Nasal glucagon as a viable alternative for treating insulin-induced hypoglycaemia in Japanese patients with type 1 or type 2 diabetes: A phase 3 randomized crossover study

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Abstract
Aim: To compare nasal glucagon (NG) with intramuscular glucagon (IMG) for the treatment of insulin-induced hypoglycaemia in Japanese patients with type 1 (T1DM) or type 2 diabetes mellitus (T2DM).

Materials and methods: This phase 3, randomized, open-label, two-treatment, two-period crossover non-inferiority study enrolled Japanese adults with T1DM or T2DM on insulin therapy, with glycated haemoglobin levels ≤ 86 mmol/mol (≤ 10%). After ≥ 8 hours of fasting, hypoglycaemia was induced with human regular insulin (intravenous infusion). Patients received NG 3 mg or IMG 1 mg approximately 5 minutes after insulin termination. The primary endpoint was the proportion of patients achieving treatment success [plasma glucose (PG) increase to ≥ 3.9 mmol/L (≥ 70 mg/dL) or ≥ 1.1 mmol/L (≥ 20 mg/dL) increase from the PG nadir within 30 minutes of receiving glucagon]. Non-inferiority was declared if the upper limit of the two-sided 95% confidence interval (CI) of the mean difference in the percentage of patients achieving treatment success (IMG minus NG) was < 10%.

Results: Seventy-five patients with T1DM (n = 34) or T2DM (n = 41) were enrolled; 72 patients (50 men, 22 women) received ≥ 1 study drug dose (T1DM, n = 33; T2DM, n = 39). Sixty-eight patients completed the study and were evaluable. All NG- and IMG-treated patients achieved treatment success (treatment arm difference: 0%; upper limit of two-sided 95% CI 1.47%); NG met prespecified conditions defining non-inferiority versus IMG. Glucagon was rapidly absorbed after both nasal and intramuscular administration; PG profiles were similar between administration routes during the first 60 minutes post dose. Study drug-related treatment-emergent adverse events affecting > 2 patients were rhinalgia, increased blood pressure, nausea, ear pain and vomiting in the NG group, and nausea and vomiting in the IMG group.

Conclusion: Nasal glucagon was non-inferior to IMG for successful treatment of insulin-induced hypoglycaemia in Japanese patients with T1DM/T2DM, supporting use of NG as a rescue treatment for severe hypoglycaemia.
1 | INTRODUCTION

Severe hypoglycaemia can be a serious complication of insulin therapy in patients with type 1 (T1DM) and type 2 diabetes mellitus (T2DM). Use of sulphonylureas and glinides by patients with T2DM can also cause hypoglycaemia. Patients treated for diabetes are at risk of severe hypoglycaemia, defined as “an event requiring assistance of another person to actively administer glucagon, or take other corrective actions.” After a patient experiences a severe hypoglycaemic episode, fear of subsequent episodes frequently becomes a barrier to achieving optimal glucose control.

Because prolonged severe hypoglycaemia is associated with complications such as neurological and cardiovascular issues, coma and death, immediate recovery from severe hypoglycaemia is important in the emergency clinical setting. Patients with hypoglycaemia who are unable to ingest carbohydrates can be treated with intravenous (IV) glucose in medical settings. Alternatively, patients can be treated by injecting glucagon, a naturally occurring peptide hormone that raises blood glucose by converting stored glycogen to glucose (glycogenolysis) and by glucose synthesis (gluconeogenesis). Injectable glucagon, a pharmaceutical product indicated for the treatment of severe hypoglycaemia, can be administered intramuscularly in the absence of medical personnel; however, it requires multistep reconstitution and injection procedures. The use of injectable glucagon in an emergency setting may be complex and daunting for caregivers without training provided by medical personnel.

Nasal glucagon (NG) is a nasally administered, single-use, drug-device combination containing 3 mg glucagon dry powder. Because NG is a ready-to-use treatment that does not require reconstitution, injection or patient inhalation (it is absorbed from the nasal cavity), it offers an appealing alternative to injectable glucagon for treatment of severe hypoglycaemia occurring outside of a hospital setting.

