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Efficacy and safety of octanorm (cutaqui[®]) in adults with primary immunodeficiencies with predominant antibody deficiency: a prospective, open-label study

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Aim: To evaluate efficacy and safety of octanorm (16.5% subcutaneous immunoglobulin) in adult patients with primary immunodeficiencies. **Patients & methods:** Primary immunodeficiencies patients (18–70 years) previously treated with intravenous immunoglobulin were included in this Phase III study. Octanorm was administered subcutaneously once weekly over 8 months. End points included infections, adverse events and quality of life. **Results:** 25 patients (mean age 35.2 years, female 60.0%) were recruited, 24 completed the study. Mean dose of octanorm was 0.11 g/kg/week. No serious bacterial infections occurred. Three patients (12.0%) had an adverse event (mild) assessed as related to octanorm. Both the mental and physical summary 36-item Short Form Health Survey scores were improved. **Conclusion:** Octanorm is effective, safe and improves quality of life. **Clinical Trial registration number:** NCT03988426.

Lay abstract: This study assessed the use of octanorm (cutaqui[®]), a 16.5% human immunoglobulin solution given as an infusion under the skin (subcutaneous), in adults with primary immunodeficiencies (PIDs). PIDs are inherited diseases that cause immune system malfunction, and patients usually require long-term immunoglobulin therapy to protect them from serious infections. Subcutaneous immunoglobulin can be self-administered at home, which may be less disruptive than intravenous immunoglobulin administration. In this study, 25 adult PID patients who had previously received intravenous immunoglobulin were switched to subcutaneous immunoglobulin with once-weekly octanorm for 8 months. No serious bacterial infections and few treatment-related side effects were reported. Patients also reported improved quality of life. Octanorm was effective and well tolerated in adults with PID in this study.

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Keywords: efficacy • octanorm • Phase III • primary immunodeficiency • quality of life • safety • SCIG • subcutaneous immunoglobulin

Primary immunodeficiencies (PIDs) are a group of genetic disorders that includes over 350 different conditions [1]. The exact incidence of PID is unknown but it could be as high as 1 in 2000 live births [2].

The most common type of PID is antibody deficiency, which includes common variable immunodeficiency and primary hypogammaglobulinemias, such as the X-linked agammaglobulinemia, and represents over 50% of all PIDs [3]. Clinical symptoms include a combination of infectious and noninfectious manifestations (lymphoproliferation, malignancy, autoimmunity, etc.). Individuals with antibody deficiencies have recurrent sinopulmonary infections with encapsulated bacteria and recurrent viral infections of the respiratory and gastrointestinal tracts [2].

Figure 1. Study design.

^aPatients must have had at least four infusions of IVIG to enroll in the study. The last infusion of IVIG could take place before or during the screening period.

^bThe first dose of octanorm[®] was to be administered within 7 weeks of the screening visit and approximately at the time when the patient's next IVIG dose would have been due.

IVIg: Intravenous immunoglobulin.

Long-term immunoglobulin (Ig) replacement therapy is indicated to control infectious manifestations and prevent complications associated with poor prognosis and low quality of life (QoL), such as bronchiectasis [2].

While the early Ig preparations were mainly given intramuscularly, administration via intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) routes have become the standard of care. Since their introduction in the 1980s, continuous development has made the IVIg and SCIg preparations more and more effective [4,5]. IVIg and SCIg therapies are similarly effective in reducing the rate of infections [6]. However, SCIgs have a more consistent pharmacokinetic profile and a more favorable safety profile [7]. In addition, SCIgs can be self-administered at home, which is often seen as less disruptive to daily activities, making it easier to work or study and reducing the time spent travelling to hospital to receive treatment, all factors that can positively influence a patient's QoL. Furthermore, small and portable pumps used to administer SCIg therapy do not interfere with normal activities at home. SCIgs can also be used when access to peripheral or central veins is difficult [7].

Octanorm (marketed as cutaquir[®] in the USA, Canada and Europe; Octapharma AG, Switzerland) is a 16.5% human Ig solution for subcutaneous administration [8,9]. The manufacturing process for octanorm is based on the well-established process of Octapharma's IVIg product octagam[®] and makes use of the same virus elimination procedures [10]. In a prospective, open-label, single-arm, Phase III study that included 61 pediatric and adult patients with PID, octanorm effectively prevented infections, with no serious bacterial infections (SBIs) reported, and was well tolerated [11].

