Tolerability and Pharmacokinetic Properties of Ondansetron Administered Subcutaneously With Recombinant Human Hyaluronidase in Minipigs and Healthy Volunteers

Samuel S. Dychter, MD[1]; Rena Harrigan, MPH[1]; Jesse D. Bahn, MSc[1]; Marie A. Printz, BA[1]; Barry J. Sugarman, PhD[1]; Emanuel DeNoia, MD[2]; David B. Haughey, PharmD, PhD[3]; Daniel Fellows, BS[3]; and Daniel C. Maneval, PhD[1]

[1]Halozyme Therapeutics, Inc, San Diego, California; [2]ICON Development Solutions, San Antonio, Texas; and [3]ICON Development Solutions, Whitesboro, New York

ABSTRACT

Background: Subcutaneous ondansetron facilitated by recombinant human hyaluronidase PH20 (rHuPH20) is an alternative for treating nausea/vomiting in patients who cannot receive ondansetron by other routes of administration.

Objective: Based on preclinical results in minipigs, a Phase I study was designed to assess the tolerability and pharmacokinetic properties of subcutaneous ondansetron + rHuPH20 compared with intramuscular, intravenous, or oral ondansetron monotherapy in healthy volunteers.

Methods: In a crossover design, 3 minipigs were dosed with subcutaneous ondansetron 0.08 mg/kg + rHuPH20, or as intramuscular or intravenous monotherapy, for the evaluation of plasma ondansetron concentrations and local tolerability. In a randomized, open-label, 4-way crossover study, subjects received a randomized sequence of SC ondansetron 4 mg + rHuPH20, or ondansetron monotherapy IM (4 mg), IV (4 mg), or PO (8 mg), over 4 daily visits. Study participants included healthy volunteers aged 19 to 65 years with adequate venous access in both upper extremities and no history of QT-interval prolongation. Primary tolerability end points (administration-site observations, systemic adverse events [AEs], and subject-assessed pain) were assessed, and pharmacokinetic parameters (AUC, C_{max}, T_{max}, $t_{½}$) were computed to compare relative rate and extent of systemic exposure. Results were described using summary statistics, and bioequivalence was determined with a linear mixed-effects model.

Results: In the preclinical study, no adverse events or significant local reactions were observed. The C_{max} (45.8 ng/mL at 0.08 hour) with subcutaneous administration + rHuPH20 was 83% greater and was achieved 68% faster than with intramuscular administration (C_{max} = 25 ng/mL at 0.25 hour). In the clinical study, a total of 12 subjects (7 women, 5 men; white majority; mean age, 44.8) were randomized. The majority of AEs were at the injection site, mild in severity, and transient. After subcutaneous administration of ondansetron + rHuPH20, geometric mean C_{max} was 35% higher than with intramuscular ondansetron, 43% lower than with intravenous ondansetron, and 126% higher than with oral ondansetron (corrected for dose). Bioequivalence tests demonstrated that systemic exposure after subcutaneous administration was similar to that after intramuscular or intravenous administration and significantly greater than that after oral administration.

Conclusions: Subcutaneous ondansetron + rHuPH20 was generally well-tolerated. Subcutaneous dosing resulted in an extent of systemic exposure similar to that with intramuscular or intravenous dosing and greater than that with oral administration, and may be an option for clinical administration of ondansetron. ClinicalTrials.gov identifier: NCT01572012. (*Clin Ther.* 2014;36:211–224)

Key words: ondansetron, pharmacokinetic, recombinant human hyaluronidase, safety, subcutaneous.

