A Phase 2 randomised trial of safety and pharmacokinetics of IgPro20 and IgPro10 in patients with diffuse cutaneous systemic sclerosis

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Abstract

Objectives: The primary objective was the safety of subcutaneous immunoglobulin, IgPro20 (Hizentra, CSL Behring) in adults with diffuse cutaneous systemic sclerosis (dcSSc). Secondary objectives included pharmacokinetics and relative bioavailability of IgPro20, and safety and pharmacokinetics of intravenous immunoglobulin, IgPro10 (Privigen, CSL Behring).

Methods: In this prospective, multicentre, randomised, open-label, crossover Phase 2 study (NCT04137224), patients (aged ≥18 years) with dcSSc were assigned to 16 weeks of IgPro20 (0.5 g/kg/week) followed by 16 weeks of IgPro10 (2 g/kg/4 weeks over 2–5 sessions), or vice-versa. Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), infusion site reactions (ISRs), clinical tests, pharmacokinetic and bioavailability were assessed.

Results: Twenty-seven patients were randomised from 9 October 2019 to 31 August 2021. In total, 22 patients (81.5%) experienced 107 TEAEs (IgPro20, 49; IgPro10, 58); most were mild/moderate. Six patients (22.2%) experienced ten SAEs (IgPro20, 6; IgPro10, 4); no treatment-related SAEs and no deaths were reported. IgPro20 ISR rate was low (2 per 100 infusions). Maximum immunoglobulin G concentration (mean [standard deviation]) was numerically lower following IgPro20 (23.7 [1.2] g/L) versus IgPro10 (46.1 [1.2] g/L), as was the geometric mean dose-normalised, baseline-corrected area under the concentration-time curve from time point 0 to tau (IgPro20, 44.8 [1.4] h*g/L; IgPro10, 60.2 [1.4] h*g/L). The bioavailability of IgPro20 relative to IgPro10 was 76.1%.

Conclusion: This study shows that in patients with dcSSc, IgPro20 is well tolerated and safety, pharmacokinetic and bioavailability profiles of IgPro20, and safety and pharmacokinetics of IgPro10, are similar to those observed in other approved indications.

NCT04137224

Key words: Pharmacokinetics, subcutaneous immunoglobulin, intravenous immunoglobulin, systemic sclerosis

Key messages:

What is already known on this topic

- Before efficacy and safety of immunoglobulin G therapy is assessed, investigation of the safety, pharmacokinetic and relative bioavailability in patients with diffuse cutaneous systemic sclerosis is warranted.

What this study adds

- This study in adults with diffuse cutaneous systemic sclerosis showed SCIG is well tolerated in these patients with acceptable safety, pharmacokinetic and bioavailability profiles.

How this study might affect research, practice or policy

- Safety and pharmacokinetic profiles of IgPro20 and IgPro10 demonstrate that they are well tolerated in patients with diffuse cutaneous systemic sclerosis.

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune rare, immune-mediated connective tissue disorder, with a worldwide prevalence rate estimated at 17.6 per 100,000. [1-3] The cumulative survival for patients 10 years post-diagnosis is 62.5%, making SSc one of the most life-threatening rheumatic diseases. [4-6] The disease is characterised by progressive vascular damage and organ fibrosis, with most patients presenting with skin thickening with variable internal organ involvement. [2, 7, 8]

The two main subsets of SSc are defined by the distribution of skin thickening: limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc). [8] Patients with dcSSc (20–40% of SSc cases) generally experience early rapid progression of skin thickening and are at high risk for early, widespread and severe internal organ involvement, [9] associated with increased morbidity, mortality and a poor quality of life. [9, 10]

Current treatment of SSc are organ-based and primarily aimed at improving symptoms and managing complications. [11] Currently, systemic therapeutic options (primarily immunosuppressants) are used off-label, are only partially effective and are associated with adverse events (AEs), including severe infection. [11, 12] With no approved disease-modifying treatment for SSc, new therapeutic options are needed.

With the implication of immune dysregulation in SSc, immunoglobulin G (IgG) therapy might be beneficial for patients with SSc as it acts on various pathogenic mechanisms of autoimmune diseases. [2, 13] IgG therapy has been used as a treatment for autoimmune disorders for many decades and has the advantage of an excellent safety profile with no increased risk of infection, as it is not an immunosuppressant. [13-16] IgPro20 (20% subcutaneous human immunoglobulin [SCIG], Hizentra, CSL Behring) and IgPro10 (10% intravenous human immunoglobulin [IVIG], Privigen, CSL Behring) have existing approvals for autoimmune diseases and as immunoglobulin replacement therapy. [17-20] There is limited and inconclusive evidence on IVIG use in patients with SSc, including lcSSc and dcSSc, while some observational studies have indicated a benefit of IVIG for multiple clinical manifestations, a randomised controlled trial of IVIG in dcSSc did not meet its primary endpoint, although it did indicate that repeated IVIG may produce a stronger efficacy effect. [16, 21-24] No trials on the use of SCIG in patients with SSc have been published to date, except for one case published on the use of SCIG products in a patient with progressive SSc. [25]

Experience in other indications shows that the pharmacokinetic (PK) and safety profiles of SCIG and IVIG are different, and mostly specific to the route of administration. SCIG results in higher trough, lower peak and reduced fluctuation of serum IgG levels than those observed with IVIG. [26] SCIG is also characterised by a lower rate of systemic AEs and a minimal “wearing off” effect at the end of the dosing interval compared with IVIG. [27, 28] The most common AEs associated with SCIG products are local infusion site reactions (ISRs),

which are predominantly mild, quickly resolve without specialised treatment and usually decrease over time. [27] Low rates of systemic AEs, flexible dosing regimens, good quality of life and cost savings are all important advantages of SCIG administration. [26, 27, 29-31]

The safety of SCIG in SSc requires further evaluation as the change in skin and subcutaneous (SC) tissues in SSc leads to fibrosis, lymphatic vessel attenuation, vasculopathy and sometimes ulceration, [2, 32, 33] which may impact the overall safety and PK (e.g., absorption) profile of IgG through SC administration. Therefore, before efficacy and safety of a SCIG product is assessed in a large-scale clinical study, a separate investigation of the safety, PK and relative bioavailability of SCIG in patients with dcSSc is warranted.

The primary objective of this prospective, multicentre, randomised, Phase 2 study was the evaluation of the safety of SCIG (IgPro20) in adults with dcSSc by recording of AEs, treatment-emergent adverse events (TEAEs), AE of special interests (AESIs), ISRs and associated clinical tests. The secondary objectives were assessing PK and relative bioavailability of IgPro20, and the safety profile and PK of IgPro10.

Methods

Study design

This prospective, multicentre, randomised, open-label, crossover Phase 2 study (ClinicalTrials.gov: NCT04137224; EudraCT: 2018-003149-41) was initiated at 15 study sites (**Sup. File 1**). Eligible patients were randomly assigned (1:1) to sequence A (IgPro20-IgPro10 treatment sequence) or sequence B (IgPro10-IgPro20 treatment sequence) by means of an external interactive response technology (**Fig. 1 and 2**).

Patient consent and involvement

Patients' written informed consent prior to any protocol procedures was obtained and documented as per the International Council for Harmonisation of Good Clinical Practice and applicable regulatory requirements. This study was carried out in accordance with the International Council for Harmonisation of Good Clinical Practice guidelines, and the Declaration of Helsinki and all applicable national and local regulations.