The real-world effectiveness of NG 3 mg has been demonstrated in two prior, open-label, phase 3 trials in adults and children/adolescents with T1DM. In a study involving mannequins intended to simulate unconscious patients, >90% of study participants delivered full doses of NG, while only 13% and 0% of caregivers and acquaintances, respectively, delivered full doses of injectable glucagon. In a randomized crossover non-inferiority trial involving 75 adults with T1DM, NG was successfully used to treat patients with insulin-induced hypoglycaemia and was non-inferior to intramuscular glucagon (IMG) based on predefined criteria. In a second randomized, two-period, crossover trial, non-inferiority between NG and IMG was also met in 66 participants with T1DM using a different formulation of NG.

The primary objective of the present study was to demonstrate that NG 3 mg is non-inferior to IMG 1 mg in Japanese patients with T1DM or T2DM who achieve treatment success during controlled insulin-induced hypoglycaemia.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This was a phase 3, multicentre, randomized, open-label, active-comparator, single-dose, two-period, two-treatment (NG and IMG) crossover study in Japanese patients with T1DM or T2DM (Figure S1).

Adults with T1DM (18–64 years) or T2DM (20–70 years) at the time of informed consent were eligible to participate. Other inclusion criteria were a body mass index of 18.5–30.0 kg/m² (T1DM) or 18.5–35.0 kg/m² (T2DM), and a glycated haemoglobin (HbA1c) value ≤86 mmol/mol (≤10%). Diabetes mellitus (DM) diagnosis was based on World Health Organization criteria. Patients with T1DM had to be on insulin therapy for ≥1 year. Patients with T2DM had to be on daily insulin therapy with or without oral anti-hyperglycaemic medications (up to three of the following: metformin; a dipeptidyl peptidase-4 inhibitor; a sodium-glucose co-transporter-2 inhibitor; a sulphonylurea [not exceeding half of maximum approved doses]; a glinide; an α-glucosidase inhibitor; or a thiazolidine) for ≥1 year.

Key exclusion criteria included known allergies or sensitivity to NG, glucagon, related compounds, or any components of the formulation; significant atopy; abnormality in 12-lead ECG that would increase risks associated with study participation; significant changes in insulin regimen and/or unstable blood glucose control within 3 months before screening; a total daily dose of insulin ≥1.2 U/kg at screening; poorly controlled hypertension or a change in antihypertensive medications within 30 days before screening; severe hypoglycaemia within 1 month before screening or a non-hypoglycaemia-based loss of consciousness within the last 2 years; and preproliferative and proliferative retinopathy or maculopathy requiring treatment or clinically unstable during the last 6 months.

An institutional review board at each site approved the study protocol. This study was conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonization Good Clinical Practice guidelines. Before study participation, all patients provided written informed consent. The study was registered at ClinicalTrials.gov (NCT03421379).

2.2 | Randomization and procedure

Before treatment on day 1, study personnel randomized patients in a 1:1 ratio to a treatment sequence: NG 3 mg in period 1 and IMG 1 mg...
injected arm. The last injection of basal insulin was ≥12 hours before hypoglycaemia induction. The last injection of prandial insulin was ≥6 hours before insulin-induced hypoglycaemia. Oral anti-hyperglycaemic medications were taken ≥12 hours before hypoglycaemia induction.

An IV catheter was inserted into each arm (one for insulin and glucose infusion; another for blood sampling). Plasma glucose (PG) level was confirmed to be 5–13.9 mmol/L (90–250 mg/dL) before hypoglycaemia induction. Hypoglycaemia was induced with an IV infusion of human regular insulin (0.3 U/mL) at a recommended start rate of 2 mU/kg/min, followed by adjustment to approximately 1 to 4 mU/kg/min at the investigator’s discretion, based on the results of bedside PG monitoring with a glucose analyser. When PG was <3.3 mmol/L (<60 mg/dL), the insulin infusion was terminated.

Approximately 5 minutes after insulin termination, either NG 3 mg or IMG 1 mg was administered. NG was delivered via a nasal delivery device by study personnel. During drug delivery, the patient was in a fully reclined lateral position on the opposite side of the nostril through which the glucagon was being administered. GlucaGen 1 mg for injection (Novo Nordisk, Plainsboro, New Jersey) was reconstituted according to the manufacturer’s instructions and injected into the deltoid muscle of the patient’s non-dominant arm, with the patient reclined laterally on the side opposite the injected arm.

