Newly formulated GROWJECT® is bioequivalent to the prior GROWJECT® formulation and causes less injection-associated pain

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Abstract. Daily treatment with subcutaneous injections of recombinant human GH can be physically and emotionally stressful for children and their caregivers owing to the pain caused by injection. In this study, 52 healthy male subjects were randomized to investigate the bioequivalence and compare the safety and injection-associated pain between the prior GROWJECT® sc formulation and the new formulation, which contains less phosphate buffer. Single subcutaneous doses of each formulation were administered in a crossover manner. Adverse events were monitored throughout the study and subjects rated injection site pain on a 5-point scale. The 90% confidence intervals of the geometric least square means ratio for the area under the human GH concentration-time curve from 0 to 24 h and maximum concentration were 1.002–1.049 and 0.971–1.075 following 6 mg and 0.992–1.038 and 0.973–1.058 following 12 mg, respectively. No severe adverse events were observed. The mean pain score was significantly higher (i.e., less painful) with the new formulation than with the prior formulation regardless of the order of treatment. The new GROWJECT® sc formulation was bioequivalent to the prior formulation and associated with less injection site pain.

Key words: human GH, injection site pain, phosphate buffer, bioequivalence

Introduction

Children with short stature owing to GH deficiency or Turner syndrome and those born small for gestational age are treated with recombinant human GH (hGH). It is administered by daily sc injections and treatment continues until the child reaches adult height. Because it is painful for the child and emotionally stressful for their parents and/or caregivers, injection can impede adherence to treatment.

To address the physical and mental stress associated with hGH injection, during the past 30 yr, hGH manufacturers have implemented numerous improvements to the injection device and formulation for easier operability and better usability. JCR Pharmaceuticals, Co., Ltd. (Ashiya, Japan), a distributor of hGH and the injection device GROWJECTOR®-L, developed a liquid formulation of hGH and launched the GROWJECT® sc injection (6 mg and 12 mg) in 2017, which eliminates the drug reconstitution step and offers convenience over the conventional freeze-dried formulation. The liquid formulation is administered via GROWJECTOR®-L, a power-operated injector with automatic needle insertion, liquid injection at a steady rate, and needle retraction capability. Subcutaneous administration with an automated injector is reported to reduce injection site pain at the puncture site compared with a manual injector (1). However, some patients...
experience more pain during the injection of aqueous solutions. Thus, the formulation of GROWJECT® sc injection (6 mg and 12 mg) was further improved to reduce the pain of injection and achieve greater treatment adherence.

Phosphate buffer is added to drug solutions to suppress deamidation. As high phosphate buffer strength is associated with injection pain (2, 3), the development of the novel formulation focused on lowering the buffer strength. We conducted a pharmacokinetic study to investigate the bioequivalence between and safety of the prior and new formulations. Pain scores were analyzed for exploratory purposes to assess our prediction that the new formulation will cause less injection site pain.

**Patients and Methods**

**Materials**

Both test drugs (new formulation, 6 mg and 12 mg injections) and reference drugs (prior GROWJECT® sc, 6 mg and 12 mg injections) contain 6 mg or 12 mg of somatropin (recombinant) per 1.5-mL cartridge. Table 1 lists the ingredients in both formulations. The buffering strength was reduced by lowering the phosphate concentration to 10 mmol/L from 50 mmol/L.

The new formulation was stable for up to 18 mo in the ongoing 24-mo storage test, whereas the prior formulation was stable for 24 mo (Table 2). Comparable and better results were observed for the new formulation in the accelerated and stress tests, respectively.

### Table 1. Description of the prior GROWJECT® sc formulation and new formulation

| Formulation                  | GROWJECT® sc injection (Prior formulation) | New formulation |
|------------------------------|-------------------------------------------|-----------------|
| Active ingredient            | Somatropin (genetical recombination)      | 6 mg/12 mg      |
| Excipients                   | Sodium dihydrogen phosphate dihydrate     | 10.11 mg a)     |
|                              | Dibasic sodium phosphate hydrate          | 3.65 mg a)      |
|                              | Sodium hydroxide                          | q.s.            |
|                              | Hydrochloric acid                         | q.s.            |
|                              | Phosphoric acid                           | q.s.            |
| Isotonizing agent            | D-Mannitol                                | 40 mg           |
| Stabilizer                   | Polyoxyethylene (160) polyoxypropylene (30) glycol | 3 mg          |
| Preservative                 | Phenol                                    | 5 mg            |
| pH                           | 6.0 to 6.4                                 | 6.0 to 6.4      |

a) 50 mmol/L phosphate buffer, b) 10 mmol/L phosphate buffer. q.s.: quantum sufficit.

