG product Ig20Gly contains glycine as a stabilizing agent to prevent and minimize IgG dimerization, has a viscosity of 14.4 mPas, and has an osmolality of 280–292 mOsm/kg, which is similar to the osmolality of extracellular fluid (280–295 mOsm/kg). Ig20Gly can be infused at up to 60 ml/h per site and has been shown to be efficacious and well tolerated in two Phase II/III clinical studies conducted in nine countries in Europe [7] and North America [8]. This pooled safety and tolerability analysis of 6676 infusions of Ig20Gly administered to 122 patients over a median duration of 1 year demonstrated that Ig20Gly was well tolerated in a diverse population of patients with PID.

The number and incidence of local and systemic AEs were low, and no causally related serious or severe AEs were reported with Ig20Gly. As expected, the rate of causally related systemic AEs (0.025/infusion) was lower than that of causally related local AEs (0.035/infusion). Regarding systemic AEs, it is also important to note that causally related, nonserious, systemic AE rates in these studies were substantially lower with SCIG than with IVIG [7,8]. As previously reported [7,8], causally related, nonserious systemic AE rates (the number of AEs divided by the

Figure 2. Percentage of infusions with local adverse events by maximum infusion rate per site (ml/h/site) for individual studies and pooled data. Individual study data previously reported [7,8]. AE: Adverse event.

number of infusions) with SCIG were approximately 3-fold to 11-fold lower than with IVIG. Furthermore, the frequency of systemic AEs in this pooled analysis may have been higher than expected due to a single patient in the North American study who reported multiple systemic AEs under some administration conditions. Systemic gastrointestinal disorders are common in individuals with PIDs [12]. The use of SCIG over IVIG is preferred in these individuals because systemic AEs, including diarrhea and gastrointestinal-related issues, on SCIG are rare [3]. As such, SCIG is less likely to exacerbate pre-existing gastrointestinal conditions than IVIG.

No treatment-related local AEs were reported in 97.3% of infusions. Notably, a 13-year-old patient reported 79 of the 232 (34.1%) local AEs causally related to Ig20Gly in the European study, all of which were mild [7]. This patient was treated with IVIG before study enrollment; however, the patient completed the study as planned and expressed preference for the SCIG Ig20Gly over other IG treatment options at the end of the study.

In further regard to the safety of SCIG, it should be noted that it has previously been reported that there were no instances of hemolysis with SCIG in either study [7,8]. Although 12 patients (6 in each study) had temporary declines in hemoglobin of ≥ 2.0 g/dl, there was no concordance between these declines and other laboratory tests at any time in either study that supported a diagnosis of hemolysis [7,8]. Additionally, there were no reported adverse events related to thrombotic risk in these studies.

The favorable tolerability of Ig20Gly infusions allowed the administration of faster infusion rates (median, 40 ml/h per site) and volumes per site (median, 30 ml per site). The median infusion duration was < 1 h. Overall, 99.8% of infusions in the two studies did not require interruptions or reductions in the infusion rate. There was no apparent association between infusion volumes and infusion rates per site and the rate of Ig20Gly causally related local AEs.

The combination of relatively large infusion volumes per site, rapid infusion rates and short infusion durations achieved with Ig20Gly is noteworthy. In the North American study, the median of the maximum infusion rate was 60 ml/h per site and was achieved in more than half of completed Ig20Gly infusions without compromising

tolerability [8], indicating that the majority of patients can tolerate the maximum recommended infusion rate of 60 ml/h per site; 71.6% of patients reached the infusion rate of ≥ 60 ml/h per site at least once during the North American trial. The median of the maximum infusion rate and volume per site was lower in the earlier European study; however, the ranges in both studies were overlapping, and the median infusion duration and number of sites required were the same (0.95 h and 2 sites/infusion, respectively) [7,8]. In general, North American physicians use higher doses than their European counterparts, as evident in the median doses used for patients before entry into the North American trial (IVIG, 146.7 mg/kg/week; SCIG, 154.0 mg/kg/week) and the European trial (IVIG, 113.1 mg/kg/week; SCIG, 114.0 mg/kg/week). Lower mean doses were also used during the European trial (125 mg/kg/week [7] vs 222 mg/kg/week in the North American study [8]), which may account for the slower median infusion rates and smaller volumes. This dose difference in the two studies is also attributable to the manner in which the Ig20Gly dose was calculated. In the North American study, a systemic exposure equivalent to previous IVIG 10% treatment was targeted, and the Ig20Gly dose was adjusted to compensate for the lower bioavailability of SC administration of IgG [13]. In the European study, patients were switched from IVIG to SCIG using a 1:1 dose adjustment ratio, with the aim of maintaining stable IgG trough levels of >500 mg/dl.

Safety was assessed in a rigorous, comprehensive manner in the two studies. Investigators were trained in a consistent manner to identify potential AEs, and all patients, including those who received home-based treatment, were evaluated at the study site at regular intervals (i.e., 8–12 weeks). Patients were given eDiaries in which to record data during and after infusions administered at home, and investigators were required to contact patients 3–5 days after each infusion to ask if an AE had occurred and to ensure all relevant AE data were recorded. Collectively, these patient-centered measures were intended to provide a complete representation of the incidence and severity of AEs, regardless of whether a patient chose to have the infusions administered in the clinic or at home.