Inclusion and exclusion criteria

The inclusion criteria were: males and females aged ≥18 years; a documented diagnosis of SSc (scleroderma) according to the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) criteria for SSc [7] with diffuse cutaneous features; [8] skin thickness scores as measured by the modified Rodnan skin score (mRSS) of 15–45 at screening (on a scale from 0–51); a disease duration ≤5 years (from the first non-Raynaud's phenomena manifestation); capability of written informed consent and adherence to all protocol requirements. Classification of dcSSc was confirmed using the criteria from LeRoy and colleagues. [8] Exclusion criteria included: primary rheumatic autoimmune disease other than dcSSc; mRSS >2 at the potential SC infusion sites; and/or a history of a skin

condition, or clinical signs and symptoms of a chronic skin disease other than dcSSc, or clinical signs and symptoms of skin irritation (**Sup. File 2**).

Treatment schedule, dosing and administration

Two treatment periods (treatment period 1 and treatment period 2; 16 weeks each) were completed by each patient, with up to 40 weeks (including screening) of study duration for an individual (**Fig. 1**). In sequence A, patients received a total dose of 0.5 g/kg of IgPro20 (Hizentra, CSL Behring) over two sessions per week in treatment period 1, followed by a total dose of 2 g/kg of IgPro10 (Privigen, CSL Behring) over two to five sessions on consecutive days every 4 weeks in treatment period 2 (**Fig. 1**). In sequence B, patients received the same treatment regimen, in the reverse order of sequence A. A follow-up visit 4 weeks after the last dose was organised for all patients who completed the study or discontinued early (**Fig. 1**).

The dosage of IgPro10 (2 g/kg/4 weeks) was based on the general recommendations for IVIG dosage in autoimmune conditions [13, 14] and on previous studies of IVIG in patients with SSc. [21, 34] The dosage of IgPro20 (0.5 g/kg/week) was calculated based on the 1:1 IVIG to SCIG ratio used in other autoimmune indications such as CIDP. [35] The total dose/volume of IgPro20 and IgPro10 were calculated based on bodyweight; however, patients weighing ≥100 kg received a fixed dose of 50 g of IgPro20 every week or 200 g of IgPro10 every 4 weeks.

The SC infusions were performed at selected infusion sites (e.g., on the abdomen, thighs and/or lateral hip) on skin areas with mRSS ≤2.

Safety of IgPro20 and IgPro10

The safety of IgPro20 and IgPro10 were the primary and secondary objectives of this study, respectively. This included recording AEs (total, severity, causality and outcome) such as TEAEs, serious adverse events (SAEs), AESIs (defined as haemolysis, thromboembolic events and acute renal injury) and ISRs. The number of events, along with the number and percentage of patients with TEAEs, SAEs, AESIs and ISRs were recorded. The median (interquartile range [IQR]) duration of ISRs, onset of ISR since the start of treatment period and time to onset of ISR since the start of last infusion were recorded. The percentage of patients with AEs were compared by treatment, treatment sequence, combination of treatment and treatment period throughout. Baseline and safety assessments were performed using the following clinical tests: physical examination, electrocardiograms (ECG), measurement of vital signs, laboratory tests (urine, serum, haematology, virology, haemolysis), pulmonary function test(s) (PFTs) and bodyweight. Reasons for infusion interruptions were also collected. The denominator for all safety analyses was the safety analysis set (SAF), defined as 'all patients who received at least one partial infusion of IgPro20 or IgPro10' (N=27).

IgPro20 infusions

Data regarding the total administered volume, total dose, maximum infusion rate per infusion site, and maximum volume per infusion site was collected for IgPro20 infusions.

PK of IgPro20 and IgPro10

For PK assessments, serum samples were collected throughout to measure IgG trough levels and additional blood samples for rich PK sampling of IgG levels were collected at the end of each treatment period to calculate PK parameters (**Fig. 1**). PK parameters included: area under the concentration-time curve from time point 0 to tau (limited to the end of a dosing interval, $AUC_{0\text{-}tau}$), baseline-corrected $AUC_{0\text{-}tau}$, area under the concentration-time curve from time point 0 to the last quantifiable time point ($AUC_{0\text{-}last}$) and maximum IgG concentration (C_{max}).

Population bioavailability of IgPro20 relative to IgPro10 was assessed using mixed model repeated measures on a log-transformed dose-normalised baseline-corrected $AUC_{0\text{-}tau}$. The model included treatment, treatment period and treatment-by-treatment-period interaction as fixed effects with an unstructured covariance matrix. The geometric mean ratio and corresponding 90% confidence interval (CI) derived from the statistical model were used to assess relative bioavailability of IgPro20 compared IgPro10 based on dose-normalised baseline-corrected $AUC_{0\text{-}tau}$.

Modified Rodnan skin score (mRSS)

An exploratory efficacy objective of this study was improvement in skin thickness following IgPro20 and IgPro10, measured by mRSS (total score and response). The mRSS was assessed at baseline, weeks 1 and 17, and end of treatment. The mRSS response definition of change was from reference visit ≤ -5 and percentage change from reference visit ≤ -25%.

Statistical analysis

The sample size was based on feasibility, not driven by power calculations for statistical hypothesis testing. All safety analyses were based on the SAF, no formal hypothesis testing was performed. Changes from baseline were analysed by treatment, by sequence and combination of treatment and treatment period.

Population bioavailability was assessed using mixed model repeated measures on log-transformed dose-normalised baseline-corrected $AUC_{0\text{-}tau}$. The model included treatment, treatment period and treatment-by-treatment-period interaction as fixed effects with an unstructured covariance matrix. Geometric mean ratio and corresponding 90% CI derived from the statistical model were used to assess the relative bioavailability of IgPro20 based on dose-normalised baseline-corrected $AUC_{0\text{-}tau}$.

Results

Patient characteristics

The first patient was enrolled on 19 September 2019 and the last patient visit occurred on 17 May 2022. Out of 30 patients screened, 27 (90.0%) patients were randomised and treated (SAF). In total, 25 (92.6%) patients completed the study, with one patient withdrawing from the study due to moving abroad and one patient withdrawing because of a TEAE (myocardial ischaemia) (**Sup. Fig. 1**). Overall, 26 patients received IgPro20, and 27 patients received IgPro10. The mean (standard deviation [SD]) age of the patients was 49.3 (12.5) years; 66.7% (N=18) of the patients included in the safety analysis were female and 96.3% (N=26) of the patients were Caucasian (**Table 1**). All patients had been previously diagnosed with dcSSc and the mean (SD) time since diagnosis was 19.2 (16.7) months. Overall, 22 (81.5%) patients were on at least one background therapy/immunosuppressant at baseline (e.g., eight patients in each group were receiving mycophenolate mofetil). Skin involvement was moderate to severe with a mean mRSS total score (SD) at baseline of 24.4 (6.4) points; medical history of ILD was recorded for seven patients (25.9%, **Table 1**).

Safety of IgPro20 and IgPro10

TEAEs

In total, 22 patients (81.5%) experienced 107 TEAEs, the majority of which were mild or moderate (102 events, **Table 2**); with 18 patients (69.2%) experiencing 49 TEAEs on IgPro20 and 13 patients (48.1%) experiencing 58 TEAEs on IgPro10. The most common TEAEs (>10% of all patients) by preferred term were headaches (IgPro20 treatment periods: one patient [3.8%] with one event; IgPro10 treatment periods: five patients [18.5%] and 11 events), coronavirus disease 2019 (three patients [11.1%] and three events in IgPro20 treatment periods only), diarrhoea (IgPro20 treatment periods: one patient [3.8%] with one event; IgPro10 treatment periods: two patients [7.4%]) and two events) and vomiting (IgPro20 treatment periods: one patient [3.8%] with one event; IgPro10 treatment periods: two patients [7.4%] and two events).

