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Research paper

Identification and characterisation of a salt form of Danirixin with reduced pharmacokinetic variability in patient populations

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ABSTRACT

The natural variability of gastric pH or gastric acid reducing medications can result in lower and more variable clinical pharmacokinetics for basic compounds in patient populations. Progressing alternative salt forms with improved solubility and dissolution properties can minimise this concern. This manuscript outlines a nonclinical approach comprising multiple biopharmaceutical, in vitro and physiologically based pharmacokinetic model (PBPK) modelling studies to enable selection of an alternative salt form for danirixin (DNX, GSK1325756), a pharmaceutical agent being developed for chronic obstructive pulmonary disease (COPD). The hydrobromide salt of DNX was identified as having superior biopharmaceutical properties compared to the free base (FB) form in clinical development and the impact of switching to the hydrobromide salt (HBr) was predicted by integrating the nonclinical data in a PBPK model (using GastroPlus™) to enable simulation of clinical drug exposure with FB and HBr salts in the absence and presence of a gastric acid reducing comedication (omeprazole, a proton pump inhibitor (PPI)). Subsequent investigation of DNX pharmacokinetics in a Phase 1 clinical study comparing FB with HBr salt forms confirmed that DNX HBr had reduced the variability of drug exposure and that exposure was not affected by PPI co-administration with DNX HBr. This case study therefore adds to the surprisingly few examples of a more soluble salt of a weak base translating to an improvement in human pharmacokinetics and illustrates a clear clinical benefit of salt selection during drug development.

1. Introduction

Danirixin (DNX, GSK1325756, Fig. 1) is a chemokine receptor 2 (CXCR2) antagonist, currently in Phase 2 development as an oral treatment for Chronic Obstructive Pulmonary Disease (COPD). Consideration of the patient population and the potential for drug interactions with commonly administered medications is critical for any drug therapy. The free base (FB) form of DNX used for initial clinical development was known to exhibit the pH-dependent solubility typical of weak bases [1,2]. The subsequent risk of pharmacokinetic (PK) variability in a COPD patient population due to reduced acid secretion in the elderly [3] and drug interactions with gastric acid reducing agents (e.g. proton pump inhibitors (PPI), histamine H2-receptor antagonists, and antacids [4]), was therefore recognised and investigated clinically.

Clinical development of DNX FB confirmed its pharmacokinetic limitations (i.e. high inter-subject variability and systemic exposure changes in the presence of food and PPIs) in healthy adults including elderly subjects [5]. Hence an extensive salt screen was carried out in an attempt to find a version that was more soluble across the whole of the physiological pH range. The hydrobromide (HBr) form of DNX was identified as an alternative salt and a series

Abbreviations: AUC, Area Under the Curve; API, Active Pharmaceutical Ingredient; Cmax, Maximum blood concentration; COPD, Chronic Obstructive Pulmonary Disease; DNX, Danirixin; HPLC, High Performance Liquid Chromatography; FaSSIF, Fasted State Simulated Intestinal Fluid; FeSSIF, Fed State Simulated Intestinal Fluid; FB, Free Base; HBr, Hydrobromide; IDR, Intrinsic Dissolution Rate; IR, Immediate Release; NCE, New Chemical Entity; PBPK, Physiologically-Based Pharmacokinetic; PPI, Proton Pump Inhibitor; RH, Relative Humidity; SGF, Simulated Gastric Fluid; TIM-1, TNO Gastro-Intestinal Model 1.

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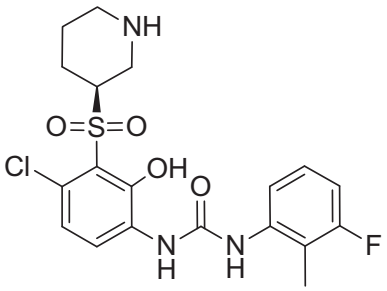

Fig. 1. Structure of Danirixin (GSK1325756).

of biopharmaceutical investigations were performed including solubility and intrinsic dissolution determinations and disproportionation predictions. An in vitro TNO gastrointestinal model (TIM-1) was then used to compare the drug available for absorption of DNX FB and DNX HBr within the gastro-intestinal tract and to investigate the likely impact of food and PPIs.

In advance of investigating DNX HBr in clinical trials a PBPK model was also developed and applied retrospectively to simulate the observed human drug exposure with DNX FB in the absence and presence of PPI, before prospectively predicting the likely impact of switching salt form to DNX HBr for subsequent clinical development. Based on the combined biopharmaceutical, in vitro and modelling data, the PK performance of DNX HBr was then investigated in a Phase 1 clinical study (201037) in healthy elderly subjects.