### 2.3 Blood sampling and analysis

#### 2.3.1 PG concentrations

Plasma glucose was monitored at bedside during hypoglycaemia induction and post-treatment recovery using a small electrode-type glucose analyser (Horiba Ltd., Kyoto, Japan). Venous blood samples were collected immediately before glucagon administration and at 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, and 240 minutes post dose to determine PG concentration. Plasma glucose measurements used to assess treatment success and pharmacodynamic (PD) endpoints were measured at a central laboratory using the commercially available hexokinase enzymatic method and Roche Modula or Cobas Analysers (Roche Diagnostics, Pleasanton, California).

#### 2.3.2 Plasma glucagon measurements

Venous blood samples were collected up to 4 hours post dose to determine the plasma concentrations of glucagon. Samples were analysed at Algorithme Pharma (Laval, Quebec, Canada) using a validated liquid chromatography with tandem mass spectrometry method (lower limit of quantification: 2.9 pmol/L [10.0 pg/mL]).

### 2.3.3 Antidrug antibodies

The presence of antidrug antibodies was assessed at completion of both treatment periods. Sera were analysed at Eurofins (Charles, Missouri) using a validated affinity capture elution enzyme-linked immunosorbent assay to screen for antidrug antibodies against glucagon.

### 2.4 Outcomes

The primary objective was to demonstrate NG 3 mg was non-inferior to IMG 1 mg for the percentage of patients achieving success of treatment for insulin-induced hypoglycaemia. The non-inferiority margin was 10%. Treatment success was defined as an increase in PG to ≥3.9 mmol/L (≥70 mg/dL) or an increase of ≥1.1 mmol/L (≥20 mg/dL) from nadir within 30 minutes after glucagon administration without additional measures to increase PG; the nadir was defined as the minimum PG value at or within 10 minutes after glucagon administration. Non-inferiority of NG was declared when the upper limit of the two-sided 95% confidence interval (CI) of the mean difference in percentage of patients achieving treatment success (IMG minus NG) was less than the non-inferiority margin of 10%.

Time to treatment success was a secondary objective. Time from glucagon dosing to treatment success was evaluated using Kaplan-Meier analysis. Between-treatment comparison of time to treatment success was performed using Cox proportional hazard models, adjusted for baseline glucose and treatment period. Other secondary objectives included description of the pharmacokinetic (PK) and PD profiles of NG 3 mg and IMG 1 mg, comparison of safety and tolerability of NG 3 mg and IMG 1 mg, and immunogenicity.

The PK or PD values were computed by non-compartmental methods of analysis using Phoenix WinNonlin Version 6.4. PK values were calculated using change from baseline plasma glucagon.

Safety was evaluated based on treatment-emergent adverse events (TEAEs), serious AEs (SAEs), adverse events (AEs) leading to discontinuation, vital signs, clinical laboratory tests, ECGs, and the Nasal and the Non-Nasal Score Questionnaire. This questionnaire consists of nine items (runny nose, nasal congestion [nostrils plugged], nasal itching, sneezing, watery eyes, itchy eyes, redness of the eyes, itching of the ears, and itching of the throat); each is scored by patients as no symptoms, or mild, moderate or severe symptoms. The percentage of patients with worsening of symptoms after dosing was calculated.

### 2.5 Statistical analyses

Assuming a non-inferiority margin of 10%, a treatment success rate of 98% for both treatment groups, and a within-patient correlation of zero, 66 completers (30 patients each with T1DM and T2DM) would provide ≥90% power to show non-inferiority between NG 3 mg and
IMG 1 mg in treatment success from insulin-induced hypoglycaemia with a one-sided α value of 0.025 (chi-squared test). Assuming an approximate 10% dropout rate, the planned enrolment was 75 patients. The proposed non-inferiority margin was based on a previously completed phase 3 study of NG in adults with T1DM.12

Efficacy analyses related to primary efficacy outcome were conducted on the efficacy analysis set, which included patients completing both treatment visits with evaluable data. PK and PD analyses used the respective PK and PD populations, comprising randomized patients who received ≥1 dose of study drug and had evaluable PK and PD data, respectively. Safety analyses were conducted on all randomized patients receiving ≥1 dose of the study drug. Patients with ≥1 treatment visit who had a PG concentration of ≥3.9 mmol/L (≥70 mg/dL) at the time of or within 10 minutes after glucagon administration were considered non-evaluable and were excluded from the analysis.