The objective of this study was to assess the efficacy, safety and QoL of octanorm in adult patients with PID in Russia.

Patients & methods

This was a prospective, open-label, noncontrolled, single-arm, multicentre, Phase III study conducted at five study sites in Russia. It consisted of an 8-week wash-in/wash-out period and a 6-month (6 × 4 weeks) efficacy period (Figure 1).

Adult patients (age 18–70 years) with confirmed PID requiring Ig replacement therapy were included if they had been previously treated with ≥4 infusions of any IVIg (constant dose of 0.2–0.8 g/kg/month) and had data on ≥2 IgG trough levels ≥5.0 g/l during these infusions. Therefore, all patients had been receiving IVIg for at least 9 weeks (if they were on a 3-week schedule) or 12 weeks (if they were on a 4-week schedule) before switching to the study drug. In addition, women of childbearing potential had to have a negative pregnancy test and to agree to use a reliable method of contraception for the duration of the study.

Patients were excluded if they had an acute infection requiring intravenous antibiotic treatment in the 2 weeks prior to or during the screening period; were treated with immunosuppressive drugs; had a history of adverse reactions to IgA; had malignancies of lymphoid cells and immunodeficiency with lymphoma; severe liver impairment; renal function impairment; known protein-losing enteropathies or proteinuria; known or suspected human immunodeficiency virus; HCV or HBV infection; had been exposed to blood or any blood or plasma products (except IVIg for PID treatment) in the previous 3 months; or had a history of hypersensitivity to these products.

Study treatment

All patients received octanorm once weekly (± 2 days with a minimum of 4 days between doses) by subcutaneous infusion using an RMS FREEDOM60 infusion pump. The dose was calculated by dividing the dose of the previously administered IVIG by the number of weeks between doses. The dose of octanorm was adjusted if patient's body weight changed by $>5\%$, if IgG trough levels were <5 g/l or if there was a clinical need for adjustment. All patients who completed the study received a total of 32 infusions of octanorm over approximately 8 months. For the first four administrations of octanorm, the maximum recommended flow rate was 15 ml/h per site. During subsequent infusions, the flow rate could be gradually increased to a maximum of 25 and 50 ml/h for all sites up to infusion 16. After infusion 16, the rate could be increased to 80 ml/h for all infusion sites, if tolerated. Starting with the 24th infusion, the maximum flow rate could be (gradually) increased up to 100 ml/h for all infusion sites, if the previous rates were well tolerated.

The patients received training at the study site to self-administer octanorm for ≥ 4 infusions. After that, all infusions were self-administered, with every fourth infusion administered at the study site to ensure proper administration technique.

Prophylactic antibiotics were not prohibited during the study, but are not routinely used in patients with PID in Russia, except those with recurrent infections despite treatment with IgG.

Assessments

Patients were provided with diaries in which they were asked to record the date, volume and speed of infusion, infusion site, occurrence of infections, adverse events (AEs) and infusion site reactions, missed work/study days, inpatient hospital stays and any changes in concomitant therapies between visits. The following assessments and procedures were performed during study site visits (weekly for the first 4 weeks then every 4 weeks): drawing of blood samples; determination of body weight; review of the patient diary; physical examination; QoL assessments; assessments of local infusion site reactions; urine sampling; and urine pregnancy tests.

The primary end point of this study was the rate of SBIs, defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and visceral abscess, per person-year on treatment. Other efficacy end points included the annual rate of all infections of any kind or severity; nonserious infections (total and by category); time to resolution of infections; use of antibiotics (number of days and annual rate); hospitalizations due to infection (number of days and annual rate); episodes of fever; days of work/study missed due to infections and their treatment; QoL assessment using the 36-item Short Form Health Survey (SF-36); and trough levels of total serum IgG throughout the study. The severity of infections was graded as mild (an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities), moderate (an AE which is sufficiently discomforting to interfere with the patient's routine activities) or severe (an AE which is incapacitating and prevents the pursuit of the patient's routine activities) by the investigator.

Safety end points included all AEs excluding infections, as well as local infusion site reactions (assessed as mild, moderate or severe by the patient using a 4-point rating scale). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA); medications were coded using the WHO Drug Dictionary. In this study, infusion site reactions were not considered AEs and were reported separately.

