Clinical Study Report

1 TITLE PAGE

A COMPARATIVE, SINGLE CENTER, OPEN-LABEL, LABORATORY-BLIND, RANDOMIZED, SINGLE DOSE, TWO PERIOD CROSSOVER STUDY TO DETERMINE THE RELATIVE BIOAVAILABILITY OF AN IMMEDIATE-RELEASE TABLET FORMULATION CONTAINING 500 MG FLUCYTOSINE AND A SUSTAINED-RELEASE PELLET FORMULATION OF FLUCYTOSINE IN HEALTHY MALES AND FEMALES UNDER FED CONDITIONS

Investigational Medicinal Products:	Reference product: Ancotil® 500 mg immediate-release (IR) tablets Test product: Flucytosine 3000 mg sustained-release (SR) pellets
Indication Studied:	Not applicable
FARMOVS Study Number:	0131FRM18
Sponsor Study Number:	DNDi-5FC-02-CM
Development Phase and Study Type:	Phase 1, Relative Bioavailability
Sponsor:	Drugs for Neglected Diseases initiative (DNDi) Contact person: Nabila Ibnou Zekri Lassout, Senior Clinical Trial Manager, Translational Sciences, DNDi, Tel: +41 22 559 19 56
Investigator Name and Address:	Dr EFW Krantz, FARMOVS Clinical Research Organisation, Pharmacology Building, University of the Free State, Nelson Mandela Drive, 9301 Bloemfontein, South Africa Tel: +27 51 410 3111 (Reception)
Study Duration:	25 Nov 2022 to 22 May 2023 *(first subject first visit [first signing of Informed Consent] until last subject last visit [last telephonic follow-up])*
Date of Report:	Final 1.0, 28 Jul 2023

This study was conducted in compliance with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines and the South African Good Clinical Practice guidelines. The essential documentation related to this study has been retained by relevant parties. This confidential document is the property of DNDi. No unpublished information contained herein may be disclosed without prior written approval from DNDi. Access to this document must be restricted to relevant parties.

2 SYNOPSIS

Title of Study	A comparative, single center, open-label, laboratory-blind, randomized, single dose, two period crossover study to determine the relative bioavailability of an immediate-release tablet formulation containing 500 mg flucytosine and a sustained-release pellet formulation of flucytosine in healthy males and females under fed conditions	
Study Numbers	FARMOVS Study No.: 0131FRM18 Sponsor Study No.: DNDi-5FC-02-CM	
Investigational Medicinal Products	Reference product: Ancotil® 500 mg immediate-release (IR) tablets Test product: Flucytosine 3000 mg sustained-release (SR) pellets	
Development Phase and Study Type	Phase 1, Relative Bioavailability Study	
Sponsor	Drugs for Neglected Diseases initiative (DNDi)	
Principal Investigator	Dr EFW Krantz	
Study Center	FARMOVS Clinical Research Organisation, Pharmacology Building, University of the Free State, Nelson Mandela Drive, 9301 Bloemfontein, South Africa	
Publications	None	
Study Period	**First subject first visit:**	25 Nov 2022 *(first signing of Informed Consent)*
	Last subject last visit:	22 May 2023 *(last telephonic follow-up)*

Study Objectives

Primary Objective

- To assess and compare the relative bioavailability of the test product, flucytosine sustained-release (5-FC SR) pellets (single dose: 2 x 3000 mg at 0 hours) and the reference product, flucytosine immediate-release (5-FC IR) Ancotil® 500 mg tablets (3 x 500 mg at 0 hours and 3 x 500 mg at 6 hours after first dosing) under fed conditions.

Secondary Objective

- To evaluate the safety and tolerability of the test and reference products in healthy males and females under fed conditions.

Exploratory Objective

- To assess the acceptability and palatability of the test formulation in healthy volunteers.

Study Design

This was an open-label, bioanalytical laboratory-blind, randomized, single dose, two period crossover study with orally administered flucytosine IR tablets and SR pellets conducted under fed conditions in at least 30 evaluable healthy males and females at a single study center.