In total, 15 patients (55.6%) experienced 52 TEAEs considered related to the study treatment (**Table 2**). The most common (>10% of all patients) treatment-related TEAE by preferred term was headache (one patient [3.8%] with one event on IgPro20; five patients [18.5%] and ten events on IgPro10, **Table 2**). Overall, four patients (14.8%) had severe TEAEs (five events); in the IgPro20 treatment periods, three patients (11.5%) experienced four of the total five events and one patient (3.7%) experienced one severe TEAE in an IgPro10 treatment period (**Table 2**).

SAEs

A total of six patients (22.2%) experienced 10 SAEs, none of which were considered related to study treatment (**Sup. Table 1**). During the IgPro20 treatment periods, five patients (19.2%) experienced six SAEs (upper gastrointestinal haemorrhage, chest pain, myocardial infarction, myocardial ischaemia, breast cancer and ILD). During the IgPro10 treatment periods, two patients (7.4%) experienced four SAEs (viral infection, chronic gastritis, vomiting and dehydration). One patient (3.7%) had two SAEs on IgPro20 (myocardial ischaemia and myocardial infarction) and was discontinued from the study (**Sup. Table 1**).

AESIs and TEAEs leading to treatment discontinuation

One grade 1 myocardial infarction was reported during the study as an AESI; this occurred during IgPro20 treatment and was judged unrelated to treatment by the investigator. One TEAE of coronavirus disease 2019 led a patient to discontinue treatment in period 1; once recovered, the patient went on to complete the study. No other AESIs or TEAEs leading to discontinuation of the study were reported. No deaths were reported in the study.

Reasons for interruptions

In total, there were 10 TEAEs (occurring in eight patients, 29.6%) that led to study drug interruptions. Two patients (7.4%) had two TEAEs leading to study drug interruptions in the IgPro10 periods (upper respiratory tract infection and viral infection; both in Period 1) and six patients (23.1%) had eight events in the IgPro20 periods (rash, upper gastrointestinal haemorrhage, abdominal distension, abdominal pain, lower respiratory tract infection, breast cancer, and two coronavirus disease 2019 (COVID-19) events; six in period 1 and two in period 2). All of the TEAEs that led to drug interruptions were unrelated to the study treatment except for rash, abdominal distension, and abdominal pain. No ISRs led to study drug interruptions.

In addition to TEAEs, infusions were interrupted due to pump malfunction during IgPro20 infusions (n=2), IgPro10 vial/bottle changes (n=1), the patient needing the bathroom during an IgPro10 infusion (n=1), to comply with maximum IgPro20 infusion rate and volume in the protocol (n=1), and user error with the pump during the IgPro20 infusion (n=1). Additional difficulties during administration which did not result in an interruption occurred for one patient during the IgPro20 infusions, these included further pump malfunctions, incomplete supplies, and a syringe malfunction.

ISRs

Overall, five patients (18.5%) experienced fourteen ISRs following IgPro20 infusions, with seven ISR events reported in one patient and one ISR event reported as not recovered/not resolved (**Table 3**). All events were related to the study treatment and were mild/moderate in severity. No ISRs led to discontinuation of the study treatment or study withdrawal. Infusion-site pain and infusion-site swelling were the most common ISRs (two patients [7.4%] experienced three events each, **Table 2** and **Sup. Table 2**). Overall, 686 IgPro20 infusions were performed, resulting in an overall ISR rate per infusion of 0.02, i.e., two ISRs per 100 infusions. The median (IQR) time to onset of ISR since the start of last infusion was 78.0 (30.0–105.0) minutes. The median (IQR) duration of ISR was 220.0 (162.0–1170.0) minutes. No ISRs were reported in patients receiving IgPro10 infusions.

Clinical tests

During the course of the study, no clinically relevant changes in mean data were observed for physical examination, vital signs, body weight, clinical laboratory tests, ECGs or PFTs (data not shown for brevity).

IgPro20 infusions

Per patient (n=26), the mean (SD) total administered volume of IgPro20 was 2,431.4 (731.5) mL and the total dose (g) was 486.3 (146.3) g. The mean (SD) maximum volume per infusion site was 43.1 (13.6) mL/site and the maximum infusion rate per infusion site was 42.5 (13.9) mL/hr/site.

PK of IgPro20 and IgPro10

At week 1 (baseline), the mean (SD) serum IgG concentrations were 13.3 (4.3) g/L and 12.3 (4.3) g/L in sequence A (IgPro20/IgPro10) and sequence B (IgPro10/IgPro20), respectively. Overall mean (SD) trough serum IgG concentrations following administration of IgPro20 ranged from 22.2 (4.1)–23.8 (12.9) g/L in treatment period 1 and from 20.6 (2.0)–22.0 (2.7) g/L in treatment period 2, which was numerically higher than following IgPro10 treatment at 17.3 (2.9)–17.9 (2.8) g/L in treatment period 1 and 17.1 (6.7)–19.6 (11.6) g/L in treatment period 2. As expected, the mean (SD) C_{max} was numerically lower following IgPro20 administration (23.7 [1.2] g/L) compared with IgPro10 administration (46.1 [1.2] g/L)46 (**Fig. 2**). Further PK parameters ($AUC_{0\text{-}tau}$, baseline corrected $_{AUC0\text{-}tau}$, $AUC_{0\text{-}last}$ and C_{max}) are presented in **Table 4**. The geometric mean (geometric SD) dose-normalised, baseline-corrected $AUC_{0\text{-}tau}$ were 44.8 (1.4) h*g/L for IgPro20 and 60.2 (1.4) h*g/L for IgPro10 (**Table 4**).

Bioavailability

The bioavailability (90% CI) of IgPro20 relative to IgPro10 was numerically higher in sequence A (0.831 [0.734, 0.940]) than in sequence B (0.698 [0.623, 0.780]); the overall population relative bioavailability of IgPro20 was 0.761 (0.703, 0.823), i.e., 76.1% bioavailability relative to IgPro10 (**Table 4**).

mRSS

Improvements in mean mRSS total score were observed following each treatment at Week 17 and Week 32 (**Sup. Table 3**). In total, 11 (40.7%) patients were mRSS responders in Weeks 1 to 17, and 18 (66.7%) were responders over Weeks 1 to 32 (**Sup. Table 3**).

Discussion

This multicentre, randomised, open-label, crossover, Phase 2 study evaluated for the first time, the safety, PK and bioavailability of IgPro20 (SCIG, Hizentra, CSL Behring) in adults with dcSSc. SC administration of IgPro20 in patients with dcSSc associated with moderate-to-severe skin thickness is well tolerated with acceptable safety, PK and bioavailability profiles. The results also indicate acceptable safety and PK profiles for IgPro10 (IVIG, Privigen, CSL Behring) in adults with dcSSc.

The safety profile of IgPro20 observed here is consistent with the established safety profiles for other approved indications such as CIDP. [17-20] Overall, the majority of TEAEs were mild or moderate in severity, and approximately half were considered related to study treatment by the investigator. None of the SAEs were considered related to study treatment. Overall, the ISR rate was low and considered comparable to the incidence of

IgPro20 ISRs in other immuno-modulatory indications. [20] No clinically relevant concerning trends were observed for vital signs, bodyweight, clinical laboratory tests, ECGs or PFTs. This study indicated that SC IgPro20 infusions at a total dose of 0.5 g/kg every week (considered as a high immunomodulatory dose) was well tolerated in this patient group presenting with pathologically changed skin and SC tissues.