Statistics

While no formal sample size calculation was performed, it was estimated that between 20 and 25 patients were to be recruited.

No confirmatory analyses were planned. For continuous quantitative variables, mean, standard deviation, median, minimum and maximum were calculated. For categorical qualitative variables, frequency and percentage of patients in the particular category were calculated. Missing data were not imputed. All analyses were conducted using the R Project for Statistical Computing (www.r-project.org/about.html).

Ethics

Study protocol and the informed consent form were approved by the Independent Ethics Committees at each study site. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice issued in July 1996, the European Directive 2001/20/EC and in compliance with the protocol and all subsequent substantial amendments and valid national laws. All patients provided written informed consent before entering the study.

Table 1. Baseline patient characteristics.	
Characteristic	n = 25
Male, n (%)	10 (40.0)
Age, years	
Mean ± SD	35.2 ± 14.0
Median (range)	33 (18–64)
Body type, n (%)	
Mesomorph	21 (84.0)
Ectomorph	4 (16.0)
BMI, kg/m ²	
Mean ± SD	23.0 ± 3.5
Median (range)	23.0 (18.0–31.1)
Immunodeficiency, n (%)	
Common variable immunodeficiency	23 (92.0)
X-linked agammaglobulinemia	2 (8.0)
Medical history, n (%)	
Chronic bronchitis	15 (60.0)
Chronic sinusitis	8 (32.0)
Chronic tonsillitis	6 (24.0)
Splenomegaly	5 (20.0)
Lymphadenopathy	5 (20.0)
Sinusitis	5 (20.0)
Gastro-oesophageal reflux disease	4 (16.0)
Interstitial lung disease	3 (12.0)
Chronic obstructive pulmonary disease	3 (12.0)
Thrombocytopenia	3 (12.0)
Iron-deficiency anemia	3 (12.0)
Gastroduodenitis	3 (12.0)
Polypectomy	3 (12.0)
Chronic urticaria	3 (12.0)
SD: Standard deviation.	

Results

A total of 25 patients with PID were recruited at the five centers (n = 10, n = 5, n = 4, n = 3 and n = 3 at each center, respectively). Of these, 24 patients completed the study; one patient decided to discontinue after 8 weeks because he moved away from the study center. The patient resumed IVIG at the new hospital they attended in accordance with that center’s protocol for PID management; therefore the reason for discontinuing octanorm was unrelated to the efficacy and safety of SCIG treatment. The median age of patients was 33 years (range: 18 to 64 years); 60% (n = 15) were female (Table 1). Most patients had common variable immunodeficiency (n = 23, 92.0%), while two patients (8.0%) had X-linked agammaglobulinemia. No patient received prophylactic antibiotics.

Extent of exposure

A total of 775 infusions were self-administered by 25 patients during the study. All 24 patients who completed the study received 32 infusions each, while the one patient who discontinued the study prematurely received seven infusions. The mean (SD) dose of octanorm was 0.11 (0.02) g/kg/week and the median (range) dose was 0.1 (0.06–0.16) g/kg/week. The median (range) duration of infusion across all infusions was 77 (20–250) min (mean [SD] 84.0 [29.6] min); the mean duration of infusion progressively decreased over the course of the study from 117.2 min for infusions 1–4 to 81.2 min for infusions 5–28 and 72.2 min for infusions 29–32. The mean (SD) maximum infusion rate was 54.2 (13.2) ml/h (median 51.8; range 28.2–67.8 ml/h). In one patient, infusion was interrupted for 5 min during visit 5 due to problems with the infusion pump. No other infusion interruptions were reported.

Table 2. Norm-based SF-36 scores in the full analysis set population.