3 | RESULTS

3.1 | Patient disposition and demographics

This study was conducted between 21 February 2018 and 20 August 2018 at four sites in Japan. Seventy-five patients were enrolled with T1DM (34 patients) or T2DM (41 patients); 72 patients received ≥1 dose of study drug (T1DM, 33 patients; T2DM, 39 patients; Figure S2). Three patients did not complete the study and one patient was considered non-evaluable due to a PG nadir of 3.9 mmol/L (70 mg/dL) during treatment visit 1; therefore, 68 patients were evaluable for the efficacy analysis.

Fifty men and 22 women (age 21–70 years; 13 patients ≥65 years) received ≥1 dose of study drug (Table S1). In patients with T1DM and patients with T2DM, respectively, the mean age ± SD was 41.7 ± 11.6 and 57.5 ± 9.2 years, diabetes duration was 13.3 ± 10.5 and 15.7 ± 9.4 years, baseline HbA1c was 61 mmol/mol (7.7% ± 1.0%) and 65 mmol/mol (8.1% ± 0.9%), and body mass index was 22.3 ± 2.2 and 25.5 ± 3.1 kg/m².

3.2 | Efficacy

In both treatment groups 100% of patients achieved treatment success by 25 minutes post dose (Figure 1). NG was non-inferior to IMG (two-sided 95% CI for the percentage of patients achieving treatment success: −1.47%, 1.47%; Wald’s method with continuity correction); thus, the primary endpoint was met.

The 68 evaluable patients (T1DM, n = 32; T2DM, n = 36) who received both NG and IMG achieved treatment success, with mean times of 12.0 minutes (95% CI 11.3, 12.7) with NG and 11.0 minutes (95% CI 10.3, 11.8) with IMG. By diabetes type, mean times to treatment success were 11.6 minutes (95% CI 10.4, 12.7) with NG and 10.8 minutes (95% CI 10.0, 11.6) with IMG for patients with T1DM, and 12.4 minutes (95% CI 11.5, 13.4) with NG and 11.3 minutes (95% CI 9.9, 12.6) with IMG for patients with T2DM. There was a statistically significant difference between treatments in the distribution curves of time to achievement of treatment success for the overall population (P = 0.005) and the T1DM patient population (P = 0.035), but not the T2DM patient population (P = 0.236; Cox proportional hazard model for all).

![Figure 1](image-url)
3.3 | Pharmacokinetics

Glucagon absorption was rapid after both nasal and intramuscular administration. The mean pre-hypoglycaemia induction glucagon concentrations were 25.2 and 24.6 pg/mL (7.2 and 7.1 pmol/L), and the maximum glucagon concentrations were reached by 15 minutes post dose, regardless of the route of administration (Figure 2A). Median observed and change from baseline glucagon Cmax, AUC(0-tlast), AUC(0-∞), and tmax were greater after NG 3 mg than after IMG 1 mg (Table S2). Patients with T1DM and T2DM had generally similar PK profiles even though plasma glucagon concentrations appeared to be
higher in patients with T1DM compared to those with T2DM after IMG administration (Figure 2B,C).

### 3.4 | Pharmacodynamics

In the overall PD population, NG 3 mg and IMG 1 mg produced similar glucose responses for the first 60 minutes post dose; glucose responses diverged after 60 minutes (Figure 3A). For NG 3 mg, PG plateaued after 60 minutes post dose and then decreased; for IMG 1 mg, PG continued to increase until 90 minutes post dose and then decreased. The change from baseline area under the effect concentration–time curve during the first 1.5 hours post dose (AUEC0-1.5) differed statistically between treatment groups: geometric least squares mean values were 114 and 121 mg/dL for NG 3 mg and IMG 1 mg, respectively (P = 0.0264). The maximal blood glucose (BGmax) and change from baseline BGmax were similar between treatment groups. Patients with T1DM or T2DM had similar PG profiles (Figure 3B,C); differences in AUEC0-1.5 between treatment groups were not statistically significant when analysed by patient type.

