# 2 Synopsis

**Name of finished product**: INC280

**Name of active ingredient**: INC280

**Study number**: CINC280X2106

**Title of study**: A single-center, open-label study to investigate the absorption, distribution, metabolism and excretion (ADME) of INC280 after a single oral dose of 600 mg [$^{14}$C]INC280 (5.55 MBq) in healthy male subjects.

**Investigator**: Jan Jaap van Lier, MD, Pharmaceutical Research Associates Group B.V., The Netherlands.

**Study center(s)**: Single center in The Netherlands.

**Publication (reference)**: None.

**Study period**

First patient enrolled: 12-NOV-2014 (first subject first visit)

Last patient completed: 31-DEC-2014 (last subject last visit)

**Phase of development**: Phase I

**Objectives**:

**Primary objectives**

- To determine the rates and routes of excretion of [$^{14}$C]INC280 related radioactivity, including mass balance of total drug-related radioactivity in urine and feces, following the administration of a single 600 mg oral dose of [$^{14}$C]INC280 to healthy male subjects.
- To determine the pharmacokinetics of total radioactivity in blood and plasma.
- To characterize the plasma pharmacokinetics of INC280.

**Secondary objective**

- To assess the safety and tolerability of a single 600 mg oral dose of [$^{14}$C]INC280 administered to healthy male subjects.

**Exploratory objectives**

- To identify and (semi-) quantify metabolites of INC280 in plasma, urine and feces in order to elucidate key biotransformation pathways and clearance mechanisms of INC280 in humans.
- To characterize the plasma exposure and pharmacokinetics of metabolites based on radiometry data.
- To perform pharmacogenetic assessments to examine whether individual genetic variation in genes confer different metabolism and pharmacokinetics (PK) responses to INC280.
- Explore novel analytical methodologies in residual samples for obtaining mass balance and drug metabolism information. Information from these exploratory analyses are not part of the ADME study and therefore not included in the CSR, but will be reported in a separate drug metabolism and pharmacokinetics (DMPK) technology report.

**Methodology**: This was a single center, open-label study to determine the ADME of INC280 after a single oral dose of 600 mg [$^{14}$C]INC280 (approximately 5.55 MBq) in six healthy male subjects. The study consisted of a Screening period (Day -21 to -2), a Baseline period (Day -1), a single dosing (Day 1) with a 168 (Day 8) hours post-dose in-house observation period, a study completion visit on Day 8, 24-hour visits (if necessary), and safety Follow up at least 29 days (Day 30) post-dose. Safety and pharmacokinetics (PK) assessments were performed throughout the study at specified time points.

**Number of patients (planned and analyzed)**: It was planned to dose approximately six healthy male subjects with the objective of having at least four subjects complete the study. Six healthy male subjects completed the study.

**Diagnosis and main criteria for inclusion**

**Inclusion Criteria:** Healthy male subjects 45 to 65 years of age inclusive, and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at Screening.

**Exclusion Criteria:** A history of clinically significant ECG abnormalities or a family history (grandparents, parents or siblings) of a prolonged QT-interval syndrome; known history or current clinically significant arrhythmias, relevant radiation exposure (>0.2 mSv) within 12 months prior to scheduled dosing with [$^{14}$C]INC280. Consumption of Seville oranges, grapefruit, grapefruit hybrids, pomelos, star fruit, pomegranate and exotic citrus fruits (as well as their juices) and cruciferous vegetables (e.g., Brussels sprouts, broccoli, cabbage, cauliflower) during the last 7 days prior to dosing. Regular orange juice is permitted. Consumption of poppy seeds three days prior to drug screen. Subjects with clinically significant abnormal ophthalmologic Baseline exam.

**Test product, dose and mode of administration, batch number**: All subjects received a single oral dose of 600 mg (5.55 MBq) [$^{14}$C]INC280 (nominal dose) as 12 x 50 mg capsules; batch no. X178 0914.

**Duration of treatment**: Single dose.

**Reference therapy, dose and mode of administration, batch number**: Not applicable.

**Criteria for evaluation**

**Determination of mass balance, metabolite profiles, and pharmacokinetic variables:** Total radioactivity in blood, plasma, urine and feces were analyzed by liquid scintillation counting. INC280 in plasma was quantified by a validated method using liquid chromatography-tandem mass spectrometry (LC-MS/MS). INC280 and metabolites in plasma, blood, urine and feces were determined using liquid chromatography with offline $^{14}$C-detection by Topcount microplate scintillation counting. Metabolite structures were characterized by LC-MS/(MS) and other methods, as appropriate.