	Baseline	Visit 13	Change from baseline
n	25	24	24
Physical functioning	51.7 (6.5)	52.4 (5.0)	1.0 (4.7)
Role physical	46.0 (9.0)	48.7 (7.4)	2.9 (9.3)
Bodily pain	49.0 (10.8)	57.5 (8.7)	8.6 (11.3)
General health	41.8 (9.3)	41.0 (9.0)	-0.5 (7.2)
Vitality	48.7 (8.9)	51.2 (8.4)	2.7 (8.4)
Social functioning	48.3 (7.8)	51.3 (7.2)	3.1 (9.3)
Role emotional	44.2 (9.4)	49.1 (7.0)	4.5 (9.3)
Mental health	45.1 (10.3)	48.4 (8.5)	3.1 (10.8)
Physical component summary	49.1 (7.7)	51.3 (6.0)	2.6 (6.6)
Mental component summary	44.7 (10.9)	48.4 (7.7)	3.5 (10.3)

Data are mean (standard deviation) unless specified otherwise.

Efficacy

Infections

No SBIs were reported during the study. As a result, no statistical analyses of the primary end point were performed.

During the efficacy period, a total of 26 other infections were reported in 14 of 24 patients (58.3%). Of these, 17 infections were mild and nine were moderate. The mean time to resolution of infections in the efficacy period was 9.53 days. During the entire treatment period (including the wash-in/wash-out period), 34 infections were reported in 16 of 25 patients (64.0%). Of these, 20 infections were mild and 14 infections were moderate. The mean time to resolution of infections during the entire treatment period was 10.32 days. No severe infections were reported during the entire study period. The rate of infections was 2.37 (95% CI: 1.24–4.54) per person-year during the efficacy period and 2.30 (95% CI: 1.25–4.20) per person-year in the entire treatment period.

Other efficacy end points

During the efficacy period, ten patients (41.7%) used antibiotics over 19 treatment episodes which lasted a total of 229 days. The number of days on antibiotic treatment was 20.89 per person-year (range: 5–76). The number of treatment episodes was 1.73 per person-year (range: 1–6). During the whole treatment period, 13 patients (52.0%) used antibiotics over 27 treatment episodes which lasted a total of 353 days. The number of days on antibiotic treatment was 23.83 per person-year. The number of treatment episodes was 1.82 per person-year.

No hospitalizations due to infection were reported during the study. During the efficacy period, six patients (25.0%) had one episode of fever each. The rate of fever was 0.55 episodes per person-year. Also during the efficacy period, three patients (12.5%) were absent from work or study due to infection a total of four times, for a total of 14 days missed. The total number of absences from work or study was 0.36 per person-year, where each absence could be a period of several days. Total number of days (rate) absent from work/study per person year was 1.28.

QoL

Mean norm-based SF-36 scores at visit 13 ranged from 41.0 to 57.5 (Table 2), and median scores ranged from 44.5 to 100. At visit 13, the mean mental component summary score was 48.4 (median 50.4) and the physical component summary score was 51.3 (median 53.4). Between baseline and visit 13, improvements were observed in both the mean physical health and mean mental health summary scores. Mean scores for seven out of eight scales also improved during this period, with the largest mean improvement observed in the bodily pain score (8.6 points). Only the mean score for general health deteriorated by 0.5.

Trough levels of total IgG

Plasma IgG trough levels were nearly constant during the efficacy period (Figure 2). The median IgG concentration was 8.15 (range: 5.68 to 3.70) g/l after screening, 9.52 (range: 4.56 to 11.70) g/l at the end of the wash-in/wash-out period and 10.71 (range: 5.63 to 12.64) g/l at the termination visit. At the same time points, the mean (SD) IgG trough concentration was 8.52 (1.86) g/l, 9.24 (2.09) g/l and 9.99 (1.79) g/l, respectively. During the efficacy period, trough IgG concentrations were ≥ 5 g/l in all patients except one, who had a trough IgG concentration

Figure 2. Trough concentrations of IgG over time. Each box plot displays the median, lower and upper quartile (forming the box), the maximum/minimum observation that is below/above ± 1.5 -times the interquartile range from the upper/lower quartile (forming the error bars), and all values above/below the same thresholds as circles. IgG: Immunoglobulin G; S1: First trough during screening; S2: Second trough during screening; W: Week.

Table 3. Adverse events excluding infections and infusion site reactions in the safety analysis set (n = 25).		
	n (%)	Number of AEs
Any AE	11 (44.0)	26
– Mild	8 (32.0)	17
– Moderate	5 (20.0)	9
– Severe	0	0
Any related AE	3 (12.0)	3
– Musculoskeletal discomfort	1 (4.0)	1
– Dizziness	1 (4.0)	1
– Headache	1 (4.0)	1

AE: Adverse event.

below 5 g/l on one occasion. This patient also had trough levels below 5 g/l at week 4 and at week 8. This patient received the planned dose on all occasions, but after infusion 11, the planned dose was increased from 0.14 to 0.16 g/kg for infusion 12 and to 0.17 g/kg for subsequent infusions.