This work was the first study to explore PK of IgG in patients with dcSSc. As expected, when comparing administration methods (SCIG and IVIG) and their associated dosing regimens, C_{max} and geometric mean dose-normalised baseline-corrected $AUC_{0\text{-}tau}$ were higher following intravenous administration, as IVIG initially provides a large peak followed by a 'wear-off' of Ig levels whereas SCIG provides lower but more stable levels. [28, 36] Overall, the IgPro20 PK profiles observed in patients with dcSSc were similar to those observed in other indications with no skin-thickening symptoms (such as PID and CIDP). [17, 18, 20] This finding indicates that the disease state did not affect overall PK or bioavailability of human IgG given by the SC route. Moreover, the bioavailability of IgPro20 was comparable to the bioavailability of IgPro20 in other indications (53–79%) [17, 19, 20] and to the reported bioavailability of other SCIG products on the market (65–69%). [37]

The secondary objectives were to evaluate the use of IVIG in patients with dcSSc and the clinical data demonstrated that the observed safety and PK profiles are similar to those observed for other approved IgPro10 indications. [19]

The pathological features of dcSSc raise the question of the feasibility of SC administration of IgG in these patients. The small vessel vasculopathy, lymphatic vessel attenuation and excessive collagen deposition in the skin and internal organs [2, 32, 33] might interfere with absorption of SCIG through the lymph vessels into the bloodstream or increase the risks for AEs. The results obtained here constitute a proof-of-concept that safety, PK and bioavailability profiles, following administration of SCIG in patients with SSc, are comparable with those observed in other indications with no skin pathology. [17-20, 38]
For patients with dcSSc, SCIG might allow an easier administration than IVIG as SCIG can be self-administered at home with a shorter infusion time and more flexible dosing regimens. [29] With dcSSc disease strongly affecting the patient's quality of life, [10, 39] an easier administration, and reduced need to have IgG administered in infusion centres, might be particularly advantageous. [40] Furthermore, safety profiles established in approved indications show that compared with IVIGs, SCIGs are characterised by a lower rate of systemic AEs making SCIG a more attractive therapeutic option for patients. [27, 41] Finally, SCIG could be an option for patients in whom IVIG infusions are difficult due to intravenous access issues.

The initial efficacy endpoint (mRSS) explored during the study reveals improvement following treatment for both sequence A and B. However, further efficacy analyses are ongoing.

The limitations of this study include the lack of a washout period in the crossover design and lack of a control arm. Furthermore, as the patient population was mostly Caucasian, broader data are required to ensure these results can be generalised. The study only included SC infusions performed on skin areas with mRSS ≤2, therefore the results are unable to confirm if SC infusions are impacted by increased skin thickness associated with SSc. Exploratory endpoints included ACR Composite Response Index in dcSSc, mRSS, physician global assessment, health assessment questionnaire disability index including scleroderma, patient global assessment and forced vital capacity predicted. Results from these exploratory efficacy endpoints are to be published in a subsequent publication. A few previous open-label and observational studies have explored the effects of IVIG on the symptoms of patients with SSc and reported improvement. [16, 21-23, 25, 42]

In conclusion, this study showed that SC administration of immunoglobulin is generally well tolerated in patients with dcSSc. The ISR rate was low with no severe or serious TEAEs affecting the skin reported, despite moderate-to-severe skin involvement in all subjects and pathological skin features. Overall safety, PK and bioavailability profiles of IgPro20, and safety and PK of IgPro10 were similar to those observed in other indications.

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Author Contributorship

CPD, OKB, SP, MO, MW, NDP, MMC, and YA: study design, study investigator, collection and assembly of data, and data analysis. JR, AP, AS, AK, JH, and MJG: study design, collection and assembly of data, and data analysis. JJ: collection and assembly of data, and data analysis. All authors interpreted the data, reviewed and revised the manuscript, and gave final approval to submit the manuscript for publication.

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Ethical approval information

This study involves human participants and was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and local regulations. It was also approved by the Ethics

Committee/Institutional Board - International Council for Harmonisation of Good Clinical Practice guidelines. Participants gave informed consent to participate in the study before taking part.

Data sharing statement

Data are available upon reasonable request. CSL Behring's policy on data sharing can be found at https://www.csl.com/research-and-development/clinical-studies/research-practices.

Patient and public involvement

Patients were study participants and were involved in rater's training for mRSS assessment during start-up. The study sponsor created the study design, recruitment, conduct, reporting, and dissemination plans. A layperson summary will be published on www.trialsummaries.com.

Competing interests

CPD: Received grants from GSK, CSL Behring, Inventiva, Horizon. Has worked as consultant for GSK, CSL Behring, Boehringer Ingelheim, Merck, Roche, Sanofi. Has been paid as a speaker for Janssen, Boehringer Ingelheim; OKB: Has received honoraria or consultation fees by the following companies: Abbvie, Astra Zeneca, CSL Behring, Boehringer Ingelheim, Janssen-Cilag, Medac, MSD, Novartis, Pfizer, Novartis and Sandoz. Received congress support from Abbvie, Boehringer Ingelheim, and Medac; SP: Received grants from Janssen. Has been paid as a speaker for Boehringer Ingelheim; MO: Has worked as consultant for Astra Zeneca; MW: Has received honoraria or consultation fees by the following companies: Novartis Pharma GmbH, Sanofi-Aventis Deutschland GmbH, DBV Technologies S.A, Aimmune Therapeutics UK Limited, Regeneron Pharmaceuticals, Inc, Leo Pharma GmbH, Boehringer Ingelheim Pharma GmbH &Co.KG, ALK-Abelló Arzneimittel GmbH, Lilly Deutschland GmbH, Kymab Limited, Amgen GmbH, Abbvie Deutschland GmbH & Co. KG, Pfizer Pharma GmbH, Mylan Germany GmbH (A Viatris Company), Astra Zeneca GmbH, Lilly Deutschland GmbH and GlaxoSmithKline GmbH & Co. KG; NDP: Has been paid as a speaker for Janssen Cilag, Boehringer Ingelheim; MMC: Received grants from MSD, Chemomab. Has worked as consultant for CSL Behring, Boehringer Ingelheim. Has been paid as a speaker for Biogen, Sandoz, Boehringer Ingelheim. JR, JJ, ASH, AK, JHH, MJG: employees of CSL Behring and own CSL Behring shares; YA: Received grants from Alpine ImmunoSciences, Medsenic, Corvus and Merck. Has worked as consultant for Boehringer, Astra Zeneca, Topadur, Medsenic and Prometheus.

Previously presented work

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Tables

Table 1. Patient characteristics. In sequence A, patients received a total dose of 0.5 g/kg of IgPro20 over two sessions per week in treatment period 1, and a total dose of 2 g/kg of IgPro10 over two to five sessions on consecutive days every 4 weeks in treatment period 2. In sequence B, patients received the same treatment regimen but vice versa. mRSS, modified Rodnan skin score; IgPro10, 10% intravenous human immunoglobulin, Privigen, CSL Behring; IgPro20, 20% subcutaneous human immunoglobulin, Hizentra, CSL Behring; N, number of patients; SD, standard deviation; SSc, systemic sclerosis.