INTRODUCTION

Ondansetron hydrochloride is a selective serotonin-blocking agent available in intramuscular, intravenous,

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and oral formulations that have been approved for the prevention of nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy and for the prevention of postoperative nausea and vomiting. The oral formulation has also been approved for the prevention of nausea and vomiting associated with radiotherapy. However, many patients who require antiemetic therapy may not be optimal candidates for intramuscular, intravenous, or oral medications. Although oral therapy can also be self-administered, administration is not always possible if a patient cannot swallow or follow instructions or is unconscious. Intramuscular administration of medications can be painful and may be associated with risks for infection, local induration, bleeding, and abscess formation.[1–3] With intravenous delivery, peripheral venous access can be challenging to establish in patients with cancer and in postoperative patients who are frail, may be dehydrated, and/or have small or collapsed veins. In addition, there are several complications known to occur with intravenous access, including, but not limited to, phlebitis, infiltration, extravasation, and infections.[4,5]

The subcutaneous route of delivery provides an alternative strategy for the parenteral administration of ondansetron. Hyaluronidases are frequently used to aid in the subcutaneous delivery of drugs (ie, anesthetics in ocular surgery) and act through depolymerization of hyaluronan, which is a glycosaminoglycan and a major component of the extracellular matrix found in all tissues.[6] Recombinant human hyaluronidase PH20 (rHuPH20) is a tissue modifier approved by the US Food and Drug Administration (FDA) for use as an adjuvant in subcutaneous fluid administration for achieving hydration, for increasing the dispersion and absorption of other injected drugs, and in subcutaneous urography for improving resorption of radiopaque agents.[7] Examples of the clinical use of rHuPH20 in combination with other therapies include HyQvia™* and trastuzumab. In May 2013, HyQvia (solution for subcutaneous use), a combination of human normal immunoglobulin (IGSC, 10%) and rHuPH20, was approved in the European Union for use as IgG replacement therapy in adult patients ($\geq$18 years) with primary immunodeficiency syndromes or with myeloma or chronic lymphocytic leukemia with severe secondary hypogammaglobulinemia and recurrent infections. A Phase III, prospective, multicenter, open-label, noncontrolled clinical trial demonstrated that the pharmacokinetic properties of a 3- or 4-week cycle of treatment administered at a single subcutaneous site were similar to those of intravenous immunoglobulin.[8] In September 2013, EU approval was granted for the use of a subcutaneous formulation of trastuzumab combined with rHuPH20 for the adjuvant treatment of *HER2*-positive breast cancer. The subcutaneous formulation is administered within 2 to 5 minutes, rather than 30 to 90 minutes with the standard intravenous formulation.

Ondansetron is FDA approved for intramuscular, intravenous, and oral delivery. Subcutaneous administration has been reported in the literature as having been successful by use of an infusion pump in the inpatient and outpatient settings.[9–12] The largest study conducted was in 521 women with severe nausea and vomiting of pregnancy.[9] Patients were started on a loading dose of 2 to 8 mg, followed by 16 to 28 mg/d by a continuous microinfusion pump. This regimen appeared to have been well-tolerated, with a statistically significant decrease in the mean Pregnancy-Unique Quantification of Emesis score. In a second study, 46 patients with nausea and vomiting of pregnancy who failed on first-line subcutaneous metoclopramide were dosed over a mean of 22 days with subcutaneous ondansetron; however, the dosing regimen was not discussed.[10] In addition, there have been 2 separate case reports of subcutaneous ondansetron infused slowly, at 1 mg/h[12] and 1.25 mg/h,[11] with no injection-site reactions reported.

These data demonstrate the feasibility of the subcutaneous administration of ondansetron in patients with nausea and vomiting, albeit in the context of using a relatively cumbersome infusion apparatus. In the present study, ondansetron was administered by manual slow-push injection, obviating infusion-pump equipment. Another opportunity that the use of rHuPH20 offers in this context is the use of a single subcutaneous infusion catheter to deliver both medicines and fluids. Subcutaneous infusion of replacement crystalloid fluids is not feasible without the use of hyaluronidase owing to the resistance to bulk fluid flow attributable to the presence of the gel-consistency hyaluronan matrix in the subcutis.[6] Accordingly, no other fluids/medications were administered in the subcutaneous line in the studies cited earlier. To validate the tolerability and pharmacokinetic profile of sub-

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