[redacted] pharmacokinetic modelling of oral and intranasal formulations of zolmitriptan in healthy volunteers

Internal reference: IMIMFCTL/ZOL_1

Development Phase: Phase I

NCT number: NCT06074016

Statistical Analysis Plan

(version 1.0, 15th September 2023)

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1. VERSIONS AND INVESTIGATOR

1.1. Version

Version	Date	Comments
1.0	15th September 2023	-

1.2. Investigators

Principal Investigators	[redacted]
Sponsor	[redacted]

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes in detail the statistical methodology applied for the analysis of pharmacokinetic (PK), pharmacodynamic (PD), and safety data in the Phase I crossover study:

"[redacted] **pharmacokinetic modelling of oral and intranasal formulations of zolmitriptan in healthy volunteers."**

This SAP is aligned with the approved protocol and reflects the analyses conducted in the Clinical Study Report (CSR).

2. BACKGROUNG INFORMATION

[redacted] selective serotonin receptor agonists and is used to treat the symptoms of migraine headaches (severe, throbbing headaches that sometimes are accompanied by other symptoms such as nausea and sensitivity to sound and light).

An orodispersible (e.g., orally disintegrating) formulation of zolmitriptan is helpful in patients who experience migraines along with nausea and vomiting. This formulation was demonstrated to be bioequivalent with the conventional tablet in terms of AUC and C_{max} for zolmitriptan and its active metabolite N-desmethyl-zolmitriptan. There were no statistically significant differences for AUC or Cmax values between nasal spray and oral formulations.

Clinical pharmacology data show that the t_{max} for zolmitriptan for the orally dispersible tablet (range 0.6 to 5h, median 3h) is similar to intranasal administration (range 0.5 to 5h, median 2h). Almost 80% of the C_{max} value is observed in the first hour, and plasma concentrations are sustained for 4 to 6 hours. For the active metabolite, N-desmethyl-zolmitriptan, the median t_{max} is slightly later (approximately 5 hours after 5 mg) (Yates, 2002, zolmitriptan oral, zolmitriptan intranasal).

Plasma protein binding is low and zolmitriptan is metabolized in the liver through the P450 cytochrome system and 3 metabolites are detected: indole-acetic acid, zolmitriptan N-Oxide and N-desmethyl-zolmitriptan (2-6 times more potent than zolmitriptan). MAOA enzymes have also been found to be related to its metabolic clearance.

Comparison of AUC after intranasal administration of 2.5 mg (22.4 ng.hr/ml) relative to the corresponding value after oral administration of 2.5 mg (22.0 ng.hr/ml) showed that the bioavailability of intranasal zolmitriptan with respect to the oral administration is 102%. Plasma concentrations and PK of zolmitriptan and the three major metabolites for the nasal spray and conventional tablets are similar.

Some instructions will be followed for the administration:

- Orally disintegrating tablet of zolmitriptan in the 5 mg strength will be taken without liquids. For oral administration, each tablet will be placed on the top of the tongue without any liquid and will be dispersed within seconds and then swallowed with the saliva.
- Zolmitriptan nasal spray comes in a ready-to-use spray unit for single use. Administration is in one nostril. How to use the device will be explained in the full protocol.

ZOL-1 study was designed as a Phase I clinical trial to characterize the PK and PD of zolmitriptan (intranasal and oral) in healthy subjects, which will be used to verify/validate nasal-CNS-PBPK (Physiologically Based Pharmacokinetic) model predictions following intranasal dosing.

For this purpose, zolmitriptan orally disintegrating tablets and zolmitriptan nasal spray were administered in 8 subjects in two sequences under fasting conditions 10 hours pre-dose and 4 hours post dose.

3. STUDY DESIGN

A single-dose, 2-period, 2-sequence, fasting, open label, crossover randomized design, comparing the pharmacokinetics (PK) and pharmacodynamics (PD) of intranasal and oral tablets of zolmitriptan.

3.1. Study drugs

Zolmitriptan Normon 5mg orodispersible tablets EFG (Normon laboratories).

Zolmitriptan nasal spray (Zomig® 5mg nasal spray (Grünenthal Health).

- 5 mg
- Oral and intranasal.

3.2. Number of subjects

Eight volunteers were planned to be included in the trial. Eight volunteers completed the trial and were included in the statistical analysis.

