Phase 1 clinical study: First-in-man 2-IB dose escalation study

Study title
RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE ESCALATION STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF SINGLE AND MULTIPLE DOSES OF 2-IMINOBIOTIN (2-IB) IN HEALTHY MALE SUBJECTS

Study code
PRA International code : NOA046EC-090461
Sponsor code : NEU01-01-01
EudraCT number : 2009-016799-60

Objectives
Primary:
To investigate the safety and tolerability of single and multiple doses of 2-IB pulse intravenous (iv) infusion in healthy male subjects
To determine the pharmacokinetics (PK) after single and multiple doses of 2-IB pulse iv infusion in healthy male subjects
Secondary:
To investigate the safety and tolerability of multiple doses of a 5% Captisol® infusion formulation in healthy male subjects
To determine the effect of a 5% Captisol® infusion formulation on the safety and PK of 2-IB
To determine the PK after multiple doses of an infusion formulation including 5% Captisol® in healthy male subjects

Methodology
Design: This study was a phase 1 randomized, double-blind, placebo-controlled, dose escalation study with 2 groups of 9 healthy male subjects receiving a single iv infusion (Group 1, Period 1) or pulsed iv infusions (Group 1, Periods 2 and 3 and Group 2) of 2-IB or placebo in 3 periods. Treatments were randomized such that each subject received 2 out of 3 foreseen dose levels of 2-IB and once placebo. There was a washout period of at least 7 days between each dosing period. During Period 1 of Group 1, 3 subgroups (Groups 1a, 1b, and 1c) of 3 subjects (2 on active and 1 on placebo) were dosed. After completion of Period 1 and after completion of all periods of Groups 1a, 1b, and 1c, there were interim safety and PK evaluations to reconsider the dosing schedule and PK sampling for the subsequent periods of Groups 1 and for Group 2.

Treatments:
Two groups of 9 healthy male subjects each received 2-IB or placebo in 3 periods, with a washout of at least 7 days between dosing periods. During Period 1 for Group 1, 3 subgroups (Groups 1a, 1b, and 1c) of 3 subjects (2 on active and 1 on placebo) were dosed. The following treatments were administered:

Group 1a	Period 1	Single iv infusion of 0.6 mg/kg 2-IB (n=2) or placebo (n=1) over 4h
	Period 2	15-min iv infusion of 0.6 mg/kg 2-IB (n=2) or placebo (n=1) every 4h (6 infusions)
	Period 3	15-min iv infusion of 2 mg/kg 2-IB (n=2) or placebo (n=1) every 4h on Day 1 (6 infusions)
Group 1b	Period 1	Single iv infusion of 0.6 mg/kg 2-IB (n=2) or placebo (n=1) over 1 h
	Period 2	15-min iv infusion of 0.6 mg/kg 2-IB (n=2) or placebo (n=1) every 4h on Day 1 (6 infusions)
	Period 3	15-min iv infusion of 2 mg/kg 2-IB (n=2) or placebo (n=1) every 4h on Day 1 (6 infusions)
Group 1c	Period 1	Single iv infusion of 0.6 mg/kg 2-IB (n=2) or placebo (n=1) over 15min on Day 1
	Period 2	15-min iv infusion of 0.6 mg/kg 2-IB (n=2) or placebo (n=1) every 4h on Day 1 (6 infusions)
	Period 3	15-min iv infusion of 2 mg/kg 2-IB (n=2) or placebo (n=1) every 4h on Day 1 (6 infusions in total)

Group 2	Period 1	15-min iv infusion of 2 mg/kg 2-IB (n=6) or placebo (n=3) + Captisol every 4h on Day 1 (6 infusions)
	Period 2	15-min iv infusion of 6 mg/kg 2-IB (n=6) or placebo (n=3) + Captisol every 4h on Day 1 (6 infusions)
	Period 3	30-min iv infusion of 12 mg/kg 2-IB (n=6) or placebo (n=3) + Captisol every 4h on Day 1 (6 infusions)

Safety assessments:
AEs: recorded from the time the Informed Consent Form is signed until completion of the follow-up visit; clinical laboratory (including clinical chemistry, hematology, coagulation, and urinalysis): each period at 24 h (Groups 1 and 2) and 48 h (Group 2 only) after the start of the first infusion; vital signs (including supine systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature): each period before the first dose and at approximately 30 min after the end of each infusion;
12-lead ECG: each period before the first dose and at 6 h, 10 h, 24 h (Groups 1 and 2), 30 h 34 h, and 48 h (Group 2 only) after the start of the first infusion; infusion site inspection: the forearm in which the infusions were given were inspected at least 2 times after each infusion

Bioanalysis : analysis of plasma and urine samples for 2-IB (Groups 1 and 2) and Captisol® (Group 2 only; analysis of urine samples optional) by the Sponsor using a validated liquid chromatography-mass spectrometry/mass spectrometry method

Procedures and assessments:
Screening: medical history, demographic data (including body weight and height), clinical laboratory (including clinical chemistry, hematology, coagulation, and urinalysis), alcohol and drug screen, hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), anti-human immunodeficiency virus (HIV) 1/2, vital signs (including supine systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature), 12-lead electrocardiogram (ECG), physical examination, adverse events (AEs), previous and concomitant medications
Admission: drug and alcohol screen, AEs, and concomitant medications
Follow-up: clinical laboratory (including clinical chemistry, hematology, coagulation, and urinalysis), vital signs (including supine systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature), ECG, physical examination, AEs, and concomitant medications
Observation period:
Group 1: 3 periods in the clinic, first period in clinic from -17 h up to 24 h after start of first drug administration, second and third period in clinic from -17 h up to 48 h after start of first drug administration;
Group 2: 3 periods in the clinic, each from -17 h up to 48 h after start of first drug administration