### Table 2. Stability of the prior GROWJECT® sc formulation and new formulation

| Stability test                  | Storage condition | Storage term | Storage form | GROWJECT® sc injection (Prior formulation) | New formulation |
|---------------------------------|-------------------|--------------|--------------|-------------------------------------------|-----------------|
|                                 | 2 to 8 °C, dark   | 24 mo        | Glass cartridge | Stable for 24 mo | Stable for up to 18 mo a) |
| Long-term storage test          |                   |              |              |                            |                 |
| Accelerated test                | 25 °C, dark       | 3 mo         | Glass cartridge | Stable for up to 1 mo | Stable for up to 2 mo a) |
| Stress test                     | 30 °C, dark       | 8 wk         | Glass cartridge | Stable for up to 2 wk | Stable for up to 4 wk |
|                                 | 40 °C, dark       | 4 wk         | Glass cartridge | Stable for up to 1 wk | Stable for up to 1 wk |

a) Ongoing until 24 mo.
Subjects and methods

Healthy individuals registered in the volunteer panel of the study site were recruited for the study. A total of 52 healthy male subjects aged between 20 and 35 yr with no significant present or previous diseases were enrolled in the study. Subjects with body mass index (BMI) between 18.5 and 25.0 and body weight between 50.0 and 75.0 kg were included. Subjects were enrolled in either Study 1 or 2 and randomly allocated to treatment sequence A (new formulation in the first period and prior formulation in the second period) or B (prior formulation in the first period and new formulation in the second period). Subjects in Study 1 received the formulations containing 6 mg of somatropin and those in Study 2 received the formulations containing 12 mg of somatropin in a crossover manner with a drug-free washout of at least 3 d. Each of the new and prior formulations was prepared individually to a dose of 0.07 mg/kg body weight and administered with a disposable syringe by sc injection. The injection site was the abdomen for all the subjects.

The study lasted for 8 days after screening. Subjects were confined to the study site for up to 24 h post-dose for pharmacokinetic evaluation and adverse event (AE) monitoring.

To measure serum hGH concentrations, 10 blood samples were collected for each dose: pre-dose and 1, 2, 3, 4, 6, 8, 10, 12, and 24 h post-dose. The bioequivalence between the two formulations was assessed using an area under the human GH concentration-time curve from 0 to 24 h (AUC0–24) and maximum concentration (Cmax). The new formulation was considered to be bioequivalent to the prior formulation when the 90% confidence interval (CI) of the ratio of the least square means (LS means) for each log-transformed pharmacokinetic parameter (AUC0–24 and Cmax) between the formulations was within the acceptable range, log (0.80) to log (1.25).

Physical examinations, 12-lead electrocardiograms (ECGs), and clinical laboratory tests were performed to monitor AEs pre- and 24 h post-dose and vital signs were monitored pre- and 2, 3, 4, and 24 h post-dose. These tests were conducted as they are generally performed in clinical studies in healthy individuals to monitor the physical condition of the subjects. Thyroid function was monitored in this study using blood tests because an abnormality in thyroid function is one of the known adverse drug reactions of the prior GROWJECT® sc formulation. Each AE was evaluated for its severity (mild, moderate, or severe), seriousness (serious or non-serious), causal relationship with the study drug (related or unrelated), and outcome (resolved, improving, unchanged, resolved with sequelae, or death).

Subjects answered a questionnaire immediately after injection to rate injection site pain during aqueous injection as 1. Intolerably painful, 2. Very painful, 3. Painful, 4. Somewhat painful, or 5. Not painful. Injection site pain was not evaluated as an AE in this study. Summary statistics are provided for the pain scores for each formulation. To consider the effect of treatment order, a paired t-test was performed to evaluate the differences in pain scores for each treatment sequence.

This clinical study was reviewed and approved by the Institutional Review Board of OPHAC Hospital (Osaka, Japan) on August 30, 2018. All subjects provided written informed consent to participate in the study prior to any study procedure. The study was conducted in compliance with the approved study protocol, the Declaration of Helsinki, 1964, as revised in 2013, and Good Clinical Practice.

Results

Demographics

The 52 subjects were randomly allocated into Study 1 (26) and Study 2 (26). The mean (SD) age, body weight, and BMI were 23.8 (2.6) yr, 63.78 (4.87) kg, and 21.30 (1.49) in Study 1 and 23.3 (3.8) yr, 61.95 (6.16) kg, and 21.08 (1.74) in Study 2, respectively.

Treatments administered

In Study 1, 26 subjects received a single sc dose of the new 6 mg formulation and 25 subjects received a single sc dose of the prior 6 mg formulation; one subject discontinued treatment owing to an AE before receiving the prior formulation. In Study 2, 26 subjects received a single sc dose of the new 12 mg formulation and the prior 12 mg formulation.

Pharmacokinetics

Following sc doses of 6 mg and 12 mg, the mean serum concentration profiles of hGH were similar between the new and prior formulations (Fig. 1).

Bioequivalence

The ratio of the LS means (90% CI) was 1.025 (1.002–1.049) for AUC0–24 and 1.022 (0.971–1.075) for Cmax following the 6 mg dose and 1.015 (0.992–1.038) for AUC0–24 and 1.014 (0.973–1.058) for Cmax following the 12 mg dose (Fig. 1). The 90% CI of the ratio of the LS means was within the acceptable log (0.80) to log (1.25) range for both AUC0–24 and Cmax following 6 mg and 12 mg doses, demonstrating the bioequivalence between the new and prior formulations for both doses.