Characteristic	Sequence A (IgPro20/IgPro10, N=13)	Sequence B (IgPro10/IgPro20, N=14)	IgPro10 (N=27)	IgPro20 (N=26)	Total (N=27)
Age (years), mean (SD)	51.4 (12.2)	47.4 (12.9)	49.3 (12.5)	50.0 (12.2)	**49.3 (12.5)**
Sex					
Female	10 (76.9)	8 (57.1)	18 (66.7)	18 (69.2)	**18 (66.7)**
Male	3 (23.1)	6 (42.9)	9 (33.3)	8 (30.8)	**9 (33.3)**
Race, n (%)					
Caucasian	13 (100.0)	13 (92.9)	26 (96.3)	25 (96.2)	**26 (96.3)**
Other	0 (0.0)	1 (7.1)	1 (3.7)	1 (3.8)	**1 (3.7)**
Weight (kg) at baseline, mean (SD)	78.9 (23.1)	72.6 (12.4)	75.6 (18.3)	74.8 (18.1)	**75.6 (18.3)**
Country					
Poland	9 (69.2)	8 (57.1)	17 (63.0)	16 (61.5)	**17 (63.0)**
United Kingdom	3 (23.1)	3 (21.4)	6 (22.2)	6 (23.1)	**6 (22.2)**
Australia	0 (0.0)	2 (14.3)	2 (7.4)	2 (7.7)	**2 (7.4)**

Germany	0 (0.0)	1 (7.1)	1 (3.7)	1 (3.8)	**1 (3.7)**
Italy	1 (7.7)	0 (0.0)	1 (3.7)	1 (3.8)	**1 (3.7)**
Duration since diagnosis of SSc (months), mean (SD)	16.7 (13.3)	21.5 (19.6)	19.2 (16.7)	17.7 (15.2)	**19.2 (16.7)**
Duration since first Raynaud's phenomena (months), mean (SD)	70.6 (131.3)	30.0 (23.4)	50.3 (94.7)	49.9 (96.6)	**50.3 (94.7)**
Duration since first non-Raynaud's phenomena manifestation (months), mean (SD)	21.9 (13.9)	24.4 (21.2)	23.23 (17.8)	21.9 (16.8)	**23.2 (17.8)**
Number of background therapies/ immunosuppressants at baseline					
0	2 (15.4)	3 (21.4)	5 (18.5)	5 (19.2)	**5 (18.5)**
≥1	11 (84.6)	11 (78.6)	22 (81.5)	21 (80.8)	**22 (81.5)**
1	3 (23.1)	6 (42.9)	9 (33.3)	8 (30.8)	**9 (33.3)**
2	7 (53.8)	4 (28.6)	11 (40.7)	11 (42.3)	**11 (40.7)**
3	1 (7.7)	0 (0.0)	1 (3.7)	1 (3.8)	**1 (3.7)**
4	0 (0.0)	1 (7.1)	1 (3.7)	1 (3.8)	**1 (3.7)**
Any medical history event	7 (53.8)	7 (50.0)	14 (51.9)	14 (53.8)	14 (51.9)
Any prior medication	9 (69.2)	10 (71.4)	19 (70.4)	18 (69.2)	**19 (70.4)**
Any concomitant medication	13 (100.0)	14 (100.0)	27 (100.0)	26 (100.0)	**27 (100.0)**

Baseline mRSS total score, mean (SD)	23.8 (5.8)	25.0 (7.1)	-	-	**24.4 (6.4)**
Any concomitant disease	12 (92.3)	13 (92.9)	25 (92.6)	24 (92.3)	**25 (92.6)**
Vascular disorders	8 (61.5)	5 (35.7)	13 (48.1)	12 (46.2)	**13 (48.1)**
Musculoskeletal and connective tissue disorders	5 (38.5)	6 (42.9)	11 (40.7)	11 (42.3)	**11 (40.7)**
Gastrointestinal disorders	6 (46.2)	4 (28.6)	10 (37.0)	10 (38.5)	**10 (37.0)**
Respiratory, thoracic and mediastinal disorders	6 (46.2)	4 (28.6)	10 (37.0)	9 (34.6)	**10 (37.0)**
Interstitial lung disease	4 (30.8)	3 (21.4)	7 (25.9)	6 (23.1)	**7 (25.9)**
Endocrine disorders	5 (38.5)	4 (28.6)	9 (33.3)	9 (34.6)	**9 (33.3)**
Metabolism and nutrition disorders	4 (30.8)	4 (28.6)	8 (29.6)	8 (30.8)	**8 (29.6)**
Reproductive system and breast disorders	5 (38.5)	3 (21.4)	8 (29.6)	8 (30.8)	**8 (29.6)**

Table 2. TEAEs and treatment-related TEAEs recorded. In period 1, patients were assigned to 16 weeks of IgPro20 (0.5 g/kg/week) or IgPro10 (2 g/kg/4 weeks split over 2–5 days). Patients then received the alternative treatment during period 2. E, number of events; IgPro10, 10% intravenous human immunoglobulin, Privigen, CSL Behring; IgPro20, 20% subcutaneous human immunoglobulin, Hizentra, CSL Behring; ISRs, infusion site reactions; N/n, number of patients; TEAE, treatment-emergent adverse events.

	Period 1				Period 2				IgPro10 Periods (N=27)		IgPro20 Periods (N=26)		Total (N=27)	
	IgPro10 (N=14)		IgPro20 (N=13)		IgPro10 (N=13)		IgPro20 (N=13)							
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
TEAE by severity														
Mild	8 (57.1)	40	4 (30.8)	11	5 (38.5)	10	6 (46.2)	21	13 (48.1)	50	10 (38.5)	32	14 (51.9)	82
Moderate	4 (28.6)	4	7 (53.8)	7	2 (15.4)	3	3 (23.1)	6	6 (22.2)	7	10 (38.5)	13	13 (48.1)	20
Severe	1 (7.1)	1	0 (0.0)	0	0 (0.0)	0	3 (23.1)	4	1 (3.7)	1	3 (11.5)	4	4 (14.8)	5
TEAEs related to study treatment														
Any TEAE	8 (57.1)	24	4 (30.8)	8	3 (23.1)	3	4 (30.8)	17	11 (40.7)	27	8 (30.8)	25	15 (55.6)	52
Serious TEAE	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
TEAE resulting in death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
TEAE leading to discontinuation of study treatment	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

TEAE leading to dose interruptions	2 (14.3)	2	4 (30.8)	6	0 (0.0)	0	2 (15.4)	2	2 (7.4)	2	6 (23.1)	8	8 (29.6)	10
TEAE leading to study withdrawal	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Detailed treatment-related TEAES														
ISRs	0 (0.0)	0	2 (15.4)	2	0 (0.0)	0	3 (23.1)	12	0 (0.0)	0	5 (19.2)	14	5 (18.5)	14
Nervous system disorders	6 (42.9)	11	1 (7.7)	2	0 (0.0)	0	1 (7.7)	2	6 (22.2)	11	2 (7.7)	4	7 (25.9)	15
General disorders and administration site conditions	1 (7.1)	1	2 (15.4)	2	0 (0.0)	0	3 (23.1)	12	1 (3.7)	1	5 (19.2)	14	6 (22.2)	15

Table 3. ISRs. In period 1, patients were assigned to 16 weeks of IgPro20 (0.5 g/kg/week) or IgPro10 (2 g/kg/4 weeks split over 2–5 days). Patients then received the alternative treatment during period 2. E, number of events; IgPro10, 10% intravenous human immunoglobulin, Privigen, CSL Behring; IgPro20, 20% subcutaneous human immunoglobulin, Hizentra, CSL Behring; ISR(s), infusion site reaction(s); N/n number of patients.