Subjects received the following products (treatments) and doses:

- **Reference (Treatment A):** Ancotil® 500 mg IR tablets (total dose of 3000 mg, administered as two doses: 3 x 500 mg [0 hours] and 3 x 500 mg [6 hours])
- **Test (Treatment B):** Flucytosine 3000 mg SR pellets (total dose of 6000 mg, administered as a single dose: 2 x 3000 mg [0 hours])

The study comprised:

- a screening period of maximum 21 days,
- two treatment periods (each of which included a PK profile period of 48 hours) separated by a washout period of 7 calendar days (5 half-lives are between 15 and 30 hours for the immediate-release formulation and approximately 80 hours for the sustained-release pellet formulation) to 21 calendar days (maximum number of days based on logistical arrangements and to allow interim safety analysis) between consecutive administrations of the investigational medicinal products (IMPs). Healthy subjects were admitted to the study center on Day -1 and remained in the study center for at least 48 hours after dosing,
- interim safety evaluations (hematology, clinical chemistry, and urinalysis) were performed at 30 hours post-dose in Treatment Periods 1 and 2, and 5 days after administration of the IMP in Treatment Period 1,
- a post-study visit, 7 to 10 days after completion of the last treatment period of the study, and
- telephonic follow-up, 1 month (for females) and 3 months (for males) post last IMP administration.

Procedures listed for the post-study visit and the follow-up phone calls were performed in the event of early withdrawal from the study.

Subjects were randomly assigned to one of two treatment sequences (A [Period 1); B [Period 2] or B [Period 1]; A [Period 2]), before the first administration of IMP.

DMC Review of Safety Data of Initially Dosed 4 Subjects

As a safety measure, 4 subjects were initially enrolled, dosed, and monitored in the study. The Safety and Data Monitoring Committee (DMC) reviewed the emerging safety data from these 4 subjects after the post-study visit had been completed. Only after confirmation by the DMC that it was considered safe to continue with dosing, the remaining 32 subjects were enrolled and dosed.

DMC Review of Safety Data and Selected PK Samples Analyzed for Safety Reasons after completion of Treatment Period 1

An interim safety analysis was performed on safety data and selected PK samples after all subjects had completed PK sampling in Treatment Period 1. Twelve PK samples per subject (selected based on data from the DNDi-5FC-01-CM fasting study) were analyzed for flucytosine and 5-FU as part of the safety analysis and the results were reviewed by the DMC before subjects continued to Treatment Period 2. Data collected and reviewed by the DMC for this interim safety analysis were flucytosine and 5-FU plasma concentrations, time of IMP administration, time of PK blood sampling, safety data (i.e., AEs, laboratory test results) and subject number. The PK parameters C_{max}, t_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were calculated. No formal statistical test was performed and therefore there was no impact on the overall risk alpha level of the study.

Study Subjects	
Planned for inclusion	Up to 36 subjects, to ensure that at least 30 evaluable subjects complete the study
Enrolled and randomized	36 subjects
Withdrawals	1 subject
Completed as per protocol	35 subjects
Analyzed	Safety: 36 subjects Pharmacokinetics: 35 subjects

Main Inclusion Criteria

Healthy males and females, 18 to 55 years (both inclusive) at the time of signing of informed consent with a body mass index (BMI) between 18.5 and 30 kg/m^2 (both inclusive) and body weight not less than 50 kg for males and 51 kg for females, were included in the study. Subjects had to be non-smokers or mild smokers (≤ 5 cigarettes or pipes per day). Female subjects of childbearing potential had to practice highly effective methods of contraception.