Safety

One subject prematurely terminated the study owing to “nasopharyngitis” after receiving the new 6 mg formulation. The AE was considered unrelated to the drug. Other AEs observed were “fever” and “increased percentage of monocytes” following the administration of the new 12 mg formulation. Both were judged as drug related. No AEs were reported following the
administration of the prior formulation at 6 mg or 12 mg. None of the subjects experienced injection site reactions including heat sensation, reddening, or induration. No clinically significant abnormal changes were observed in the vital signs, 12-lead ECGs, and clinical laboratory tests, including thyroid function and blood/urine glucose tests.

Pain score

Figure 2 shows the number and percentage of subjects reporting each pain score for each formulation after combining the doses. No subjects reported a pain score of 1 (Intolerably painful) for either formulation. The number of subjects reporting a pain score of 2 (Very painful), 3 (Painful), 4 (Somewhat painful), and 5 (Not painful) was as follows: in sequence A: 0 (0.0%), 2 (7.7%), 14 (53.8%), and 10 (38.5%) for the new formulation and 1 (4.0%), 11 (44.0%), 12 (48.0%), and 1 (4.0%) for the prior formulation, respectively; in sequence B: 0 (0.0%), 1 (3.8%), 17 (65.4%), and 8 (30.8%) for the new formulation and 2 (7.7%), 4 (15.4%), 20 (76.9%), and 0 (0.0%) for the prior formulation, respectively. A pain score of 2 or 3 was reported by only 5.8% of the subjects after receiving the new formulation and 35.3% after receiving the prior formulation. The majority of subjects reported a score of 4 and the percentage of subjects reporting a score of 5 was higher with the new formulation than with the prior formulation.

The summary statistics for the pain scores are provided in Table 3 and Fig. 3. The mean pain score was significantly higher (less painful) with the new
formulation than with the prior formulation regardless of treatment sequence (A or B): 4.31 (± 0.62) and 3.52 (± 0.65) in treatment sequence A (paired t-test; p < 0.0001) and 4.27 (± 0.53) and 3.69 (± 0.62) in treatment sequence B (paired t-test; p = 0.0032), respectively.

**Discussion**

Our study showed comparable pharmacokinetic and safety profiles between the new and prior GROWJECT® sc formulations. The self-rated pain score results indicated that the new formulation reduces pain at the site of sc injection.

The new GROWJECT® sc injection was developed by changing the type and strength of buffering and isotonizing agents, some of which are associated with injection pain.

The mean serum hGH concentration curves were almost identical between the new and prior formulations for both 6 mg and 12 mg doses and showed that the formulation than with the prior formulation regardless of treatment sequence (A or B): 4.31 (± 0.62) and 3.52 (± 0.65) in treatment sequence A (paired t-test; p < 0.0001) and 4.27 (± 0.53) and 3.69 (± 0.62) in treatment sequence B (paired t-test; p = 0.0032), respectively.

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new formulation, which contains less phosphate buffer, did not affect serum hGH levels. The two formulations were shown to be bioequivalent, in accordance with the Japanese guideline for bioequivalence studies of generic products.

One AE led to study discontinuation; however, this event was not attributed to the drug. Three AEs followed the administration of the new formulation and none followed the administration of the prior formulation. This result does not suggest any differences in the safety profile between the two formulations because the observed AEs with the new formulation were of no clinical concern.

Pain improvement with the new formulation was achieved as expected by reducing the phosphate buffer strength; the majority of subjects experienced less pain, which was confirmed by statistically significant differences in pain score between the new and prior formulations. The injection site in this study was the abdomen, which is in line with clinical practice for hGH therapy; thus, the pain score results in our study can be interpreted as the results that would be obtained with actual treatment with the GROWJECT® sc formulation. Gandell et al. conducted market research to investigate perceptions of im and sc routes of injection and how these perceptions affect treatment adherence. The survey was directed to health care providers (HCPs) and women of childbearing age administered treatment via im or sc injection. When specific barriers to injection regimen adherence were rated by the HCPs, patient perception of injection-associated pain (39% for sc and 51% for im) was one of the major barriers to patient adherence. Women of childbearing potential rated pain as one of the major concerns about injections (40% for sc and 58% for im) and most commonly perceived less pain as the major benefit of sc administration (4). In addition to safety and efficacy concerns, minimizing injection pain is a key factor behind adherence to regular sc injections.

The study subjects were treated with both the test and reference formulations in a randomized crossover manner, which could eliminate confounding factors to evaluate the study results. The limitation of this study is the possibility that the results may not reflect those that would be obtained in children because healthy adult male subjects were recruited for this study.

**Conclusion**

The new GROWJECT® sc formulation, containing less phosphate buffer, was demonstrated to be bioequivalent to the prior GROWJECT® sc formulation. Both formulations were safe and well-tolerated. Moreover, the new formulation resulted in less injection site pain than the prior formulation.

**Conflict of interests:** This clinical study was fully sponsored by JCR Pharmaceuticals, Co., Ltd.

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