In the current analysis of Ig20Gly, the median number of infusion sites used was 2, and the median of the maximum infusion rate and volume per site was 40 ml/h per site and 30.3 ml per site, respectively; however, patients tolerated a wide range of infusion rates and volumes of Ig20Gly, suggesting that the rate and volume used for IG administration should be individualized for each patient. For the 20% IG product IgPro20 (Hizentra®, CSL Behring AG, Bern, Switzerland) [14], the prescribing information recommends the use of up to eight infusion sites simultaneously, with a maximum volume of 25 ml per site and a maximum rate of 25 ml/h per site for PID (volumes up to 50 ml per site and rates up to 50 ml/h per site for chronic inflammatory demyelinating polyneuropathy) [15]. Less concentrated products require a larger volume than more highly concentrated products to administer an equivalent dose of IgG, which is often achieved by using multiple infusion sites. One example of such a product with an IG concentration of 16% is SUBCUVIA (Baxter Healthcare Ltd, Berkshire, UK), for which the recommended maximum injection volume is 5–15 ml per site and the recommended maximum infusion rate is 20 ml/h, with no limit on the number of infusion sites [16]. Similarly, a product with an IG concentration of 10%, GAMMAGARD LIQUID, requires ≤ 30 ml per site (in up to 8 sites) at an infusion rate of 20–30 ml/h per site in patients weighing ≥ 40 kg [17].

One limitation of this analysis is the retrospective combination of data from two studies conducted in geographically separate populations, which may have different clinical practices. Although the study designs were similar in the North American and European trials, the dose of Ig20Gly was calculated differently in the trials, resulting in slightly different infusion parameters between studies. This difference, however, resulted in the ability to gather and compare safety and tolerability parameters across a wider dose range than would otherwise have been possible. In addition, infusion parameters collected during clinical studies may not reflect real-world administration practices.

Conclusion

The results of this pooled analysis demonstrate that Ig20Gly appears to be safe and well tolerated in a diverse population of patients with PID. Low rates of causally related local and systemic AEs were observed. There was no association between the infusion volume or rate and the rate of casually related local AEs; 99.8% of infusions were administered without interruption or rate reductions. The favorable tolerability permitted fast infusion rates, large infusion volumes per site and a median infusion duration of <1 h. The flexibility in selection of infusion rates/volumes per site and favorable tolerability make Ig20Gly a valuable treatment option for adult and pediatric patients with PID.

Summary points

- Immunoglobulin (IG) replacement therapy is indicated for the treatment of primary immunodeficiency diseases (PID) with defective antibody production.
- This pooled analysis assessed adverse events (AEs), tolerability and infusion parameters in patients with PID who received the subcutaneous IG 20% product, Ig20Gly, at volumes of ≤ 60 ml/site and at rates of ≤ 60 ml/h/site.
- A total of 122 patients aged 2–83 years received 6676 infusions (mean $\pm$ SD of 54.7 ± 14.6 infusions per patient) of Ig20Gly.
- There were no serious or severe AEs related to Ig20Gly treatment reported.
- Thirty-five patients (28.7%) reported 232 causally related local AEs (frequency rate of 0.035 per infusion) and 27 patients (22.1%) reported 165 causally related systemic AEs (frequency rates of 0.025 per infusion).
- Overall, 99.8% of infusions were administered without interruption or a reduction in the infusion rate and there was no apparent association between infusion volume or rate with the rate of Ig20Gly causally related local AEs.
- The median (range) number of sites per infusion was 2 (1–5) and of infusion volume per site was 30.3 (6.4–76.0) ml.
- Subcutaneous immunoglobulin 20% solution, Ig20Gly, was well tolerated in a broad population of patients across a wide age range with PID from two continents.

Trial registration

This study reports data from two prospective, open-label clinical trials conducted in North America (registered on www.clinicaltrials.gov: NCT01218438) and Europe (registered on clinicaltrialsregister.eu: EudraCT #:2010-019459-23 and www.clinicaltrials.gov, NCT01412385).

Author contributions

All authors were involved in the conception and design of the study, data generation, data analysis and interpretation, preparation and writing of the manuscript, critical review of the manuscript and approved the final version of the manuscript. D Suez, G Krivan, S Jolles, M Stein, S Gupta, K Paris, PM van Hagen and N Brodzski were investigators who enrolled patients in the North American and European trials. W Engl was the statistician, and H Leibl, B McCoy, and L Yel were clinical leads involved in each trial.

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Financial & competing interests disclosure

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Ethical conduct of research

This is a pooled analysis of two prospective, open-label clinical trials in Europe (ClinicalTrials.gov NCT01412385; Borte M *et al.* *Clin. Exp. Immunol.* 187[1], 146–159 [2017]) and North America (ClinicalTrials.gov NCT01218438; Suez D, *et al.* *J. Clin. Immunol.* 36[7], 700–712 [2016]). Both studies were performed in accordance with the Declaration of Helsinki and the international standards of Good Clinical Practice. Patients were enrolled at 15 sites in the USA and Canada for the North American study, and at 16 sites in seven countries for the European study. Written informed consent was obtained from all patients before undergoing any study procedure.

Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms (if any) agreed upon their receipt. The source of this data is: NCT01218438; NCT01412385. The datasets, including redacted study protocol, redacted statistical analysis plan, and individual participant data behind the results reported in this article, will be available 3 months after manuscript publication to researchers who provide a methodologically sound proposal after de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization. Data requests should follow the process outlined in the Data Sharing section of the Sponsor's website: <http://www.shiretrials.com/en/our-commitment-to-transparency/data-sharing-with-researchers> and should be directed to clinicaltrialdata@shire.com

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Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

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