# Czech Hizentra Noninterventional Study With Rapid Push: Efficacy, Safety, Tolerability, and Convenience of Therapy With 20% Subcutaneous Immunoglobulin

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## ABSTRACT

**Purpose:** Immunoglobulin substitution therapy is an essential therapeutic approach for patients with primary antibody deficiencies. Different methods of administration, including intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG) preparations, provide effective and tolerable treatment and enable the adjustment of therapy to patients' needs. A new 20% SCIG represents a new therapeutic option and a new route of administration using rapid-push application. The aim of the Czech Hizentra Noninterventional Study With Rapid Push (CHHINSTRAP) is to evaluate patient satisfaction with as well as the tolerability and efficacy of nonmedical switch to 20% SCIG from previous treatment with IVIG or SCIG and rapid push as a new way to administer SCIG. CHHINSTRAP is the first Phase IV, noninterventional, open-label, prospective, multicentric study of this type conducted in Central and Eastern Europe.

**Methods:** Primary end points, including efficacy, adverse effects, convenience of use, and overall satisfaction, were evaluated by Treatment Satisfaction Questionnaire for Medication version II. Secondary end points, such as serum IgG trough levels, infusion duration, number of application sites, frequency of infections, related hospital admissions, and antibiotic consumption, were obtained from patients at each follow-up visit.

*Accepted for publication August 19, 2019*
https://doi.org/10.1016/j.clinthera.2019.08.013
0149-2918/$ - see front matter

**Findings:** Together, 50 eligible patients with primary antibody deficiency were switched from SCIG or IVIG to an equivalent dose of 20% SCIG and were followed up for 12 months during 5 consecutive visits. The results indicate that patients switched from previous IVIG or SCIG preparations had significantly higher serum trough IgG levels and a lower incidence of infections and related events, such as hospital admissions or consumption of antibiotics. These findings were also reflected in gradually increasing convenience of use and overall satisfaction reported by patients. Apart from duration of application, no differences were found between patients previously receiving SCIG or IVIG. Moreover, our study found a high level of safety of 20% SCIG rapid push, which was comparable to other preparations and application methods.

**Implications:** On the basis of the results of CHHINSTRAP study, we conclude that 20% SCIG is a tolerable and effective immunoglobulin preparation, representing a new therapeutic approach in patients with primary antibody deficiencies. Its efficacy and tolerability have been found in patients on nonmedical switch from previous treatment with IVIG or SCIG. (*Clin Ther*. 2019;41:2231–2238) 

**Keywords:** Nonmedical switch, Primary antibody deficiency, Rapid push, Subcutaneous immunoglobulin replacement therapy, Treatment satisfaction.

## INTRODUCTION

Primary antibody deficiencies (PADs) are the most prevalent inborn errors of immune system, representing more than half of all patients with primary immunodeficiencies (PIDs).[1,2] PADs are characterized by impaired immunoglobulin production with broad spectrum of manifestations, ranging from selective deficiencies, which are often asymptomatic, such as selective IgA deficiency or IgG1 to IgG4 subclass deficiencies, to complex disorders with disturbed production of specific antibodies and immune system dysregulation, such as common variable immunodeficiency. The patients with PADs are particularly endangered by recurrent bacterial respiratory infections, including rhinosinusitis, bronchitis, or pneumonia, which are the hallmark of PADs and manifest in most patients.[3] The therapeutic approach is based on regular immunoglobulin replacement, which leads to significant reduction of infections.[4] Crucial progress in the treatment of PADs occurred in 1952, when Ogden Carr Bruton described an inborn X-linked agammoglobulinemia (later called Bruton syndrome) and provided a specific treatment in the form of IgG administration.[5] Since then, many application forms of immunoglobulin replacement therapy have been developed in attempts to cover patients' needs. Currently, 2 application routes are available in current clinical practice: intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin (SCIG). IVIG was established in the late 1970s, and SCIG was implemented into clinical practice in 1990s.[6,7] Both approaches are recommended as substitution therapy in primary and secondary antibody immunodeficiencies[8]; however, they differ in many aspects, such as pharmacokinetic properties, adverse reactions, or modes of administration.[9]