Reference Product (Treatment A), Dose and Mode of Administration, Batch Number	
Generic name:	Flucytosine
Trade name:	Ancotil®
Marketing Authorization Holder:	MEDA Pharma / Mylan Medical SAS, France
Manufacturer:	ICN Polfa Rzeszów S.A ul. Przemysłowa 2, 35-959 Rzeszów, Poland
Country of origin:	Poland
Dosage form and strength:	500 mg IR tablets
Study dose:	3000 mg (b.i.d. dose: 3 x 500 mg [0 hours] and 3 x 500 mg [6 hours])
Route of administration:	Oral
Batch number:	Initially dosed 4 subjects: Both treatment periods – Batch / Lot 1: 80196184 Subsequently dosed 32 subjects: Treatment period 1 – Batch / Lot 1: 80196184; Treatment period 2 – Batch / Lot 2: 80210744
Batch size	Initially dosed 4 subjects: Both treatment periods – Batch / Lot 1: 939 bottles, each bottle contained 100 tablets Subsequently dosed 32 subjects: Treatment period 1 – Batch / Lot 1: 939 bottles, each bottle contained 100 tablets; Treatment period 2 – Batch / Lot 2: 948 bottles, each bottle contained 100 tablets
Expiry date:	Initially dosed 4 subjects: Both treatment periods – Batch / Lot 1: Jan 2023 Subsequently dosed 32 subjects: Treatment period 1 – Batch / Lot 1: Jan 2023; Treatment period 2 – Batch / Lot 2: Apr 2024
Assayed product content:	Initially dosed 4 subjects: Both treatment periods – Batch / Lot 1: 504.7 mg (acceptance range: 475.0 mg – 525.0 mg) Subsequently dosed 32 subjects: Treatment period 1 – Batch / Lot 1: 504.7 mg (acceptance range: 475.0 mg – 525.0 mg); Treatment period 2: Batch / Lot 2: 496.8 mg (acceptance range: 475.0 mg – 525.0 mg)
Test Product* (Treatment B), Dose and Mode of Administration, Batch Numbers	
Generic name:	Flucytosine
Manufacturer:	Mylan Laboratories Limited (now Viatris)
Country of origin:	India
Dosage form and strength:	3000 mg SR pellets
Study dose:	6000 mg (single dose: 2 x 3000 mg [0 hours])
Route of administration:	Oral
Batch number:	EX03042021
Batch size:	54.201 kg
Expiry date:	Oct 2023
Assayed product content:	99.0%

* The sample used in this study was from a production batch.

Duration of Treatment

The study consisted of two treatment periods. Subjects received the reference product in one of the treatment periods as two doses of 3 x 500 mg 5-FC IR tablets administered 6 hours apart and the test product (as a single dose of 6000 mg 5-FC SR pellets in the morning) in the other treatment period in a crossover manner, according to the randomization schedule.

Administration of Investigational Medicinal Products

The subjects received either the reference product or the test product according to the randomization schedule, under

fed conditions. Subjects received each treatment once.

Treatment Compliance

To ensure treatment compliance the IMP was self-administered by subjects under direct supervision of the investigator. Mouth and hand checks were performed after each dosing by the investigator to ensure that the subjects had swallowed the IMP.

Protocol Deviations

The protocol was adhered to except for the following minor deviations. No major protocol deviations occurred.

- Seven (7) subjects had at least 1 post-dose PK blood sample collected outside of the agreed time window during the study (of the 8 deviations: 6 samples were delayed between 3 and 5 minutes [2 at 0.5 hours, 1 at 2 hours, 1 at 6 hours, 1 at 7 hours, and 1 at 10 hours]; and 2 samples were delayed for 7 minutes [1 at 10 hours, 1 at 12 hours]). As actual blood sampling times were used during PK analysis, these deviations did not influence the PK analysis.
- The first two subjects dosed with the test product in the study needed 30 mL extra water, in addition to the 240 mL water stated in the protocol, to finish all of the IMP. Following these deviations and after discussion with the DMC, the study center implemented a clearly defined treatment administration procedure allowing subjects to comply with the protocol requirements and to finish the test product with 240 mL water. In addition, the principal investigator (PI) (the same person) dosed all subjects receiving the test product to ensure homogeneity and compliance with the treatment administration procedure.
- The interim safety samples of Subject 010, scheduled for 5 days after dosing in Treatment Period 1, was performed 2 days late. The subject could not visit the study center on the scheduled date for personal reasons.
- The post-study procedures for Subject 009, who was withdrawn from the study after Treatment Period 1, were performed 3 days late (i.e., 10 days after withdrawal from the study, instead of 7 days).