**Safety**: Safety assessments consisted of collecting all AEs, serious adverse events (SAEs), including their severity and relationship to study drug, slit lamp eye exams with dilatation, and pregnancies (if female partners of any male participant who took study drug become pregnant within three months following the dose of study drug). They also included the regular monitoring of vital signs, laboratory evaluations, and ECGs.

**Statistical methods**: No formal statistical hypothesis was tested. Unless otherwise specified, categorical data were presented as frequencies and percentages; continuous data were presented as n, arithmetic mean, standard deviation (SD), median, minimum, and maximum. For plasma INC280 concentration and PK parameter data, the geometric mean and geometric CV% were also presented.

Novartis Biostatistics and programming provided summary tables and listings for PK, demography, disposition, treatment, AEs, labs and other safety related data. Novartis ClinPharm/DMPK calculated the PK parameters and provided summary tables, figures, and listings for all PK data and parameters. Novartis DMPK also evaluated the data on metabolite profiles, provided the information on metabolite structures, summarized the data on excretion of radioactivity and reported mass balance calculations (as percent of the radioactivity dose).

**Summary - Conclusions**

**Demographic and background characteristics**: All six treated subjects were male and Caucasian. The median age of the subjects was 52.0 years (range: 46 to 58 years) and median BMI was 25.866 kg/m$^2$ (range: 24.91 to 26.50 kg/m$^2$).

**ADME results**:

**Absorption**

The exposure to parent drug relative to total radiolabeled components (radioactivity) was high (31% of radioactivity AUCinf). Maximum concentration (Cmax) of INC280 and radioactivity was achieved 2 hours after dosing.

On average 42.1 ± 23.0% of the dose in feces (pools 168 hours) consisted of unchanged drug (range: 9.3%-72.6%) but was only detected in trace amounts in urine, indicating significant metabolism of the absorbed dose.

Assuming that the drug is stable against intestinal bacterial enzymes, the mean oral absorption of INC280 (urinary excreted radioactivity plus fecal as metabolites) was estimated to 49.6 ± 20.9% with a range between 21.0% and 81.7%.

**Pharmacokinetics in plasma**

The plasma concentrations of INC280 showed a median Tmax of 2.00 hours (range 1 to 2 hours) after intake. The geo-mean values of Cmax and AUCinf were estimated at 3110 ng/mL and 13200 ng*h/mL, respectively which was higher compared to the geo-mean values of 1680 and 6260 ng/mL, for Cmax and AUCinf respectively in a previous single dose study in healthy subjects (N=24) at the same administered dose (study CINC280X2103). However, the individual Cmax and AUCinf values in this study ranged from 750 to 5410 ng/mL and 4970 ng*h/mL to 20000 ng*h/mL, respectively, which remains within the variability of the previous study where the Cmax and AUCinf range was [311 ng/mL- 6560 ng/mL] and [1690 ng*h/mL-20700 ng*h/mL], respectively.

The pharmacokinetic parameters of radioactivity and INC280 in plasma showed moderate inter-individual variability in terms of both Cmax (CV: 48.9% for radioactivity and 46.7% for INC280) and AUCinf (CV: 34.9% for radioactivity and 36.9% for INC280).

**Distribution**

The apparent distribution volume associated with the terminal phase ($V_z$/F) calculated from plasma concentrations was geomean (CV%) 473 L (100). Thus, INC280 was largely distributed within the human body when comparing to the volume of total body water of 42 L. The ratio of compound-related radioactivity between blood and plasma showed substantial variations, but no special affinity of INC280 and/or its metabolites to erythrocytes could be concluded.

**Biotransformation**

In addition to unchanged INC280 (42.9% of radioactivity AUC0-12h, metabolite pattern analysis), the metabolite M16 (imidazo-triazinone/ lactam formation) represented the main circulating metabolites detected in the plasma radiochromatograms (21.5%).