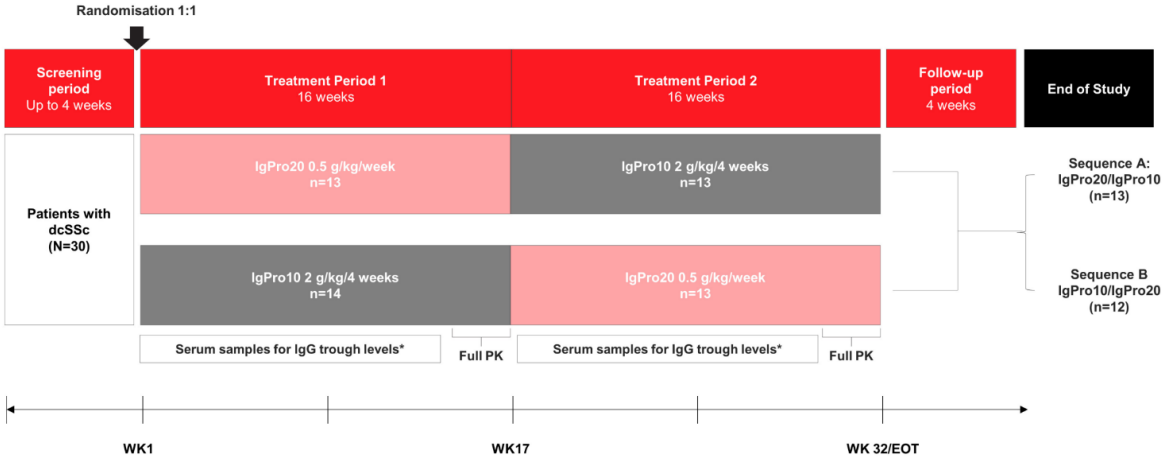
	Period 1				Period 2				IgPro10 Periods (N=27)		IgPro20 Periods (N=26)		Total (N=27)	
	IgPro10 (N=14)		IgPro20 (N=13)		IgPro10 (N=13)		IgPro20 (N=13)							
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any ISR	0 (0.0)	0	2	2	0 (0.0)	0	3 (23.1)	12	0 (0.0)	0	5 (19.2)	14	5 (18.5)	14
ISR Leading to Dose Interruptions	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
ISR Leading to Discontinuation of Study Treatment	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
ISR Leading to Study Withdrawal	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
ISR Related to Study Treatment	0 (0.0)	0	2 (15.4)	2	0 (0.0)	0	3 (23.1)	12	0 (0.0)	0	5 (19.2)	14	5 (18.5)	14
ISR by Severity														
Mild	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	3 (23.1)	6	0 (0.0)	0	4 (15.4)	7	4 (14.8)	7
Moderate	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	3 (23.1)	6	0 (0.0)	0	4 (15.4)	7	4 (14.8)	7
Severe	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Outcome of ISR														
Recovered/Resolved	0 (0.0)	0	2 (15.4)	2	0 (0.0)	0	3 (23.1)	11	0 (0.0)	0	5 (19.2)	13	5 (18.5)	13
Not Recovered/Not Resolved	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1

Table 4. PK of IgPro20 and IgPro10, and relative bioavailability of IgPro20. *IgPro20 followed by IgPro10 treatment sequence; †IgPro10 followed by IgPro20 treatment sequence. AUC0-tau, area under the concentration-time curve from time point 0 to tau (limited to the end of a dosing interval); AUC0-last, baseline-corrected AUC0-tau, area under the concentration-time curve from time point 0 to the last quantifiable time point; CI, confidence interval; Cmax, maximum IgG concentration; IgPro10, 10% intravenous human immunoglobulin, Privigen, CSL Behring; IgPro20, 20% subcutaneous human immunoglobulin, Hizentra, CSL Behring; SD, standard deviation.

	IgPro10		IgPro20		Relative Bioavailability
	n	Geometric mean (geometric SD)	n	Geometric mean (geometric SD)	Geometric mean ratio (90% CI)
$AUC_{0\text{-}tau}$ (h*g/L)					
Period 1	12	17672.0 (1.1)	12	3835.7 (1.2)	
Period 2	12	16942.7 (1.2)	11	3581.1 (1.1)	
Overall	24	17303.5 (1.2)	23	3711.7 (1.2)	
Baseline-corrected $AUC_{0\text{-}tau}$ (h*g/L)					
Period 1	12	9895.0 (1.3)	12	1539.4 (1.3)	
Period 2	12	8021.4 (1.3)	12	1648.7 (1.4)	
Overall	24	8909.0 (1.3)	24	1593.1 (1.4)	
$AUC_{0\text{-}last}$ (h*g/L)					
Period 1	12	17349.7 (1.1)	12	5361.6 (1.2)	
Period 2	13	16520.5 (1.2)	12	4898.0 (1.2)	
Overall	25	16913.5 (1.2)	24	5124.6 (1.2)	
C_{max} (g/L)					
Period 1	12	45.0 (1.2)	12	24.2 (1.2)	
Period 2	13	47.1 (1.2)	12	23.2 (1.1)	
Overall	25	46.1 (1.2)	24	23.7 (1.2)	
Dose-normalised baseline-corrected $AUC_{0\text{-}tau}$ (h*g/L)					
Sequence A*	12	52.0 (1.4)	12	42.0 (1.5)	0.831 (0.734, 0.940)
Sequence B†	12	69.7 (1.3)	12	47.8 (1.3)	0.698 (0.623, 0.780)
Overall	24	60.2 (1.4)	24	44.8 (1.4)	0.761 (0.703, 0.823)

Figure legends

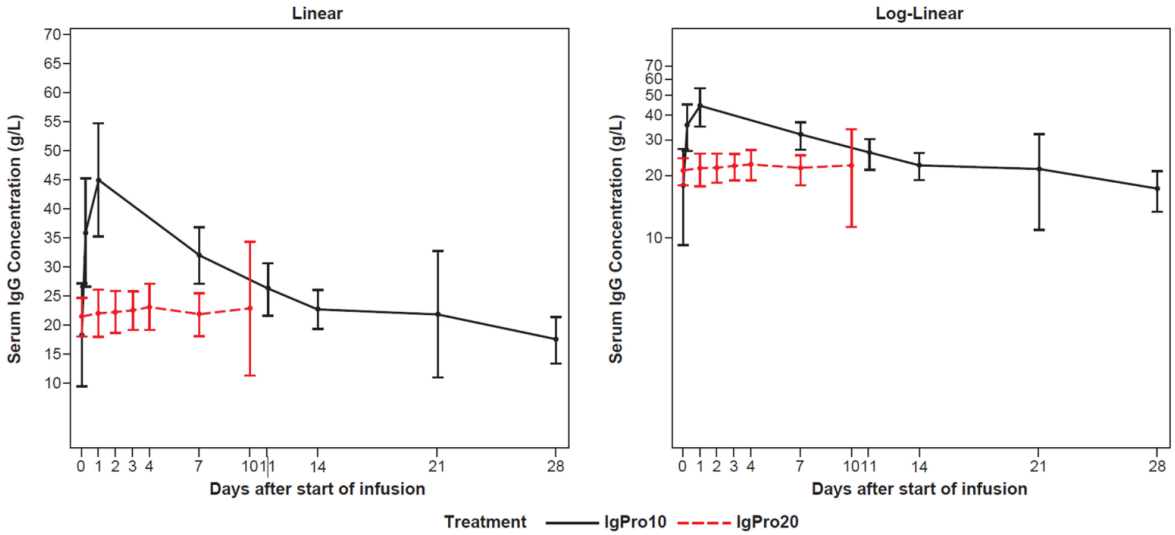
Figure 1. Study design.



*Several PK samples to measure IgG trough concentrations were collected to assess the steady state of IgPro20 or IgPro10 and carry-over effects on treatment period 2 from treatment period 1. In addition, PK samples were frequently collected over the last dose period to fully characterise the PK of IgPro20 and IgPro10. dcSSc, diffuse cutaneous systemic sclerosis; EOT, end of treatment; IgG, immunoglobulin G;

IgPro10, 10% intravenous human immunoglobulin, Privigen, CSL Behring; IgPro20, 20% subcutaneous human immunoglobulin, Hizentra, CSL Behring; PK, pharmacokinetics.

Figure 2. Mean (SD) serum IgG concentration–time profiles of patients with dcSSc following the first infusion of the last cycle of IgPro20 (0.5 g/kg/week) or IgPro10 (2 g/kg/4 weeks split over 2–5 days).



IgG, immunoglobulin G; IgPro10, 10% intravenous human immunoglobulin, Privigen, CSL Behring; IgPro20, 20% subcutaneous human immunoglobulin, Hizentra, CSL Behring; SD, standard deviation.

