Introduction

- GSXK is a weak base with good solubility at gastric pH and good permeability, it belongs to BCS class II (Biopharmaceutical Classification System).
- GSXK showed high PK variability (CV% 70-100% in Cmax and AUCs) when orally administered as an immediate release tablet in fasted conditions. This variability could be related to a variety of factors such as differences in gastric emptying patterns or poor formulation performance [1]. In phase I studies, variability was limited by food.
- A 3-way cross-over study in human volunteers was carried out to assess the relationship(s) between GSXK absorption and gastric emptying time and to guide formulation development. Treatments were: 1) solution in capsule, 2) IR tablet – fasted state, 3) IR tablet – fed state.
- Gamma scintigraphy was used to evaluate formulation performance by visualizing the disintegration process and by measuring the gastric emptying time in relation to the use of food or of different formulations.

Objectives

To develop a population PK model to assess any relationship(s) between gamma scintigraphy emptying profile and GSXK plasma disposition after administration of a solution or a tablet formulation in fasted and fed states.

Methods

- A GI-transit-absorption kinetics model was developed. Different number of sequentially linked compartments (stomach, intestine, …) were explored [2].
- The drug was measured as radioactivity transit through the stomach and GI transit process from the stomach to the jejunum was described by a rate-limited process:

\[ Ka = \frac{\text{Rate}_{\text{max}} \times \text{Time}}{\text{T}50 \times \text{Time}} \]

- Where Rate_{\text{max}} is the fastest transit rate, T50 is the time at which rate is the 50% maximum rate and \( \gamma \) is the sigmoidicity factor.
- The disposition PK model connected to this GI absorption model was a three compartment model with first order elimination rate constant (\( k_{20} \)) from the central compartment and distribution (\( k_{32}, k_{24}, k_{42} \)) into 2 additional peripheral compartments.
- A Mixed effect modelling (NONMEM, version VI) was used to estimate the model parameters.

Results

Dosage forms landed in a formulation and food dependent manner.
1) Solution in capsules: esophagus
2) Tablet fasted: antrum
3) Tablet fed: fundus

- A relative bioavailability F (to solution) was estimated for tablet in fasted and fed conditions.
- F for tablet (fasted and fed) was not statistically different from solution; variability was much higher.

Objective

To develop a population PK model to evaluate variability in oral absorption using gamma scintigraphy.

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