Study Medication
Active medication: 2-IB
Strength:
for Groups 1a, 1b, and 1c: 1.0 mg/mL in pH 4.0 citrate buffer
for Group 2: 4.0 mg/mL in pH 4.0 citrate buffer and 5% Captisol®
Batch number: 2-IB: G01287, SAFC Pharma
Batch number: Captisol®: 17CX01-HQ0039, Cydex Pharmaceuticals Inc.
Dosage form : iv infusion

Placebo
Substance:
for Groups 1a, 1b, and 1c: pH 4.0 citrate buffer
for Group 2: pH 4.0 citrate buffer with 5% Captisol®
Batch number: Captisol®: 17CX01-HQ0039, Cydex Pharmaceuticals Inc.
Strength : not applicable
Dosage form : iv infusion

Results
Safety
Treatment-emergent adverse events (TEAEs) were defined as AEs that started or worsened after the subjects received the first dose of study medication. A total of 86 TEAEs were reported for 17 subjects (77% of the 22 subjects who received any study medication). All of these events had resolved by the time of the follow-up visit. No deaths or other serious AEs (SAEs) were reported; 2 subjects discontinued study treatment due to TEAEs (both at the highest dose level, due to nausea of

moderate intensity and dizziness, abdominal pain and headache of mild intensity [Subject 0011], and due to nausea and dizziness of moderate intensity, as well as pallor (mild intensity) and malaise (moderate intensity) [Subject 0016]).

Pharmacokinetics

Concentration data in plasma

Variability in plasma concentrations was generally low.
Group 1: with single infusions over 4, 1, or 0.25 h, 2-IB plasma concentrations peaked at different times and different concentrations, but dropped to below the lower limit of quantitation (LLOQ) by 12 h after dosing. AUCs were similar regardless of infusion duration.
Groups 1 and 2: with 6 doses over 4 hours at 0.6 mg/kg, 2 mg/kg, 2 mg/kg + Captisol®, 6 mg/kg + Captisol®, and 12 mg/kg + Captisol®, there was minimal accumulation of the study drug over multiple doses, and trough levels between doses were low.

Other PK parameters in plasma

With a single dose of 2-IB, the duration of the infusion did not substantially affect the AUC overall, particularly comparing the 4-hour infusion with the 1-hour infusion. With multiple doses of 2-IB at different levels and formulations, the PK parameters show that exposure increased in a linear and dose-proportional manner, that the inclusion of Captisol® in the formulation did not substantially affect the PK parameters of 2-IB, and that there was only minimal accumulation after 6 doses. Clearance was uniform throughout the range of doses and regimens, generally around 0.4 L/h/kg. There was low interindividual variability in the PK parameters.

The AUCs after administration of different dose levels and formulations of 2-IB appeared to change in a dose-proportional manner, consistent with the other linear PK characteristics observed in the study. Comparing the administered doses to the cumulative amount of unchanged 2-IB excreted in urine ($A_{e0\text{-}12}$) after single doses, shows that renal clearance is an important route of elimination of 2-IB. However, in steady state, after multiple dose treatment the mean $A_{e(0\text{-}4)}$ (amount excreted over a dosing interval) as a percentage of the dose decreased with increasing dose. With multiple dosing of 2-IB, the $A_{e(0\text{-}12)}$ increased with dose, but the increase appeared to be less than dose proportional.

Conclusions

Safety

• Treatment with single and multiple doses of 2-IB with and without Captisol® by iv infusion of up to 6 doses of 6 mg/kg was safe and well tolerated by all healthy male subjects.
• There were no clinically relevant differences in clinical laboratory, vital signs, ECG, or physical examinations between placebo and all active treatments (up to and including the dose level of 12 mg/kg)
• The 12 mg/kg dose regimen was well tolerated by 4 out of 6 subjects. However, as 2 out of 6 subjects were withdrawn due to non-serious adverse events (nausea and dizziness), one after the first and one after the third of 6 doses, it is concluded that the highest tolerable dose in this trial is 6 mg/kg.

Pharmacokinetics 2-IB

• The main PK exposure parameters (AUC and C_{max}) of 2-IB (for single and multiple doses) were linear, with low interindividual variability.
• The duration of the infusion had little effect on the ultimate AUC after a single dose.
• There was little accumulation and substantial differences between peaks and troughs during multiple dose administration every 4 hours.
• The exposure to 2-IB appeared to be dose-proportional throughout the range of doses and regimens.
• Captisol® did not have an appreciable effect on the PK parameters of 2-IB, although an approximately 17% higher AUC was observed in the 2 mg/kg 2-IB with Captisol® group compared to the 2 mg/kg without Captisol® group.
• In steady state, over the dose range studied the mean (SD) amount of 2-IB excreted as unchanged drug in the urine during a dosing interval ($A_{e\ 0\text{-}4}$) decreased from 100 (6)% of the administered dose for 0.6 mg/kg to 26 (11)% of the administered dose for the 12 mg/kg dose level.