### 3.5 | Safety

There were no deaths or discontinuations attributable to AEs in the present study. One patient with T2DM experienced an SAE of positional vertigo requiring hospitalization. The SAE occurred 36 days after receiving NG and approximately 28 days after receiving IMG, and the investigator judged it unrelated to study drug and procedures. The most frequently reported study drug-related TEAEs affecting >2 patients were rhinalgia, increased blood pressure, nausea, ear pain, and vomiting in the NG group and nausea and vomiting in the IMG
group (Table 1). The frequency of nausea was slightly higher following IMG 1 mg, but the frequency of vomiting was similar to that following NG 3 mg. TEAE profiles were comparable between patients with T1DM and those with T2DM (data not shown). Onset and duration of TEAEs occurring in ≥2 patients in total from both treatment groups are shown in Table S3.

During the study, there were no clinically relevant changes in laboratory or ECG values; however, 15 patients had shifts in systolic blood pressure (SBP) or diastolic blood pressure (DBP) from normal at baseline to high at the maximum post-treatment result after NG administration, compared to six patients after IMG administration. SBP and DBP results shifted from normal at baseline to high levels post dose in nine (12.7%) and six patients (8.5%), respectively, after NG administration, and in five patients (7.1%) and one patient (1.4%), respectively, after IMG administration. Two patients experienced maximum SBP >180 mmHg after NG 3 mg. These changes in blood pressure were transient and returned to baseline or normal levels without treatment. Mean changes in vital signs after NG administration were generally small, comparable between patients with T1DM and those with T2DM, and not considered clinically relevant.

The solicited nasal and non-nasal symptoms for which ≥10% of patients in the overall population reported any worsening of symptom severity after NG administration were nasal congestion (overall and T1DM populations) and watery eyes (overall, T1DM, and T2DM populations; Table 1). A single patient with T1DM (1.4% of overall) reported watery eyes as shifting from non-severe at baseline to severe at any post-baseline time point. No other severe symptoms were reported. No symptoms were reported as serious events.

3.6 | Immunogenicity

Before hypoglycaemia induction, two patients (2.8%) were positive for antiglucagon antibodies; however, only one of these patients was also antidrug antibody-positive at follow-up. No patient samples had neutralizing activity against the glucagon receptor.

No treatment-emergent antidrug antibodies were detected during this study; no patient who was negative for antidrug antibodies at baseline had detectable antidrug antibodies post baseline.

4 | DISCUSSION

The present study achieved its primary objective, demonstrating NG 3 mg to be non-inferior to IMG 1 mg regarding the percentage of patients achieving treatment success following controlled insulin-induced hypoglycaemia. All patients in both treatment groups achieved treatment success, and the upper limit of the 95% CI was within the non-inferiority margin of 10%; therefore, NG 3 mg was non-inferior versus IMG 1 mg for the treatment of insulin-induced hypoglycaemia in Japanese patients with T1DM or T2DM.

The goal of glucagon rescue treatment is to rapidly restore blood glucose so a patient regains sufficient cognitive function to safely consume oral carbohydrates. The mean time to treatment success was 1 minute faster in patients with IMG versus NG (overall population), and the difference was statistically significant; however, time to treatment success, measured at the start of glucagon administration, did not include time required for IMG reconstitution and injection preparation. In real-world circumstances, the difference in time to treatment success would be offset by the time required to prepare and reconstitute injectable glucagon. Furthermore, administration of injectable glucagon by non-medical caregivers can be complicated, in a stressful situation, by errors and failures to administer the drug11; therefore, this difference is not considered clinically relevant in light of the real-world circumstances of severe hypoglycaemia.