Supplemental Materials

Supplemental File 1. Patient recruitment centres

Site
Royal Adelaide Hospital Port Rd. Adelaide South Australia 5000 Australia
Vincent's Hospital Fitzroy (Melbourne) 41 Victoria Parade Fitzroy Melbourne 3065 Australia
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Supplemental File 2. Complete list of the study exclusion criteria

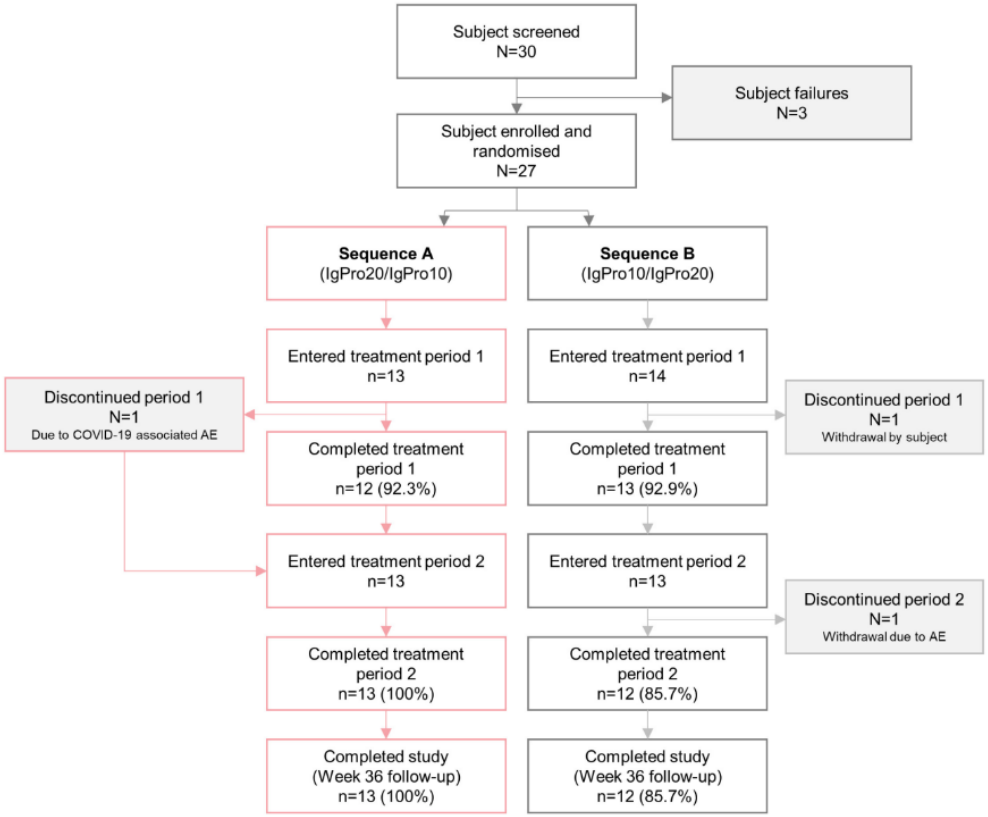
Patients were not enrolled into the study if they met any of the following exclusion criteria:

1. Primary rheumatic autoimmune disease other than dcSSc, including but not limited to rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disorder, polymyositis, or dermatomyositis, as determined by the investigator. Note: patients with fibromyalgia, secondary Sjogren's syndrome, and scleroderma-associated myopathy at screening were not excluded
2. Patient had mRSS >2 at the potential SC infusion sites
3. History of skin condition or clinical signs and symptoms of a chronic skin disease other than SSc or skin manifestation of an allergic disease or other dermatological conditions precluding SC infusion at potential SC infusion sites (e.g., dermatitis, eczema, psoriasis)
4. Patient had clinical signs and symptoms of skin irritation (e.g., pruritus, burning, erythema) or hypo/hyperpigmentation (e.g., scars, tattoos) at the potential SC infusion sites
5. Significant pulmonary arterial hypertension as documented by mean pulmonary arterial pressure >30 mmHg on right heart catheterisation requiring SC or IV prostacyclin or use of dual oral therapies
6. FVC <50% predicted or a diffusing capacity of the lung for carbon dioxide (DLCO) ≤40% predicted (corrected for haemoglobin [HGB])
7. SSc renal crisis within 2 years before screening
8. Evidence of chronic kidney disease with an estimated glomerular filtration rate of <45 mL/min/1.73 m^2 (as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation) or if patient is receiving dialysis. Patients with current confirmed diagnosis of diabetes mellitus requiring medication with an estimated glomerular filtration rate <90 mL/min/1.73 m^2
9. History of documented thrombotic episode e.g., pulmonary embolism, deep vein thrombosis, myocardial infarction, or thromboembolic stroke at any time (note: history of superficial thrombophlebitis is not exclusionary)

10. Known documented thrombophilia abnormalities including current blood hyper viscosity (within 4 weeks before screening), protein S or protein C deficiency, anti-thrombin-3 deficiency, plasminogen deficiency, antiphospholipid syndrome, Factor V Leiden mutation, dysfibrinogenemia, or prothrombin G20210A mutation
11. Recent surgery requiring general anaesthesia within the last 4 weeks before screening
12. Greater than three specified current risk factors for TEEs (documented and currently ongoing conditions): atrial fibrillation, coronary disease, diabetes mellitus, dyslipidaemia, hypertension, obesity (body mass index ≥ 30 kg/m2), recent significant trauma, or immobility (wheelchair-bound or bedridden)
13. Cardiac insufficiency (New York Heart Association Class III or IV), cardiomyopathy, significant persistent arrhythmia, unstable or advanced ischemic heart disease, or uncontrolled hypertension
14. Ongoing active serious infection (including, but not limited to, pneumonia, bacteraemia/septicaemia, osteomyelitis/septic arthritis, bacterial meningitis, visceral abscess) at screening or hospitalisation and/or treatment with IV antibiotics for a serious infection within 2 months before screening
15. A positive result at screening of any of the following viral markers: human immunodeficiency virus-1/-2, hepatitis C virus, or hepatitis B virus
16. Malignancy in the past 2 years, except for non-melanoma skin cancer, cervical carcinoma in situ, or other in situ cancer if it has been excised and treated within the past year
17. Known medical conditions whose symptoms and effects could alter protein catabolism and/or IgG utilisation (e.g., protein-losing enteropathies, nephrotic syndrome) and proteinuria (defined as albumin-to-creatinine ratio > 30 mg/g)
18. Note: Transient and clinically insignificant proteinuria as based on the investigator's judgment should be discussed with the Medical Monitor and is not exclusionary
19. Known hyperprolinaemia type I or II
20. Known Immunoglobulin A (IgA) deficiency or serum IgA level < 5% lower limit of normal
21. History of clinically significant or uncontrolled illness that, in the opinion of the investigator, would prevent participation in the study
22. Psychiatric, addictive, or other disorders that compromise the ability to give informed consent for participating in this study. This includes patients with a recent history of abusing alcohol or illicit drugs
23. Clinically significant abnormal 12-lead ECG that, in the opinion of the investigator, would prevent participation in the study
24. Clinically significant abnormal laboratory testing at screening that, in the opinion of the investigator, would prevent participation in the study

25. Currently receiving or having received therapy not permitted during the study or during predefined windows before screening
26. Known allergic or other severe reactions to immunoglobulins or other blood products, including a history of haemolysis after IVIG infusion
27. Known or suspected antibodies to the IP or to excipients of the IP
28. A female who is pregnant, breastfeeding, or is a woman of childbearing potential who does not agree to use acceptable methods of contraception; a male who does not agree to use acceptable methods of contraception
29. Participated in another study with an investigational agent within 3 months
30. Involved in the planning and/or conduct of the study (applies to CSLB staff and dependents, staff at the study site, site examiner, or third-party vendors)
31. Individuals who have been institutionalised as a result of an official or court order
32. Any issues or conditions that would render the patient unsuitable for participation in the study.