In the opinion of the investigator and the sponsor, these deviations were considered minor as they did not compromise subject safety or the integrity of the study data. During the blinded data review meeting it was considered whether these protocol deviations impacted the PK analysis. It was concluded that no subjects needed to be excluded from the PK population due to these protocol deviations.

Pharmacokinetic Parameters

Primary PK parameters for flucytosine and 5-FU (metabolite):

- Maximum observed plasma concentration (C_{max})
- Area under the plasma concentration versus time curve, from time zero to t, where 't' is the time of the last quantifiable concentration ($AUC_{(0-t)}$)

Secondary PK parameters for flucytosine and 5-FU (metabolite):

- Time to maximum observed plasma concentration (t_{max})
- Area under the plasma concentration versus time curve, with extrapolation to infinity ($AUC_{(0-\infty)}$)
- Terminal elimination rate constant (λ_z)
- Apparent terminal elimination half-life ($t_{½}$).

Safety Endpoints

- Frequency and cumulative incidence of adverse events (AEs) and serious adverse events (SAEs) for 5-FC test and reference products, assessed through clinical, electrocardiogram (ECG) and laboratory safety assessments (hematology, clinical chemistry, and urinalysis) from baseline to post-study visit. Medical history and prior and concomitant medication were also recorded.

Exploratory Endpoint

- Acceptability and palatability were assessed using questionnaires, i.e., an Investigator questionnaire (to assess acceptability) and a participant questionnaire (to assess palatability).

Statistical Methods

Sample Size

Based on available information on IR and SR flucytosine, it was planned to include up to 36 eligible subjects to complete the study with at least 30 evaluable subjects. Sample size considerations were driven by the primary

pharmacokinetic evaluation and the planned comparison between the test and reference treatments.

Assuming the intra-subject coefficient of variation (CV) being no more than 28%, with 30 subjects in total (i.e., 15 subjects per sequence), a crossover design had 80% power to reject both the null hypothesis that the ratio of the test mean to the standard mean was below 0.8 and the null hypothesis that the ratio of the test mean to the standard mean was above 1.25; i.e., that the test and standard were not equivalent, in favor of the alternative hypothesis that the means of the two treatments were equivalent, assuming that the expected ratio of means was 1, the crossover ANOVA $\sqrt{MSE}$ (in scale) was 0.28 (the standard deviation [SD] differences, σ(ln scale) was 0.396), that data were analyzed in the natural log scale using t-tests for differences in means and that each t-test was made at the 5% level. CV was calculated with the ANOVA final analysis. If the test was significant, the power of the analysis had to be re-calculated based the final outputted CV% assuming the same initial design characteristics (type 1 error, null hypothesis, alternative hypothesis).

Sample sizes for enrolment were increased by approximately 15% to account for possible drop-outs/withdrawals. Subjects who withdrew or were withdrawn from the study were not replaced, as at least 30 evaluable subjects completed the study.

Randomization

A randomization schedule was provided by Luxembourg Institute of Health (LIH), Competence Center for Methodology and Statistics. The randomization schedule was generated utilizing the PROC PLAN procedure of SAS® software.

Pharmacokinetic Analysis

Pharmacokinetic population: All subjects who completed the PK sampling in both periods and for whom primary PK parameters could be calculated for both treatment periods, and who had no major protocol deviations thought to impact the analysis of the PK data were included in the statistical PK analysis of the study.

Reference Product: Data from subjects who experienced vomiting during the study could be deleted from the statistical analysis if vomiting occurred at or before 2 times median t_{max} of each dose of the reference product. For subjects with pre-dose plasma concentrations, the subject's data could be included in all PK measurements and calculations if the pre-dose concentration was ≤ 5% of C_{max}. If the pre-dose value was > 5% of C_{max}, the subject's data could be dropped from all bioavailability evaluations.