After administration of NG 3 mg, glucose levels began to rise quickly regardless of DM type; by 15 minutes post administration, blood glucose had increased to ≥3.9 mmol/L (70 mg/dL), the lower limit of the normal range. The profiles of mean glucose response versus time were similar between NG 3 mg and IMG 1 mg during the first 60 minutes post administration. These study results support the use of NG as a rescue treatment for severe hypoglycaemia.

The present study also assessed PK profiles in patients with either T1DM or T2DM, and found these were similar between DM types after NG administration, even though plasma glucagon concentrations appeared to be higher in patients with T1DM versus T2DM after IMG administration (Figure 2B,C). This variance in plasma glucagon concentration can be explained by differences in body weight between patients with T1DM and those with T2DM (Table SS1); however, the glucagon concentrations were remarkably increased regardless of DM type.

Glucagon must be absorbed rapidly in order to reach a concentration sufficient to produce a maximal PD response, which in turn quickly increases glucose levels to treat severe hypoglycaemia. Glucagon absorption was rapid after nasal administration, similar to absorption after intramuscular injection. Observed and change from baseline glucagon Cmax and AUC(0-tlast) were higher with NG 3 mg than with IMG 1 mg; however, TEAEs (including those related to glucagon, such as headache, vomiting and nausea) were similar between the two treatment groups, suggesting greater exposure with NG administration did not affect safety. NG was well tolerated in Japanese patients with T1DM or T2DM, with no reported clinically important treatment-related TEAEs or SAEs that limit the use of glucagon to treat severe hypoglycaemia. As expected, NG-treated patients had more nasal and non-nasal symptoms, which are considered administration route-related (Table 1).9,12

Limitations of the present study include lack of study blinding, which means that the possibility of bias cannot be completely ruled out, particularly for safety evaluation including solicited nasal and non-nasal symptoms. The condition of hypoglycaemia was artificially carefully controlled in this study to ensure PG levels did not fall low enough to cause unconsciousness or coma. In real-world conditions, NG would be used to rescue unconscious patients outside of a hospital setting and PG levels might be lower than those observed in the present study. The patient population in this study may not be fully representative of the real-world population for which NG might be...
used, particularly because the study population did not include many elderly patients. A recent survey showed that elderly patients with T2DM comprise a high-risk population for severe hypoglycaemia in Japan. In addition, the effect of glucagon on sulphonylurea-induced or -related hypoglycaemia was not evaluated in this study; the aforementioned survey showed that sulphonylurea use is one of the major causes of severe hypoglycaemia other than insulin in Japan. Finally, the experimental design, including hypoglycaemia induction with hospitalization at the study site, is quite different from experiencing hypoglycaemia in the real world.

The efficacy findings of the present study are similar to those of Suico et al., in which the same formulation of NG 3 mg was demonstrated to be non-inferior to IMG 1 mg in 66 patients with T1DM. The overall PD glucose profile of NG 3 mg in the present study was also similar to that shown in Suico et al., with a slightly lower BGmax; however, it is difficult to compare absolute changes from baseline in maximal blood glucose between the two studies. Exposure with NG was higher in the present study; however, the incidence and rate of most TEAEs were lower than those reported in Suico et al. The overall efficacy, safety and PD profile of NG 3 mg in the present study are also consistent with a previous randomized crossover non-inferiority study involving eight clinics in the T1DM Exchange Clinic Network, as well as with the findings of a phase 1 trial in children and adolescents (ages 4 to <17 years) with T1DM, and support the expansion of NG to patients with T2DM.

In conclusion, NG 3 mg was non-inferior to IMG 1 mg for the successful treatment of insulin-induced hypoglycaemia in Japanese patients with T1DM or T2DM. These findings support the use of NG 3 mg as a rescue treatment for severe hypoglycaemia.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

M.M. contributed to conception of the work, interpretation of the data, and writing of the manuscript. Y.T. contributed to conception of the work, analysis and interpretation of the data, and writing of the manuscript. R.N. contributed to conception and design of the work, interpretation of the data, and writing of the manuscript. Y.N. contributed to interpretation of the data, and writing of the manuscript. K.O. contributed to conception and design of the work, interpretation of the data, and writing of the manuscript. H.N. contributed to interpretation of the data and writing of the manuscript.

DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK or genetic data. Data are available to request 6 months after the indication study has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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