Safety

During the study, a total of 59 AEs occurred in 18 patients (72.0%), excluding infusion site reactions. 26 noninfusion site/noninfection AEs occurred in 11 patients (44.0%; Table 3). One AE of ‘pustule in place of infusion’ was considered to be an infusion site reaction (therefore excluded from the total count of 59 AEs) as well as an infection (therefore included in the count of 34 infections). No severe AEs were reported. No AEs that led to withdrawal or death were reported.

Three patients (12.0%) had a total of three AEs (musculoskeletal discomfort, dizziness and headache) that were considered related to octanorm (Table 3), none of these led to withdrawal of treatment or dosage adjustment. All

Table 4. Infusion site reactions.

	Number of infusion site reactions	Number of infusions with reaction (%) n = 775	Number of patients with reaction (%) n = 25
Any infusion site reaction	201	116 (15.0)	15 (60.0)
Infusion site erythema	103	100 (12.9)	11 (44.0)
Infusion site pruritus	71	69 (8.9)	6 (24.0)
Dermatitis contact	10	9 (1.2)	5 (20.0)
Infusion site paresthesia	6	6 (0.8)	2 (8.0)
Infusion site rash	3	3 (0.4)	1 (4.0)
Infusion site urticaria	2	2 (0.3)	1 (4.0)
Infusion site pustule	1	1 (0.1)	1 (4.0)
Infusion site induration	1	1 (0.1)	1 (4.0)
Infusion site discharge	1	1 (0.1)	1 (4.0)
Infusion site pain	1	1 (0.1)	1 (4.0)
Infusion site hyperesthesia	1	1 (0.1)	1 (4.0)
Infusion site hematoma	1	1 (0.1)	1 (4.0)

three treatment-related AEs were mild, occurred during the first month of the study and resolved within 1 day. No other related systemic AE was recorded thereafter. The rate of related systemic AEs per infusion was 0.004.

During the primary treatment period, seven systemic AEs with a temporal association to the infusion developed. Six of these AEs occurred at infusion rates of 30–50 ml/h, and only one occurred at higher infusion rates (Supplementary Table 1).

Infusion site reactions

A total of 15 patients developed an infusion site reaction (60.0%). Overall, 201 infusion site reactions occurred during 116 infusions; overall 116/775 infusions (15.0%) were associated with infusion site reactions. No severe infusion site reactions were reported. Four patients had ≥ 1 moderate infusion site reaction, while 11 patients had only mild reactions. The majority (659/775; 85%) of the infusions were not associated with any infusion site reaction. One hundred and two infusions (13.2%) were associated with mild and 17 infusions (2.2%) were associated with moderate infusion site reactions. The most common types of infusion site reactions were erythema, pruritus and contact dermatitis (to the adhesive used to hold the infusion needle on the skin) (Table 4).

The number and severity of infusion site reactions tended to decrease over time. During the first 4 weeks, 77/100 infusions (77%) were associated with no infusion site reactions, 20% were associated with mild reactions and 3% with moderate infusion site reactions whereas during the last 4 weeks no infusion site reactions were seen in 84/96 infusions (87.5%) and mild reactions were seen in 12 (12.5%). No patients had a moderate infusion site reaction during the last 4 weeks.

Discussion

The results of this prospective, open-label, uncontrolled, multicentre, Phase III study indicate that, in adult patients with PIDs, octanorm is effective and well tolerated. No SBIs occurred during this study. The rate of all infections was 2.37 per person-year during the efficacy period, with all infections being mild or moderate in severity, and no severe infections occurred during the entire treatment period. In addition, no hospitalizations due to infection were reported and the total number of days (rate) absent from work or study was 1.28 per person-year. QoL was assessed using the SF-36 showing improvement in seven out of the eight multi-item scales accompanied by an improvement in mean physical and mental health summary scores. Trough IgG levels were above 5 g/l in all but one patient, in whom IgG trough level dropped below 5 g/l on one occasion during the efficacy period. Three treatment-related systemic AEs (musculoskeletal discomfort, dizziness and headache) were reported during the first month of the study. All were mild in severity and resolved within 1 day. The majority of octanorm infusions (85.0%) were not associated with any infusion site reaction, while 13.2% were associated with mild and 2.2% were associated with moderate infusion site reactions. The most common infusion site reactions were erythema, pruritus and contact dermatitis.