2. Materials and methods

2.1. DNX salt screen

DNX FB of 99.5% purity was used as input to the screen. For each experiment, a slight excess of one equivalent of each counter-ion was added to pre-mixed slurries of DNX FB in water at a concentration of 1 mg/mL. Liquid counter-ions were dosed as dilute molar solutions in water. The mixtures were left stirring at room temperature whilst the concentration of active pharmaceutical ingredient (API) in solution was assayed after 0.5, 4 and 24 h by high performance liquid chromatography (HPLC).

2.2. Intrinsic Dissolution Rate (IDR) analysis

DNX FB and HBr were analysed in a Surface Dissolution Imager (SDI – Sirius Analytical, Forrest Row, East Sussex, UK) to determine the IDR and solubilisation behaviour of the different versions in a range of bio-relevant media. The SDI is a low volume flow cell integrated with a UV–Vis camera providing real-time ultra-violet images of the drug dissolution process and determining the extent of dissolved API.

DNX FB and HBr were tested at a constant flow rate of 0.3 mL/min in pH 1.6 Simulated Gastric Fluid (SGF), 0.01N HCl, pH 3 sodium phosphate and pH 4 potassium citrate buffers. The UV wavelength for analysis was 254 nm and samples were allowed to dissolve for 15 min after which time profiles were obtained and an average IDR value determined. The powders were compressed into 2 mm diameter compacts at 70 cNm to ensure a constant surface area during the test. For further details and background on the SDI see Østergaardjesper et al. [6].

2.3. Solubility determination

The solubility of DNX FB and HBr salt was determined in the following media at ambient temperature: simulated gastric fluid pH 1.6, fasted state simulated intestinal media (FaSSIF) pH 6.5 (SIF powders (http://www.biorelevant.com/fassif-fessif-fassgf/how-to-make/), fed state simulated intestinal media (FeSSIF) pH 6.5 (Biorelevant), and Britton Robinson Buffers pH 2, 4, 6, and 8. The drug substance was added to 1 ml of media and allowed to mix on a roller mixer, samples were taken after 0.5, 4 and 24 h, filtered and then assayed by HPLC.

2.4. Disproportionation modelling

A DynoChem® (Scale-up Systems Ltd., Dublin, Ireland) mechanistic model for predicting the likelihood of disproportionation for salts of weakly basic APIs in formulated drug products was used (DynoChem® Version 4.1.0.0). Disproportionation was assessed at 25 mg and 50 mg dose strengths at a range of simulated atmospheric humidity conditions. For further details of the disproportionation modelling method see Supplementary Material 1. Due to the early phase of development of the drug, a method has not yet been developed to validate the in silico predictions for the tablet formulations.

2.5. Tablet manufacture

DNX FB tablets were manufactured using wet granulation, compression of the resultant blend and film coating of the tablet cores. The FB formulation consisted of the following components: microcrystalline cellulose, mannitol, croscarmellose sodium, hypromellose, magnesium stearate and Opadry White OY-S-28876. The DNX HBr tablets were manufactured using roller compaction, compression of the resultant blend and film coating of the tablet cores. The HBr formulation consisted of the following components: microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, sodium stearyl fumarate and Opadry White OY-S-28876. The differences in the manufacturing process and the composition of the FB and HBr tablet formulations were not expected to impact the release profile of DNX. Both tablets were used for the in vitro dissolution assessments, TNO TIM-1 studies and the clinical study.

2.6. Dissolution testing

The dissolution procedure for DNX tablets was determined in SGF pH 1.6 (consisting of 2.0% w/v sodium chloride adjusted to pH 1.6 using 1 M hydrochloric Acid and pH 4 citrate buffer maintained at 37 °C). The dissolution was conducted using US Pharmacopoeia (USP) Apparatus 2, equivalent to the Paddle apparatus of European Pharmacopoeia, operating at 75 rpm with online UV monitoring at 315 nm, with background correction of 500 nm. Typically tablets of each formulation were tested in duplicate during formulation screening.

2.7. TIM-1 experiments

The TNO TIM-1 model is a dynamic gastro-intestinal model which has been designed and produced by TNO Triskelion, Holland [7]. The TNO TIM-1 model consists of a stomach, duodenum, jejunum and ileum compartment. It can mimic the dynamic conditions found within the stomach and the small intestine, i.e. peristalsis, gastric emptying, pH controlled compartments, enzyme secretion, intestinal transit as well as being dosed with the relevant food that will be used in an in vivo study. Experiments were conducted in the fasted and fed states using DNX FB 50 mg tablet and DNX HBr 50 mg tablet comparing standard pH conditions with elevated pH conditions in the stomach compartment to simulate PPI administration. It should be noted that the TNO TIM-1 model shows the amount of drug available for absorption and is not an absorption profile and