Supplementary Figure 1. Flowchart of patients with dcSSc throughout the study.



AE, adverse event; COVID-19, coronavirus disease 2019; dcSSc, diffuse cutaneous systemic sclerosis; IgPro10, 10% intravenous human immunoglobulin, Privigen, CSL Behring; IgPro20, 20% subcutaneous human immunoglobulin, Hizentra, CSL Behring.

Supplementary Table 1. Serious TEAEs by system organ class and preferred term (SAF). In period 1, patients were assigned to 16 weeks of IgPro20 (0.5 g/kg/week) or IgPro10 (2 g/kg/4 weeks split over 2–5 days). Patients then received the alternative treatment during period 2. E, number of events; IgPro10, 10% intravenous human immunoglobulin, Privigen, CSL Behring; IgPro20, 20% subcutaneous human immunoglobulin, Hizentra, CSL Behring; N/n, number of patients; SAE, serious adverse events; SAF, safety analysis set; TEAE, treatment-emergent adverse events.

	Period 1				Period 2				IgPro10 Periods (N=27)		IgPro20 Periods (N=26)		Total (N=27)	
	IgPro10 (N=14)		IgPro20 (N=13)		IgPro10 (N=13)		IgPro20 (N=13)							
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any serious TEAE	1 (7.1)	1	2 (15.4)	2	1 (7.7)	3	3 (23.1)	4	2 (7.4)	4	5 (19.2)	6	6 (22.2)	10
Infusion site reactions	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Thromboembolic events	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Myocardial infarction	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Cardiac disorders	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	2	0 (0.0)	0	1 (3.8)	2	1 (3.7)	2
Myocardial infarction	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Myocardial ischaemia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Gastrointestinal disorders	0 (0.0)	0	1 (7.7)	1	1 (7.7)	2	0 (0.0)	0	1 (3.7)	2	1 (3.8)	1	1 (3.7)	3
Chronic gastritis	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.7)	1	0 (0.0)	0	1 (3.7)	1
Upper gastrointestinal haemorrhage	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Vomiting	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.7)	1	0 (0.0)	0	1 (3.7)	1
General disorders and administration site conditions	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Chest pain	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Infections and infestations	1 (7.1)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (3.7)	1	0 (0.0)	0	1 (3.7)	1

Viral infection	1 (7.1)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (3.7)	1	0 (0.0)	0	1 (3.7)	1
Metabolism and nutrition disorders	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.7)	1	0 (0.0)	0	1 (3.7)	1
Dehydration	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.7)	1	0 (0.0)	0	1 (3.7)	1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Breast cancer	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Interstitial lung disease	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Any study treatment-related serious TEAE	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Supplementary Table 2. All recorded TEAEs, outcomes, detailed ISRs and nervous system disorders. In period 1, patients were assigned to 16 weeks of IgPro20 (0.5 g/kg/week) or IgPro10 (2 g/kg/4 weeks split over 2–5 days). Patients then received the alternative treatment during period 2. E, number of events; IgPro10, 10% intravenous human immunoglobulin, Privigen, CSL Behring; IgPro20, 20% subcutaneous human immunoglobulin, Hizentra, CSL Behring; ISR, infusion site reaction; N/n, number of patients; TEAE, treatment-emergent adverse events.

	Period 1				Period 2				IgPro10 Periods (N=27)		IgPro20 Periods (N=26)		Total (N=27)	
	IgPro10 (N=14)		IgPro20 (N=13)		IgPro10 (N=13)		IgPro20 (N=13)							
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
All TEAEs														
Any TEAE	8 (57.1)	45	9 (69.2)	18	5 (38.5)	13	9 (69.2)	31	13 (48.1)	58	18 (69.2)	49	22 (81.5)	107
Serious TEAE	1 (7.1)	1	2 (15.4)	2	1 (7.7)	3	3 (23.1)	4	2 (7.4)	4	5 (19.2)	6	6 (22.2)	10
TEAE resulting in death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
TEAE leading to discontinuation of study treatment	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Outcome of TEAE														
Recovered/Resolved	8 (57.1)	40	9 (69.2)	17	4 (30.8)	8	8 (61.5)	27	12 (44.4)	48	17 (65.4)	44	21 (77.8)	92
Not Recovered/Not Resolved	3 (21.4)	5	1 (7.7)	1	2 (15.4)	5	4 (30.8)	4	5 (18.5)	10	5 (19.2)	5	8 (29.6)	15

Detailed ISRs														
Infusion site pain	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (7.7)	2	0 (0.0)	0	2 (7.7)	3	2 (7.4)	3
Infusion site swelling	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (15.4)	3	0 (0.0)	0	2 (7.7)	3	2 (7.4)	3
Infusion site discharge	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Infusion site erosion	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Infusion site erythema	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Infusion site haemorrhage	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Infusion site reaction	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Infusion site vesicles	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Injection site hypersensitivity	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Injection site mass	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1
Thromboembolic events	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0	0	0	0
Detailed nervous system disorders														
Headache	5 (35.7)	10	1 (7.7)	1	0 (0.0)	0	0 (0.0)	0	5 (18.5)	10	1 (3.8)	1	6 (22.2)	11
Dizziness	1 (7.1)	1	0 (0.0)	0	0 (0.0)	0	1 (7.7)	2	1 (3.7)	1	1 (3.8)	2	1 (3.7)	3
Somnolence	0 (0.0)	0	1 (7.7)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (3.8)	1	1 (3.7)	1

Supplementary Table 3. mRSS total score and mRSS responders by sequence and treatment.

	Sequence A (IgPro20/IgPro10, N=13)	Sequence B (IgPro10/IgPro20, N=14)	IgPro10 (N=27)	IgPro20 (N=27)	Total (N=27)
mRSS total score†					
Baseline, mean (SD)	23.8 (5.8)	25.0 (7.1)			**24.4 (6.4)**
Change from Baseline					
Week 17 before infusion, mean (SD)	-5.7 (4.8)	-3.4 (4.3)			**-4.6 (4.6)**
Week 32 end of treatment, mean (SD)	-7.6 (6.3)	-7.5 (5.4)			**-7.6 (5.8)**
mRSS responders*					
Week 1 to Week 17					
n (%)	6 (46.2)	5 (35.7)			**11 (40.7)**
95% CI for the proportion	23.2, 70.9	16.3, 61.2			**24.5, 59.3**
Week 17 to Week 32					
n (%)	2 (15.4)	2 (14.3)			**4 (14.8)**
95% CI for the proportion	4.3, 42.2	4.0, 39.9			**5.9, 32.5**
Week 1 to Week 32					
n (%)	9 (69.2)	9 (64.3)			**18 (66.7)**
95% CI for the proportion	42.4, 87.3	38.8, 83.7			**47.8, 81.4**
During assessment period§					
n (%)			7 (25.9)	8 (29.6)	
95% CI for the Proportion			13.2, 44.7	15.9, 48.5	

*Response criterion: change from reference visit ≤ -5 and percent change from reference visit ≤ -25%.

†mRSS total score ranges from 0 to 51 (higher is worse, negative change is improvement)

§Assessment period for IgPro10 = Week 1 to Week 17 (Sequence B) and Week 17 to Week 32 (Sequence A); for IgPro20 = Week 1 to Week 17 (Sequence A) and Week 17 to Week 32 (Sequence B). Percentages are calculated with the number of subjects in each sequence/ treatment as the denominator (N).

N, number of subjects; n, number of subjects meeting criterion; CI, Wilson score confidence interval; mRSS, modified Rodnan skin score.