The results of this study are in line with those of a previous prospective, open-label, single-arm, Phase III study that included 61 pediatric and adult patients (age 2–73 years) with PID who had been previously treated with IVIG and were switched to octanorm [11]. As in the present study, no SBIs were reported in the previous study, and the rate of other infections was 3.43 (upper 95% CI: 4.57) per person-year. Systemic AEs related to octanorm were reported in 18.0% of patients, and 76.7% of infusions were not associated with any infusion site reaction. Similar to the present study, SF-36 mean mental and physical summary scores improved during the study, with improvement in the scores of 7 out of 8 scales; however, a deterioration was observed in the bodily pain scale [11]. In the entire population, 67.2% of patients used antibiotics during the study, the number of days on antibiotic treatment was 51.77 per person-year and the number of treatment episodes was 2.14 per person-year. Among European patients, 61.5% used antibiotics, the number of days on antibiotic treatment was 32.23 per person-year and the number of treatment episodes was 1.89 per person-year [11]. Therefore, the proportion of patients who used antibiotics and the number of days on antibiotic treatment were higher than in the present study, while the number of treatment episodes was similar. The most likely explanation for these differences is variation in regional clinical practices for PID management, including prophylactic antibiotic use. In Russia, where our study was conducted, prophylactic antibiotic use is not the norm, whereas prophylactic antibiotics are more widely used in North America and parts of Europe [12]. Another possible reason for the small differences in results between our study and the previous Phase III study of octanorm was that the Phase III study included pediatric patients. In addition, the average dose of octanorm was higher in the previous Phase III study (0.18 vs 0.11 g/kg) [11]; however, as a conversion factor of 1.5 was used to convert the IVIG dose to SCIG dose in this study, the dosing in the two studies is not directly comparable. Such differences preclude any meaningful comparison between the two studies.

The findings of the present study are also consistent with the studies of other SCIG preparations. In a prospective, open-label, single-arm, Phase III study of IgPro20 (a 20% SCIG stabilized with L-proline; Hizentra®; CSL Behring, King of Prussia, USA) that included 49 patients with PID who had been previously treated with IVIG, no SBIs were reported [13]. The rate of all infections was 2.76 per person-year, the rate of missed days of work/study was 2.06 per person-year and the rate of hospitalizations was 0.20 per person-year [13]. In a prospective, noncontrolled trial of a 20% SCIG preparation (Cuvitru; Takeda, Tokyo, Japan) conducted in Europe in 49 patients with PID, the rate of validated acute SBI was 0.022 per person-year, while the rate of all infections was 4.38 per person-year [14]. In a second prospective, open-label Phase II/III study of Cuvitru, conducted in North America in 77 patients with PID, the rate of validated SBIs was 0.012 per person-year and the annualized rate of all infections was 2.41 events/patient [15].

SCIGs have a number of advantages compared with IVIGs. In a meta-analysis of 24 randomized clinical studies that compared the efficacy and safety of IVIGs and SCIGs in patients with PIDs, the standard mean difference in serum IgG levels was 0.336 (95% CI: 0.205–0.467; $p < 0.01$) and the odds ratio for occurrence of AEs was 0.497 (0.180–1.371; $p = 0.1$) [6]. Compared with IVIGs, SCIGs have been reported to produce fewer systemic AEs [7]. In addition, SCIGs are easier to self-administer without the need for venous access or hospital visits, which may be particularly important in children and the elderly. As a result, SCIGs are associated with improved QoL and treatment satisfaction [7]. None of the patients enrolled in the present study had difficulties with self-treatment. SCIG also reduce the costs to patients and healthcare providers due to decreased time spent in hospital [7].

The limitation of the present study was the relatively small number of patients and the lack of data on prophylactic antibiotic use prior to study enrollment. Another limitation is the lack of a control group, such that some of the improvements in QoL may be attributable to participation in a clinical trial, rather than administration of SCIG. However, we believe a more likely reason for the improvement in QoL was patients' ability to receive treatment at home [16].