Test Product: Data from subjects who experienced vomiting within 24 hours of the test product administration could be excluded from the PK analysis and comparisons. For subjects with pre-dose plasma concentrations, the subject's data could be included in all PK measurements and calculations if the pre-dose concentration was ≤ 5% of C_{max}. If the pre-dose value was > 5% of C_{max}, the subject's data could be dropped from all bioavailability evaluations.

During the blinded data review meeting it was decided if any subjects needed to be excluded from the PK population. No subjects were excluded from the PK population for the above-mentioned reasons. Data from the 35 subjects who completed the study were available for PK analysis.

Analysis of relative bioavailability of the primary PK parameters: The test product was compared to the reference product with respect to the C_{max} and the $AUC_{(0-t)}$ using a linear mixed effect model with sequence, product and period as fixed effects and subject(sequence) as random effect (subject as random intercept) after logarithmic transformation of the data. Point estimates and 90% CIs for the "test/reference" geometric mean ratio of these parameters were provided from the linear-mixed-effects-model (geometric lest squares means ratios).

Relative bioavailability of the test and reference products was assessed on the basis of the flucytosine (5-FC) 90% CIs for estimates of the geometric mean ratios between the primary PK parameters of the test and reference products in a two One-Sided Schuirmann test (TOST) procedure.

Analysis of the secondary PK parameters: The PK parameters t_{max}, λz and t½ were analyzed non-parametrically using the Wilcoxon signed rank test based on the median of differences between test and reference treatments across subjects. The median of differences represented the median of individual differences between the test treatment (Treatment B) and the reference treatment (Treatment A) across all subjects.

For $AUC_{(0-\infty)}$, the same strategy with the linear mixed effect model with sequence, subject(sequence), product and period effects after logarithmic transformation of the data was used as well as the point estimates and 90% CIs for the "test/reference" geometric mean ratio.

Interim safety analysis:

DMC Review of Safety Data of Initially Dosed 4 Subjects

As an additional safety measure, 4 subjects were initially enrolled, dosed, and monitored in the study. The DMC had to review the emerging safety data from these 4 subjects after their post-study visits had been completed. Only after confirmation by the DMC that it was considered safe to continue with dosing of the remaining 32 subjects, were they enrolled and dosed.

DMC Review of Safety Data and Selected PK Samples Analyzed for Safety Reasons after completion of Treatment Period 1

An interim safety analysis was performed on safety data and selected PK samples after all subjects had completed PK sampling in Treatment Period 1. Twelve (12) PK samples per subject (selected based on data from the DNDi-5FC-01-CM fasting study) were analyzed for flucytosine and 5-FU as part of the safety analysis and the results were reviewed by the DMC before subjects continued to Treatment Period 2. Data collected and reviewed by the DMC for this interim safety analysis were flucytosine and 5-FU plasma concentrations, time of IMP administration, time of PK blood sampling, safety data (i.e., AEs, laboratory test results) and subject number. The PK parameters C_{max}, t_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were calculated. No formal statistical test was performed and therefore there was no impact on the overall risk alpha level of the study.

Safety Analysis

Safety population: All subjects who received at least one dose of IMP were included in the safety analysis of the study.

Safety data were listed as described in the statistical analysis plan (SAP). Demographic characteristics and AEs were summarized by treatment group.

Pharmacokinetic Results and Conclusions

Data from the 35 evaluable subjects who completed the study were available for PK analysis.

Relative bioavailability of the test and reference products was assessed on the basis of the flucytosine (5-FC) 90% CIs for estimates of the geometric mean ratios between the primary PK parameters of the test and reference products in a two One-Sided Schuirman test (TOST) procedure. PK data of 5-FU (metabolite) was to serve as supportive data only.