The new manufacturing technologies and processes enabled the development of 20% SCIG* stabilized in proline, which offers the possibility of achieving higher concentrations and administering higher amounts of immunoglobulins to a limited subcutaneous space. Moreover, a new application method, rapid push, was introduced with 20% SCIG, which does not require the use of infusion pump for its administration. Its efficacy and tolerability in adult and pediatric patients have now been proved in multiple Phase III studies.[10–12] On the basis of these results, 20% SCIG was successfully registered by the State Institute for Drug Control of the Czech Republic in 2013.

*Trademark: Hizentra® (CSL Behring, King of Prussia, Pennsylvania).

On the other hand, various aspects of the nonmedical switch from different IVIG or SCIG to 20% SCIG remained unresolved because only a limited number of studies were previously performed in Europe on this subject.[13,14] We present the results of the Phase IV, noninterventional, open-label, prospective, multicentric study Czech Hizentra Noninterventional Study With Rapid Push (CHHINSTRAP), which focused on patient satisfaction with and the tolerability and efficacy of nonmedical switch from previous treatment with IVIG or SCIG preparations.

## METHODS

The study was reviewed and approved by the Ethical Committee of Motol University Hospital, Prague, Czech Republic, and further approved by the State Institute for Drug Control of the Czech Republic. Patients were recruited from 2014 to 2016 and followed up for 12 months. Before enrollment, informed consent was obtained from all patients. The inclusion criteria were as follows: (1) diagnosis of PID (based on diagnostic criteria defined by European Society for Immunodeficiency[15]), (2) indication for immunoglobulin therapy,[8] (3) previous immunoglobulin replacement therapy, and (4) eligibility for the rapid-push method of application. Patients with hypersensitivity to any IVIG or SCIG preparation and/or patients with hyperprolinemia were excluded.

All enrolled patients were treated with equivalent dose of 20% SCIG, which was administered before study initiation. In patients previously treated with IVIG, the application dose was calculated according to following formula: total monthly dose of IVIG (in grams) divided by 4 (planned number of 20% SCIG applications per month). The dose of 20% SCIG in patients previously treated with SCIG in weekly intervals remained unchanged. Apart from the single administration at the baseline visit (V1), all remaining applications were performed at the patients' residence by themselves without the presence of a health care professional.

The primary end points were evaluated by a standardized Treatment Satisfaction Questionnaire for Medication version II (TSQM). The questionnaire provides 4 dimensions, which were evaluated as primary points: efficacy, adverse events (AEs), convenience of use, and overall satisfaction data. The score of each component ranges from 0 to 100 points, with a higher score representing a higher satisfaction and fewer AEs.[16] Furthermore, the number of infections and related hospital admissions, antibiotic consumption, volume per administration, number of injection sites, duration of infusions, IgG dose, and serum trough levels were evaluated as secondary end points.

The entire study period was divided into 5 follow-up visits (V1–V5). The evaluation of eligibility for enrollment was performed during a screening visit (V0) based on inclusion and exclusion criteria, IgG trough level, patient history (including number of infections and hospital admissions), and antibiotic consumption in the past 12 months. Patient education, including the demonstration of application method and various aspects of the switch, was conducted at V1. Further visits (V2–V5) were performed in 3-month intervals. TSQM, serum IgG trough level, and patient diary recording duration of infusions and number of application sites, number of infections, related hospital admissions, and antibiotic consumption were evaluated on each visit.

All obtained data were statistically analyzed by repeated-measures ANOVA test (for independent variables) and Fisher exact test (for nominal variables) using GraphPad software, version 6.04 (GraphPad Software Inc, San Diego, California). The differences were considered significant at $P < 0.05$.

