Relative Bioavailability of a Single 4-mg Dose of Somatropin Administered by Subcutaneous Injection or by Needle-free Device and Coadministered With the Growth Hormone Inhibitor Octreotide Acetate in Healthy Adult Subjects

Darin B. Brimhall, DO, FACP[1]; Niclas Petri, PhD[2]; and Pina D'Angelo, MSc[3]

[1]Novum Pharmaceutical Research Services, Las Vegas, Nevada; [2]Ferring Pharmaceuticals A/S, Copenhagen, Denmark; and [3]Novum Pharmaceutical Research Services, Pittsburgh, Pennsylvania

ABSTRACT

Purpose: Somatropin, used to treat growth hormone deficiency, has been traditionally administered by subcutaneous (SC) injection with needle and syringe. Needle-free devices offer ease of administration and may improve adherence and outcomes. This study evaluated the relative bioavailability of somatropin delivered with a needle-free device compared with traditional SC injection.

Methods: In this randomized, single-dose, crossover study, healthy adults aged 18 to 35 years received single 4-mg doses of somatropin via a needle-free device or SC injection, along with octreotide to suppress endogenous growth hormone production. Blood samples were analyzed for serum somatropin and insulin-like growth factor-1 (IGF-1) concentrations over 24 hours after somatropin dosing. Pharmacokinetic and pharmacodynamic parameters were evaluated by using noncompartmental methods, and bioequivalence was determined based on ln transformation of the $AUC_{0–24}$, $AUC_{0–\infty}$, C_{max}, area under the effect-time curve from time 0 to 24 hours ($AUEC_{0–24}$), and maximum effect concentration (E_{max}). Bioequivalence was concluded if the 90% CIs of the needle-free device compared with the SC injection, constructed by using the two 1-sided hypotheses at the $\alpha = 0.05$ level, for these pharmacokinetic/pharmacodynamic parameters fell within the 80.00% to125.00% regulatory acceptance range.

Findings: A total of 57 subjects completed both study periods and were included in the pharmacokinetic analyses. Point estimates (90% CIs) of the geometric mean ratio (needle-free device/SC injection) based on serum somatropin were 1.013 (0.987–1.040) for $AUC_{0–24}$, 1.012 (0.986–1.038) for $AUC_{0–\infty}$, and 1.200 (1.137–1.267) for C_{max}. For IGF-1, baseline-corrected point estimates (90% CIs) were 0.901 (0.818–0.993) for $AUEC_{0–24}$ and 0.867 (0.795–0.946) for E_{max}. Non–baseline-corrected values were 0.978 (0.953–1.004) for $AUEC_{0–24}$ and 0.953 (0.923–0.984) for E_{max}. Both treatments were well tolerated; blood glucose levels increased in nearly all subjects (98.3%). All adverse events were mild and resolved spontaneously within 24 hours.

Implications: Bioequivalence was shown for a single 4-mg dose of somatropin delivered by using a needle-free device compared with SC injection based on ln-transformed $AUC_{0–24}$ and $AUC_{0–\infty}$ but not ln-transformed C_{max}. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮) © 2018 The Authors. Published by Elsevier HS Journals, Inc.

Key words: biological availability, healthy volunteers, pharmacokinetics, recombinant human growth hormone, therapeutic equivalency.

INTRODUCTION

Treatment with recombinant human growth hormone (rhGH) is recommended as early as possible in children diagnosed with growth hormone deficiency

Accepted for publication March 26, 2018.
https://doi.org/10.1016/j.clinthera.2018.03.017
0149-2918/$ - see front matter

(GHD) to normalize height during childhood and to allow normal height to be achieved in adulthood.[1] Traditionally, rhGH is administered by subcutaneous (SC) injection using a needle and syringe; however, some patients report this method of administration to be painful, increasing the potential for nonadherence.[2] Needle-free devices were developed as an alternative to the needle and syringe for administration of rhGH, which has shown bioequivalence when given by either method in healthy subjects and patients with GHD.[2–4]

Somatropin, a naturally occurring growth hormone (GH), is manufactured by using recombinant DNA technology to have the same amino acid sequence as the natural hormone and is marketed under multiple trade names. Zomacton is approved in the United States for the treatment of children with growth failure due to inadequate secretion of endogenous GH[5] and in the European Union for the treatment of pediatric GHD and growth retardation due to Turner syndrome confirmed by chromosomal analysis.[6] This somatropin formulation is administered by using a standard sterile disposable syringe or a ZomaJet needle-free injection device (Antares Pharma, Ewing, New Jersey, for Ferring Pharmaceuticals, Inc).[5,6] The ZomaJet device transjects somatropin through the epidermis and into the SC layer of the skin; with the new formulation, it allows injection of more concentrated somatropin, which lowers the injection volume by 3-fold.[7]

At the time of the current study, somatropin was available in 5-mg vials for reconstitution, and a 10-mg vial of powdered somatropin for reconstitution was under development for use with the ZomaJet device. This study compared the relative bioavailability of a single 4-mg dose reconstituted from a 10-mg vial of somatropin and administered via the ZomaJet versus that of a single 4-mg dose reconstituted from a 5-mg vial and administered via a traditional SC injection.

SUBJECTS AND METHODS

Subjects

Healthy men and women aged 18 to 35 years were eligible if they had a body mass index of 19 to 30 kg/m^2 and serum GH levels appropriate for their age and sex. Subjects were excluded if they had a history of allergy or sensitivity to injected proteins (or any drug hypersensitivity or allergy deemed by the investigator to potentially compromise patient safety); significant history or current evidence of chronic infectious disease, system disorder, or organ dysfunction; current abnormal medical condition (including the common cold or seasonal or chronic allergies); psychiatric disorders requiring hospitalization or medication within the last 2 years; medical conditions requiring regular treatment with prescription drugs; use of pharmacologic agents known to affect or inhibit drug-metabolizing enzymes; or history of hemophilia. Pregnant or lactating women and those of childbearing potential were also excluded.

Subjects were not permitted any nonstudy medications after check-in at the study center. Before check-in, subjects were instructed not to use any prescription medications for 14 days or over-the-counter medications for 7 days. Tobacco products were prohibited from 90 days before dosing and throughout the study.

Study Design

This randomized, single-dose, crossover study was conducted from October to November 2011 at a single site in Las Vegas, Nevada. The study was conducted in accordance with ethical principles of the Declaration of Helsinki and in compliance with the US Code of Federal Regulations and International Conference on Harmonisation and Guideline for Good Clinical Practice (E6)R1, as well as the Belmont Report. The Novum Independent Institutional Review Board approved the protocol and informed consent form, and all subjects provided written informed consent before participating.

The study consisted of 2 dosing periods separated by a 7-day washout period and compared single 4-mg doses of somatropin administered by using a needle-free device and standard SC injection. Subjects were screened for eligibility within 28 days before the first study period and were randomized to receive somatropin* 4 mg reconstituted from a 10-mg vial formulation and administered via the ZomaJet needle-free device or somatropin 4 mg reconstituted from a 5-mg vial administered via SC injection† using a 30-gauge needle.[8] A 4-mg dose of somatropin was selected to ensure detectable serum levels of

*Trademark: Zomacton® (Ferring Pharmaceuticals, Inc, Parsippany, New Jersey).

†Trademark: Tev-Tropin® (Teva Pharmaceuticals USA, Inc, North Wales, Pennsylvania; somatropin was available at the time of study as Tev-Tropin; it is currently available as Zomacton).