Summary of Statistical Analyses of Plasma Flucytosine (5-FC) Pharmacokinetic Parameters (PK Population) – Test vs Reference

Parameter (unit)	LS Geometric Mean		Mean Ratio (%)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Test n = 35	Reference n = 35			
C_{max} (µg/mL)	48.16	36.05*	133.60	124.20 ; 143.70	18.16
$AUC_{(0-t)}$ (h•µg/mL)	627.92	450.88	139.27	132.41 ; 146.47	12.51
$AUC_{(0-\infty)}$ (h•µg/mL)	648.55	458.07	141.58	135.00 ; 148.49	NC
t_{max} (h) (median)	5.95	8.00	p-value: < 0.0001		

CV = coefficient of variation; LS = least square; n = number of subjects assessed; NC = not calculated

* Refers to the peak concentration after the second dose administration of the reference product.

Reference (Treatment A): Ancotil® 500 mg IR tablets (total dose of 3000 mg, administered as two doses: 3 x 500 mg [0 hours] and 3 x 500 mg [6 hours])

Test (Treatment B): Flucytosine 3000 mg SR pellets (total dose of 6000 mg, administered as a single dose: 2 x 3000 mg [0 hours])

Test vs Reference

Flucytosine (5-FC)

The 90% CIs for the primary PK parameter C_{max} for flucytosine (5-FC) for the test compared to the reference were 1.2-fold and 1.4-fold higher for the test product at the doses administered in this study under fed conditions. The 90% CIs for the primary PK parameter $AUC_{(0-t)}$ for flucytosine (5-FC) for the test compared to the reference were

1.3-fold and 1.5-fold higher for the test product at the doses administered in this study under fed conditions.

Metabolite (5-FU)

As described in the protocol, the PK data of 5-FU (metabolite) were to serve as supportive data. Out of the 1190 samples in the PK population (35 subjects x 2 periods x 17 sampling time points), only 51 concentration values were above 1 ng/mL. This means that 95.7% of the samples (1139 samples) had BLQ values. The maximum concentration detected was 10.9 ng/mL. For this reason, no interpretation of the data was possible.

Safety Results and Conclusions

Interim Safety Results

DMC Review of Safety Data of Initially Dosed 4 Subjects

As an additional safety measure, 4 subjects were initially enrolled, dosed, and monitored in the study. The DMC members convened on 05 Jan 2023 to review the emerging safety data from these 4 subjects after the post-study visit had been completed. The DMC members had no substantive safety concerns and confirmed that it was considered safe to continue with enrolment and dosing of the remaining 32 subjects.

DMC Review of Safety Data and Selected PK Samples Analyzed for Safety Reasons after completion of Treatment Period 1

A second review by the DMC of the emerging safety data and selected PK samples was performed after all subjects had completed PK sampling in Treatment Period 1. Twelve (12) PK samples per subject were analyzed for flucytosine and 5-FU as part of the safety analysis. The DMC convened on 10 Feb 2023 to review the results before subjects continued to Treatment Period 2. Data collected and reviewed by the DMC for this interim safety analysis were flucytosine and 5-FU plasma concentrations, time of IMP administration, time of PK blood sampling, safety data (i.e., AEs, laboratory test results) and subject number. The PK parameters C_{max}, t_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were calculated. No formal statistical test was performed and therefore there was no impact on the overall risk alpha level of the study.

The DMC members noted that higher peak concentrations and higher exposures were observed with the SR reference formulation compared to the IR test pellets: 50.06 µg/mL versus 31.42 µg/mL for the mean C_{max}, respectively, and 621.69 µg.h/mL versus 443.76 µg.h/mL for the mean exposure, respectively. The fed status of the subjects seemed to have had an impact on the treatment absorption (subjects received a standard high-fat, high-calorie meal before dosing) and advised that further data would be necessary before concluding that these increased exposures were safe.

The DMC members concluded that there were no safety signals of concern at the time of review of the available data and supported continuation of the study, i.e., dosing of the enrolled subjects in Treatment Period 2.