## RESULTS

### Patient Characteristics

A total of 50 white patients (21 males and 29 females; mean age, 43.3 years; age range, 12–78 years) from 9 Czech national centers for diagnosis and treatment of PIDs were enrolled during the recruitment period; 48 of them completed all scheduled visits. Two patients withdrew their consents. The largest subgroup consisted of 11 patients (22.9%) 30–39 years of age followed by 9 patients (18.7%) 40–49 years of age. Common

Table I. List of diagnoses of the patients in the Czech Hizentra Noninterventional Study With Rapid Push.

| Diagnosis | No. (%) of Patients (N = 48) |
|---|---|
| Common variable immunodeficiency | 34 (71) |
| IgG subclass deficiency | 9 (18.5) |
| Hyper-IgM syndrome | 1 (2) |
| Activated PI3 kinase δ syndrome | 1 (2) |
| Hyper-IgE syndrome | 1 (2) |
| X-linked agammaglobulinemia | 1 (2) |
| Severe combined immunodeficiency | 1 (2) |

variable immunodeficiency (34/48 [71%]) and IgG subclass deficiency (9/48 [18.5%]) were the most common diagnosis (Table I). Hyper-IgM syndrome, activated PI3 kinase δ syndrome, hyper-IgE syndrome with antibody deficiency, X-linked agammaglobulinemia, and severe combined immunodeficiency were all represented by 1 patient per group. All patients had been previously treated with IVIG (35/48 [73%]) or SCIG (13/48 [27%]). In total, 2896 20% SCIG administrations were monitored for 48 patient-years. No significant differences were found between the SCIG and IVIG groups in sex, age, trough serum IgG levels, and dose of administration at baseline. Patient characteristics are summarized in Table II.

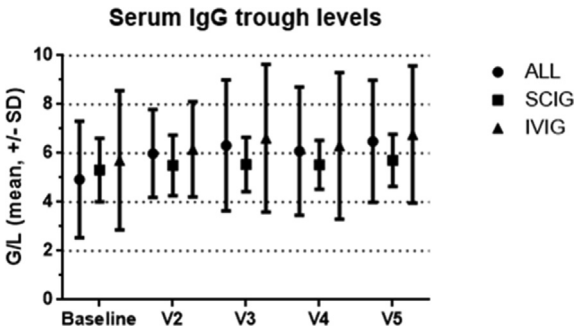


Figure 1. Serum IgG trough levels from Baseline to End of study (V5) showed gradual statistically significant increase (***p <0,001), no significant differences were observed between IVIG and SCIG group.

## Efficacy

All included patients were switched to the treatment scheme with an equivalent mean (SD) dose of 2.20 (1.22) g per administration and a cumulative dose of 9 (4.88) g per 4-week interval (corresponding to a monthly mean [SD] dose of 170 [0.123] mg/kg) at V1, which remained unaltered for the duration of the study (mean [SD] dose of 2.53 [1.11] g per administration and 10.2 [4.44] g per 4-week cumulative dose [240 (0.217) mg/kg per month]) compared with V5. These differences corresponded to the minimal changes of the dosage from V1 to V5, which were statistically insignificant. Despite the unchanged application dose, the serum IgG trough levels were constantly increasing. The mean (SD) serum IgG trough concentration at screening (baseline) before the switch was 4.9 (2.39) g/L compared with 6.5 (2.5) g/L at the end of the study (V5). The differences were statistically significant ($P < 0.001$). No differences were observed between patients receiving previous treatment with IVIG and SCIG (Figure 1).

The increase of IgG serum concentration was paralleled with the decrease in number of infections and related hospital admissions for infection. Both parameters were the most important clinical markers assessed in this study. One year before study initiation, 33 patients (69%) experienced infectious episodes and were treated accordingly with antibiotics and/or antimycotic drugs. Seven of these patients (15% of all included patients) received antibiotics twice, and 3 patients (6% of all included) received antibiotics 3 times during the study period. In total, 46 courses of antibiotics and/or antimycotics were reported. As for severe bacterial infection, 11 episodes of pneumonia

Table II. Characteristics of patients in the Czech Hizentra Noninterventional Study With Rapid Push.