Conclusion

The results of the present study suggest that octanorm, a 16.5% human Ig solution for subcutaneous administration, is effective and safe in adult patients with PID. Octanorm provided excellent protection from SBI, with no SBIs being reported during the study. Furthermore, a low rate of other infections was seen. All other infections reported were mild-to-moderate in severity. Octanorm had a favorable safety profile, with only three patients experiencing a drug-related AE and a low number of infusion site reactions observed.

Future perspective

Subcutaneous immunoglobulin (SCIG) preparations have a significant potential, particularly for Russian patients with PIDs. In most countries, intravenous immunoglobulins can be administered only in a hospital environment, although some centers do allow intravenous administration by nurses in the patient's home. Russia is a vast country that is relatively sparsely populated. As a result, many patients with PIDs have to travel long distances to the nearest hospital. Regular travel requires significant monetary expenditure and time off work or study, which in turn leads to decreased QoL and treatment adherence. In contrast, SCIG can be self-administered at home. As a result, administration of SCIG does not interfere with daily activities and allows patients to maintain their normal lifestyles. SCIGs can be particularly beneficial in children, the elderly, patients with poor venous access and patients with protein loss enteropathy, allowing them to maintain stable immunoglobulin G levels.

Summary points

- Subcutaneous immunoglobulins (Ig) have similar efficacy to intravenous Igs in the treatment of patients with primary immunodeficiencies (PIDs); however, they have more favorable pharmacokinetic and safety profiles and can be self-administered.
- Octanorm (cutaqui[®]) is a 16.5% human Ig solution for subcutaneous administration that is approved for the treatment of PID in Canada, the USA and Europe.
- This prospective, multicenter, open-label, noncontrolled, single-arm, Phase III study was conducted to assess the efficacy, safety and quality of life with octanorm in adult patients with PIDs in Russia.
- A total of 25 patients were recruited from five study sites and 24 patients completed the study.
- Octanorm was administered over an 8-month period at an average dose of 0.11 g/kg/week.
- No serious bacterial infections were reported during the study and the rate of all infections was 2.37 per person-year during the efficacy period and 2.30 per person-year during the entire treatment period.
- Mean mental and physical summary 36-item Short Form Health Survey scores were improved at the end of the treatment period.
- Three patients (12.0%) had a total of three systemic adverse events that were considered related to octanorm, none of which were considered serious and none led to withdrawal of the treatment.
- Of the 775 infusions administered during the study, 85.0% were not associated with infusion site reactions, 13.2% were associated with mild reactions and 2.2% with moderate reactions.
- The results of the present study show that octanorm (cutaqui[®]) is effective and safe in adult patients with PID and that it is associated with improvements in quality of life.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/imt-2020-0012

Data sharing

The authors certify that this manuscript reports original clinical trial data. The most important details of the study protocol are publicly available at <https://clinicaltrials.gov/> (NCT03988426); data reported in this manuscript are available within the article and after final quality review by the FDA will be posted publicly at the same clinicaltrials.gov location, according to the required timelines. Additional data from the study are available upon reasonable request.

Author contributions

E Latysheva enrolled patients, taught them how to use the pump and self-administer the drug, and filled out and analyzed the primary documentation and eCRF data during the study. E Latysheva also read and approved all drafts of the manuscript during its preparation. Y Rodina participated in the selection and registration of patients, completed and analyzed the basic documentation during the study and also read and approved all draft manuscripts during its preparation. L Sizyakina was the principal investigator from the Rostov State Medical University and participated in the clinical trials of octanorm as the principle by recruiting patients, and completing and analyzing relevant documentation. L Sizyakina also read and approved all drafts of this article. A Totolian participated in the selection and registration of patients, and completed and analyzed the basic documentation and eCRF data during the study. A Totolian also read and approved all draft manuscripts during its preparation. I Tuzankina participated in project management, briefing of participants, filling out forms, monitoring execution and monitoring the course and effect of treatment.

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that this study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP) issued in July 1996, the European Directive 2001/20/EC and in compliance with the protocol and all subsequent substantial amendments and valid national laws and the study protocol and the informed consent forms were approved by the independent ethics committees at each study site. All patients provided written informed consent before entering the study.