Minor proportions of other metabolite peaks were detected and attributed to the metabolites M8 and M28, each accounting on average for 5.4-5.9% of the plasma AUC0-12h. The metabolites M8 and M28 were formed by hydroxylation of the methylene group and N-dealkylation/hydroxylation (or lactam formation), respectively. The metabolites M18, M26 and M13 amounted to less than 3% of the plasma AUC0-12h, each. The metabolites were formed by N-dealkylation, hydrogenation and carboxylic acid formation, respectively. Numerous other metabolites contributed to less than 2% of the plasma AUC0-12h each.

A considerable part of the oral dose was cleared by biotransformation:

The metabolic reactions involved lactam formation, hydroxylation, N-dealkylation, formation of a carboxylic acid, hydrogenation, N-oxygenation, glucuronidation and combinations thereof.

The main circulating metabolite M16 had been found in previous studies in the rat [DMPK R1100027], monkey [DMPK R1300820] and in vitro investigations of metabolism [DMPK R1000705].

**Elimination**

INC280 was eliminated mainly due to metabolism and subsequent biliary/fecal and renal excretion. The study showed that the apparent plasma clearance (CL/F) of INC280 was moderate to high (30.0 to 121 L/h). Mean apparent elimination half-lives of total radiolabeled components (radioactivity) and INC280 in plasma were 10.6 and 7.84 hours, respectively.

**Excretion and mass balance**

INC280-related radiolabeled material was excreted mainly with the feces in the range between 66.6% and 92.7% of dose (mean: 77.9%) and in urine between 8.9% and 31.5% (mean: 21.8%) within 7 days (168 hours).

The recovery of the radioactive dose from the excreta was complete at 7 days after dosing (mean: 99.7% of dose; range: 94.8%-104.1%).

**Safety results**:

- Four out of six subjects (66.7%) experienced at least one AE during the study. All the AEs reported were of grade 1 severity.
- One subject experienced two AEs (headache and somnolence both of grade 1 severity) suspected to be related to study drug.
- There were no deaths, SAEs, or other significant AEs during the study. No clinically significant laboratory abnormalities were observed during the study. No subject discontinued due to an AE.
- No clinically significant abnormalities in vital signs, ECG, and ophthalmic exam results were observed during the study.

**Conclusion**:

- No safety concerns were identified in this study. A single 600 mg oral dose of [$^{14}$C]INC280 was safe and well tolerated in healthy male subjects.
- Peak concentrations of INC280 and total radiolabeled components (radioactivity) after oral dosing of 600 mg [$^{14}$C]INC280 showed substantial systemic availability of INC280.
- The extent of oral absorption was estimated to account for 49.6% of the administered dose but showed considerable variability (range: 21.0%-81.7%). Maximum concentration (Cmax) of radioactivity and INC280 in plasma were reached at 2 hours after oral dosing.
- The mean apparent terminal half-lives of total radiolabeled components (radioactivity) and INC280 in plasma were 10.6 and 7.84 hours, respectively.
- The most abundant radioactive component in plasma was unchanged INC280 (42.9% of radioactivity AUC0-12h). The metabolite M16 (imidazo-triazinone formation) was the main metabolite and accounted for 21.5% of the radioactivity AUC0-12h.
- The pharmacokinetic parameters of radioactivity and INC280 in plasma and blood displayed moderate to high variability in terms of Cmax and AUC.
- The apparent distribution volume of INC280 was moderate to high (Vz/F of 144 to 1570 L).
- INC280 and its metabolites were slightly more confined within the blood than the plasma compartment. INC280 and/or its metabolites displayed no special affinity to erythrocytes.
- The biotransformation of INC280 occurred essentially by the following pathways: lactam formation, hydroxylation, N-dealkylation, formation of a carboxylic acid, hydrogenation, N-oxygenation, glucuronidation and combinations thereof.
- The recovery of the radioactive dose from the excreta was complete at 7 days after dosing.

**Date of report:** 02-Dec-2015 (content final)

**Clinical Trial Results Website**

## Sponsor

Novartis

## Novartis Study Code

CINC280X2106

## EudraCT Number

2014-002646-53

## Swiss Authorization Date and Authorization number

26 April 2021
67648

## Information on comparators drug dosage, route of administration, batch numbers

Not Applicable

## Investigators & Information on study centers

| Investigator | Facility Name<br>Address<br>Country |
|---|---|
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