| Characteristic | Total (N = 48) | IVIG (n = 35) | SCIG (n = 13) |
|---|---|---|---|
| Males, No. (%) | 19 (39.6) | 15 (31.3) | 4 (8.3) |
| Females, No.(%) | 29 (60.4) | 20 (41.7) | 9 (18.7) |
| Age, mean (SD), y | 43.3 (16.09) | 40.6 (15.58) | 52.5 (17.46) |
| Baseline serum IgG, mean (SD), g/L | 4.93 (2.39) | 5.06 (2.52) | 4.57 (2.04) |
| Monthly baseline dose, mean (SD), mg/kg | 170 (123) | 140 (112) | 180 (127) |

IVIG = intravenous immunoglobulin; SCIG = subcutaneous immunoglobulin.

occurred before the study initiation. A total of 13 patients (27%) had to be hospitalized because of infection. Together, 21 patients (44%) experienced infections during the study duration, and a total of 34 courses of antibiotics were prescribed. Only 4 patients (8%) were hospitalized during the study period, and only 1 episode of pneumonia was recorded.

## Tolerability

The mean (SD) volume of the first application was 11.2 (6.08) mL, with only a slight increase of 1.6 (0.53) mL during the 12-month study period. The mean single application volume at V5 (the end of study) was 12.8 (5.55) mL, which was administered in 4-week intervals. Overall, this volume was very well tolerated, and the drug was administered into a single application site in most patients. No significant differences were noted in the number of injection sites between patients receiving previous IVIG or SCIG treatment. However, we found significant differences in duration of infusions. The mean (SD) time of single administration in a group of patients previously treated with SCIG was significantly shorter than in those treated with IVIG (21.6 [10.08] minutes at V1 and 21 [10.1] minutes at V5 in the SCIG group compared with 30.6 [15.55] minutes and 32.2 [16.87] minutes in the IVIG group). The mean (SD) application time for both groups (all patients) was 28.2 (14.74) minutes and 29.1 (16.03) minutes, respectively (Figure 2).

Only a minimal number of AEs were observed during the study period. Together, 3 AEs were reported during the study, which was equivalent to a prevalence of 6.25% patient-years and 0.1% of all applications compared with 4 AEs reported in the 12-month prestudy period (equivalent to 8.33% patient-years, 0.36% of all applications). None of the AEs were regarded as severe; in fact, all reactions were graded as mild according to the Common Terminology Criteria for Adverse Events[17] (grade 1 or 2) and mostly presented as pain and/or skin reaction at the site of administration. None of these events led to termination of the study. Statistical analysis was not performed because of the low occurrence of AEs in both periods of data collection.

## Satisfaction

The patients' satisfaction with the treatment was the most important parameter and was appointed as the primary end point of the study. This parameter was composed of 4 attributes: efficacy, AEs, convenience of use, and overall satisfaction. These attributes were all evaluated by patients using TSQM. At V1, the mean (SD) efficacy, convenience, and overall satisfaction was 66 (9.74) points, 63.6 (13.77) points, and 67.1 (13.81) points, respectively, reflecting the level of satisfaction with the previous treatment

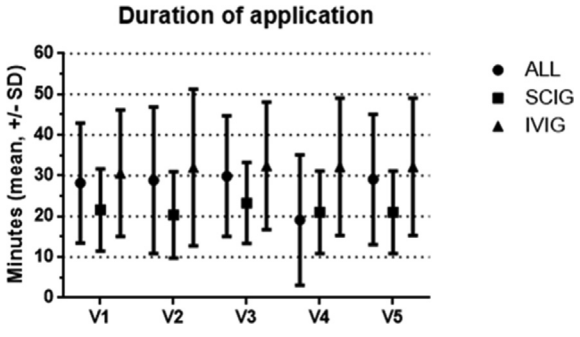


Figure 2. Duration of applications was stable during entire study (V1 – V5) without any significant changes, however the time of duration in SCIG group was significantly shorter (*p <0,05).