Overall Safety Results

Six (6) subjects had a total of 9 AEs during the study. Three (3) of these events were considered by the investigator as possibly related to the IMP (1 event related to the reference product and 2 events related to the test product). Eight (8) out of the 9 reported events were of mild intensity and 1 event was of moderate intensity (related to the reference product).

IMP-related TEAEs were single events of palpitations (of mild intensity, related to the test), increased transaminases (of moderate intensity, related to the reference), and headache (of mild intensity, related to the test). These TEAEs had resolved by the end of the study. The 3 IMP-related TEAEs reported during the study were assessed as expected based on the known safety profile of Ancotil®. None of these TEAEs led to withdrawals from the study.

There were no additional associated liver function abnormalities related to the TEAE of increased transaminases (increased ALT and AST levels): Subject 007 – ALT level 98 IU/L and AST level 137 IU/L at 30 hours post-dosing with the reference product). This increase in transaminases levels was reported as an AE of moderate intensity, related to the reference product. The PI reported that the subject confirmed that he had not ingested alcohol before admission but indicated that he had played a few soccer games during the washout period. The PI noted that this could have contributed to the raised liver enzymes. The increased transaminases had returned to normal at the post-study visit (within ~9 days after last dosing). No SAEs were reported.

There were no clinically significant and/or IMP-related changes in vital signs after administration of the IMPs. All ECGs were assessed as normal or abnormal NCS by the investigator. All physical examinations were normal or where abnormalities were identified these findings were considered NCS.

Exploratory Evaluation – Acceptability and Palatability

Results of the questionnaire related to acceptability of the test product completed by the investigator indicated that the investigator considered the administration of the test product to 94.4% of subjects easy (score: 4 [easy]).

Results of the questionnaire related to palatability (taste, odor, mouthfeel and ease of swallowing) of the test product completed by subjects indicated that the majority of subjects felt positive regarding the palatability of the test product.

Discussion and Overall Conclusions

This study in healthy males and females was designed to establish a pharmacokinetic (PK) profile under fed conditions for the orally administered test and reference products to evaluate relative bioavailability (BA).

Data from the 35 evaluable subjects who completed the study were available for PK analysis. One (1) subject, Subject 009, was withdrawn from the study by the investigator (positive drugs of abuse test on admission to Treatment Period 2).

Relative bioavailability of the test and reference products was assessed on the basis of the flucytosine (5-FC) 90% CIs for estimates of the geometric mean ratios between the primary PK parameters of the test and reference products in a two One-Sided Schuirman test (TOST) procedure. PK data of 5-FU (metabolite) served as supportive data only.

Pharmacokinetics

Flucytosine (5-FC)

Results showed that the bioavailability of flucytosine from the test product (SR flucytosine pellets) exceeded the bioavailability of flucytosine from the reference product (Ancotil® IR tablets) at the doses administered in the study (i.e., test product: a single dose of 6000 mg and reference product: two doses of 3 x 500 mg [0 hours] and 3 x 500 mg [6 hours]). The mean ratio of $AUC_{(0-t)}$) was 1.4-fold higher for the test product compared to the reference product.

Metabolite (5-FU)

As described in the protocol, the PK data of 5-FU (metabolite) were to serve as supportive data. Out of the 1190 samples in the PK population (35 subjects x 2 periods x 17 sampling time points), only 51 concentration values were above 1 ng/mL. This means that 95.7% of the samples (1139 samples) had BLQ values. The maximum concentration detected was 10.9 ng/mL. For this reason, no interpretation of data was possible.

Safety

In general, all the IMPs were well tolerated by healthy subjects in this study. No deaths or SAEs were reported during the study and all AEs were of mild or moderate intensity.

Exploratory Evaluation – Acceptability and Palatability

In general, administration of the test product was considered acceptable by the investigator, and the majority of subjects felt positive regarding the palatability of the test product.

Date of Report: Final 1.0, 28 Jul 2023

This study was conducted in compliance with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines and the South African Good Clinical Practice guidelines.