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References

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

- Picard C, Bobby Gaspar H, Al-Herz W *et al.* International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. *J. Clin. Immunol.* 38(1), 96–128 (2018).
- Bonilla FA, Khan DA, Ballas ZK *et al.* Practice parameter for the diagnosis and management of primary immunodeficiency. *J. Allergy Clin. Immunol.* 136(5), 1186–1205 e1181–1178 (2015).
- **Clinical practice guidelines on the recognition and diagnosis of primary immunodeficiencies (PID).**
- Bonilla FA, Barlan I, Chapel H *et al.* International Consensus Document (ICON): common variable immunodeficiency disorders. *J. Allergy Clin. Immunol. Pract.* 4(1), 38–59 (2016).
- **An international consensus statement on common variable immunodeficiency from the American Academy of Allergy, Asthma and Immunology, the European Academy of Allergy and Clinical Immunology, the World Allergy Organization, and the American College of Allergy, Asthma and Immunology.**
- Gardulf A, Hammarström L. Subcutaneous administration of immunoglobulins: what are the advantages? *Clin. Immunother.* 6(2), 108–116 (1996).
- **Summarizes the advantages of subcutaneous immunoglobulin therapy in patients with primary immunodeficiencies.**
- Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clin. Immunol.* 112(1), 1–7 (2004).
- Shabaninejad H, Asgharzadeh A, Rezaei N, Rezapoor A. A comparative study of intravenous immunoglobulin and subcutaneous immunoglobulin in adult patients with primary immunodeficiency diseases: a systematic review and meta-analysis. *Expert Rev. Clin. Immunol.* 12(5), 595–602 (2016).
- **Meta-analysis comparing the efficacy and safety of intravenous and subcutaneous immunoglobulin in adults with PIDs.**
- Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. *BioDrugs* 21(2), 105–116 (2007).
- **Highlights the findings of international studies of subcutaneous immunoglobulin in adults and children with PIDs.**
- cutaqui[®] [immunoglobulin (human) subcutaneous] 16.5% solution for injection (165 mg/ml) package insert. Octapharma Pharmazeutika Produktionsges.M.B.H, Oberlaaer Strasse, Vienna, Austria (2018).
- cutaqui[®] [immune globulin subcutaneous (human) - hipp] 16.5% solution package insert. Octapharma Pharmazeutika Produktionsges.M.B.H, Oberlaaer Strasse, Vienna, Austria (2017).
- Gelbmann N, Zochling A, Pichotta A *et al.* Octanorm [cutaqui[®]], a new immunoglobulin (human) subcutaneous 16.5% solution for injection (165 mg/ml) – biochemical characterization, pathogen safety, and stability. *Biologicals* 60, 60–67 (2019).
- Kobayashi RH, Gupta S, Melamed I *et al.* Clinical efficacy, safety and tolerability of a new subcutaneous immunoglobulin 16.5% (octanorm [cutaqui[®]]) in the treatment of patients with primary immunodeficiencies. *Front. Immunol.* 10, 40 (2019).
- **Phase III study of octanorm in adult and pediatric patients with PIDs.**

12. Kuruville M, De La Morena MT. Antibiotic prophylaxis in primary immune deficiency disorders. *J. Allergy Clin. Immunol. Pract.* 1(6), 573–582 (2013).
13. Hagan JB, Fasano MB, Spector S *et al.* Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPro20, in patients with primary immunodeficiency. *J. Clin. Immunol.* 30(5), 734–745 (2010).
14. Borte M, Kriván G, Derfalvi B *et al.* Efficacy, safety, tolerability and pharmacokinetics of a novel human immune globulin subcutaneous, 20%: a Phase II/III study in Europe in patients with primary immunodeficiencies. *Clin. Exp. Immunol.* 187(1), 146–159 (2017).
15. Suez D, Stein M, Gupta S *et al.* Efficacy, safety, and pharmacokinetics of a novel human immune globulin subcutaneous, 20% in patients with primary immunodeficiency diseases in North America. *J. Clin. Immunol.* 36(7), 700–712 (2016).
16. Rider NL, Kutac C, Hajjar J *et al.* Health-related quality of life in adult patients with common variable immunodeficiency disorders and impact of treatment. *J. Clin. Immunol.* 37(5), 461–475 (2017).