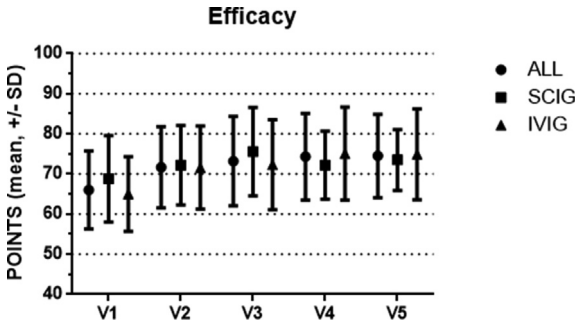


Figure 3. The level of efficacy evaluated by patients in TSQM was gradually increasing from V1 – V5, the results were statistical significant (***p <0,001), no significant differences were observed between IVIG and SCIG group.

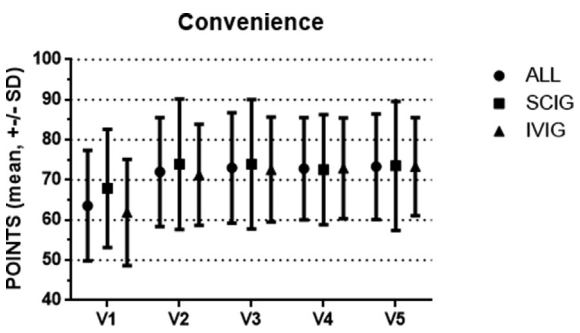


Figure 4. The level of convenience evaluated by patients in TSQM was gradually increasing from V1 − V5, the results were statistical significant (***p <0,001), no significant differences were observed between IVIG and SCIG group.

regimen. All 3 parameters were gradually increasing throughout the study, although the highest increases of 5.7 (0.37) points, 8.34 (0.19) points, and 5.2 (2.79) points, respectively, occurred in the first 3 months of the study between V1 and V2. At V5, the mean (SD) efficacy was 74.5 (10.38) points, the mean (SD) convenience was 73.3 (13.18) points, and the mean (SD) overall satisfaction was 76.3 (11.17) points. The differences among individual visits were statistically significant (Figures 3−5).

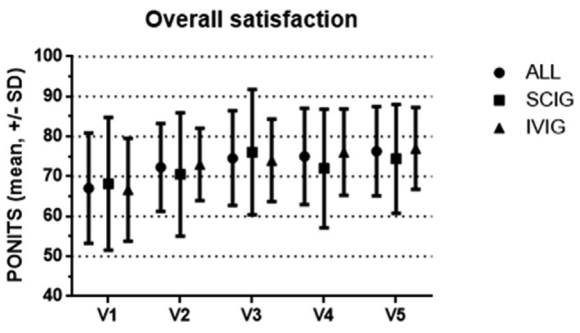


Figure 5. The level of overall satisfaction evaluated by patients in TSQM was gradually increasing from V1 − V5, the results were statistical significant (***p <0,001), no significant differences were observed between IVIG and SCIG.

## DISCUSSION

We present the results of the first Phase IV, noninterventional, open-label, prospective, multicentric study regarding the nonmedical switch from IVIG and SCIG administered by infusion pump using the rapid push method conducted in Central and Eastern Europe. A total of 50 patients from 9 Czech national centers for diagnosis and treatment of PIDs were enrolled and followed up for 12 months in 5 consecutive visits in 3-month intervals. The primary end points of efficacy, AEs, convenience of use, and overall satisfaction and the secondary end points of IgG trough levels, duration of infusions, number of infections and hospitalizations, antibiotic consumption, and incidence of AEs were assessed.