4. OBJECTIVES

4.1. PK objective

To characterize plasma pharmacokinetics after oral and intranasal administration to support/validate PBPK predictions.

PK parameters: Cmax, Clast, Tmax, Tlag, AUC_{0}–24h, AUC_{0}–t, AUC_{0}–∞, t½, CL/F, Vd/F, λz.

Analytes: Zolmitriptan and N-desmethyl-zolmitriptan (NDZT).

4.2. PD objectives (Exploratory)

Plasma VIP (exploratory), if available.

4.3. Safety

Treatment-emergent adverse events (TEAEs) from Day 1 until the end of study and potentially clinically significant abnormalities (PSCAs) in vital signs, ECG, and laboratory parameters.

5. Analysis Population

Three analysis sets are defined (in practice they coincide due to study completeness):

1. PK population: volunteers who completed the study with baseline and post-treatment samples (N=8).
2. Safety population: volunteers who received ⩾1 treatment (N=8).

3. Per Protocol (PP): randomized subjects who received both treatments and completed the study without relevant protocol deviations.

The PP population is equivalent to the ITT population; therefore a single **ITT/PP analysis** will be performed.

6. General Statistical Principles

- Significance level: if hypothesis testing is performed, $\alpha = 0.05$ (two-sided), unless otherwise specified.
- The analysis is mainly descriptive; statistical testing will be performed when appropriate.
- Confidence intervals: 95% confidence intervals will be reported in descriptive summaries by time where applicable.
- Interim analysis: none planned or performed.
- Covariate adjustment: not applied.
- Multicenter: not applicable (single center).

7. DATA PREPARATION AND RULES

7.1. Sampling times

Scheduled/recorded sampling times will be used according to the study design (oral: predose and 0.25–24 h; intranasal: predose and 5 min–24 h).

7.2. Handling of Missing Data

No imputation strategy is specified. Due to the short duration of the study and the monitoring performed, the risk of missing data is very low; analyses will be based on observed data.

7.3. Deviations

Protocol deviations will be documented and assessed for their potential impact on the quality or integrity of the analyses.

8. STATISTICAL METHODS

8.1. Descriptive Analyses (All Variables)

For each variable and, where applicable, by treatment and by time, the following will be presented:

- n
- mean
- median
- standard deviation (SD)
- standard error of the mean (SEM)
- minimum
- maximum
- 95% confidence interval

8.2. PK Analysis (Primary)

For each variable and, where applicable, by treatment and by time, the following will be presented:

8.2.1. PK Calculation

- **Software:** Phoenix™ PK/PD
- **Model:** non-compartmental analysis (NCA) for the specified parameters (Cmax, AUCs, t½, CL/F, Vd/F, λz, etc.)

8.2.2. Comparison between formulations (Exploratory)

In a crossover study with n=8, PK inference is generally exploratory and the focus remains descriptive.

The following will be provided:

- Descriptive comparison of PK parameters (means/medians and variability) by route of administration.

If inferential analysis is included (optional), a mixed-effects model for repeated measures or a classical crossover model may be applied for PK parameters.

Mixed models for quantitative variables may include:

- Time
- intervention (route/formulation)
- interaction terms where appropriate.

8.3. PD Analysis (HR and BP)

8.3.1. Temporal Evolution

Descriptive statistics by time and treatment (mean, SD, etc.).

8.3.2. Models for Quantitative Variables (When applicable)

Linear mixed-effects models for quantitative variables including:

- time effect.
- intervention (route/formulation).
- interaction terms where appropriate.

8.3.3. Exposure-Response Relationship (Correlation)

Pearson correlation between plasma concentration and HR/BP.

8.4. Quantitative Variables

Chi-square test or Fisher’s exact test when applicable.

9. LISTING, TABLES, AND FIGURES (OUTPUTS)

9.1. PK

- Concentration-time curves (linear and semi-log) by treatment
- Table of PK parameters (NCA) by treatment
- Individual concentration listings per volunteer

9.2. PD

- Tables and plots of HR and BP vs time
- Scatterplots of HR vs concentration

9.3. Safety

- Tables of adverse events (by SOC/PT, severity, relationship)
- Individual listings

10.SOFTWARE

- PK: Phoenix™ PK/PD for NCA
- Statistics: R or SAS for mixed models and descriptive analyses.

11.DESVIATION FROM THE SAP

Any deviation from the methods described in this SAP will be documented, justified, and reported in the Clinical Study Report.