All enrolled patients were treated with a dose of 20% SCIG equivalent to their prestudy IVIG or SGIG dose. Despite the insignificant change of dosage (170 mg/kg per month at V1 vs 240 mg/kg per month at V5), the serum IgG trough levels were rapidly and significantly increasing (from 4.9 g/L at baseline to 6.5 g/L at the end of the study). The increase was comparable in both group of patients previously treated with IVIG or SCIG. These findings support the European recommendations regarding an IVIG vs SCIG conversion ratio of 1:1 despite distinct pharmacokinetic properties. This is in the contrast with the US conversion method recommending the ratio 1:1.5.[18]

As expected, the higher serum IgG trough levels was accompanied with a decrease in incidence of infections (33 [69%] vs 21 [44%]), including pneumonias (11 vs 1 episode). Moreover, it led to the reduction of hospitalizations for infections (13 vs 4 events) and decreased use of antibiotics (46 vs 34 courses) compared with the prestudy period.[4] The application volume of 12−13 mL per 1 application site and 1 week was sufficient for most patients. The maximal recommended single-site application volume of up to 50 mL allows for the possibility of increasing the volume and thus extending the application intervals from 1 to 2 weeks, an approach whose efficacy was recently confirmed in clinical practice.[19] Not surprisingly, the duration of individual infusions were significantly lower in patients with previous experience with SCIG (21 min in the SCIG group vs

32.2 min in the IVIG group at V5). Lastly, administration of 20% SCIG by rapid push had a low incidence and low severity of AEs, which were comparable with previous treatment.

Essentially, the components of primary end points, including efficacy, convenience, and overall satisfaction, were gradually increasing as evaluated by patients throughout the study period. Interestingly, no differences were found between patients receiving previous treatment with IVIG and SCIG. The most prominent increase was observed in the first 3 months after the switch. These results are consistent with previously published studies.[13,14,20] However, administration with infusion pump was assessed in all these studies. CHHINSTRAP indicates that the rapid-push method, performed at patients' residences without the presence of a health care professional, was the preferred means of administration.

## CONCLUSION

The new immunoglobulin preparation is subcutaneous use of a 20% concentration of IgG solution. The higher concentration allows reduction of application volume and provides a new rapid-push application method that enables the administration of IgG solution by hand without the need for an infusion pump, thus benefiting a heterogeneous group of patients with various PADs, ranging from common variable immunodeficiency, IgG subclass deficiency, X-linked agammaglobulinemia, activated PI3 kinase δ syndrome, and hyper-IgM syndrome to other PIDs associated with hypogammaglobulinemia. The switch from SCIG or IVIG to an equivalent dose of 20% SCIG led to increased serum trough levels of IgG and a decrease in related infections rate. Apart from efficacy, our study also found a high level of tolerability comparable with other preparations and application methods. Moreover, the level of efficacy, convenience, and overall satisfaction, as evaluated by the patients, was significantly higher compared with their previous treatment. Thus, 20% SCIG represents a new and tolerable therapeutic option that facilitates individualized care for patients with PADs and significantly improves treatment adherence.

## ACKNOWLEDGMENTS

T. Milota and A. Sediva substantially contributed to the conception and design of the work and its critical revising for important intellectual content and had final approval of the version to be published. M. Bloomfield, P. Kralickova, D. Jilek, V. Novak, J. Litzman, H. Posova, L. Mrazova, J. Poloniova, M. Prucha, and P. Rozsival substantially contributed to the conception and design of the work and to the acquisition, analysis, or interpretation of data. V. Rauschova and G. Philipp substantially contributed to the conception and design of the work.

## FUNDING SOURCES

The study was supported by CSL Behring. The sponsor contributed to study design and conception and provided financial compensation to investigators for their work, including data collection, analysis, interpretation, and manuscript preparation.

## DISCLOSURES

This clinical study was supported and sponsored by CSL Behring Biotherapies for Life, Switzerland and CSL Behring, Czech Republic. T. Milota, A. Sediva, P. Kralickova, D. Jilek, V. Novak, J. Litzman, H. Posova, L. Mrazova, J. Poloniova, M. Prucha, and P. Rozsiva were investigators on the studies described in the manuscript and received payment from the sponsor CSL Behring for their work. V. Rauschova and G. Philipp are full-time employees of the sponsor. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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