Clinical Study Report

1 TITLE PAGE

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

Investigational Medicinal Products:	Reference Product: Ancotil® 500 mg immediate-release (IR) tablets Test Products: Three different formulations of flucytosine 3000 mg sustained-release (SR) pellets
Indication Studied:	Not applicable
FARMOVS Study Number:	0125FRM18
Sponsor Study Number:	DNDi-5FC-01-CM
Development Phase and Study Type:	Phase 1, Relative Bioavailability
Sponsor:	Drugs for Neglected Diseases *initiative* (DND*i*) Contact person: François Simon, Senior Clinical Trial Manager, Translational Sciences, DND*i*, Tel: +41 22 907 77 25
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Study Duration:	17 Jan 2022 to 22 Apr 2022 *(first subject first visit [first signing of Informed Consent] until last subject last visit [post-study visit])*
Date of Report:	Final 1.0, 31 Mar 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 DND*i*. No unpublished information contained herein may be disclosed without prior written approval from DND*i*. Access to this document must be restricted to relevant parties.

2 SYNOPSIS

Title of Study	A comparative, single center, open-label, laboratory-blind, randomized, four period crossover study to determine the relative bioavailability of an immediate-release tablet formulation containing 500 mg flucytosine and three sustained-release pellet formulations of flucytosine in healthy males and females under fasting conditions	
Study Numbers	FARMOVS Study No.:	0125FRM18
	Sponsor Study No.:	DNDi-5FC-01-CM
Investigational Medicinal Products	Reference Product:	Ancotil® 500 mg immediate-release (IR) tablets
	Test Products:	Three different formulations of flucytosine 3000 mg sustained-release (SR) pellets
Development Phase and Study Type	Phase 1, Relative Bioavailability Study	
Sponsor	Drugs for Neglected Diseases *initiative* (DND*i*)	
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	• Safety and pharmacokinetics of flucytosine and fluorouracil in healthy participants administered new flucytosine sustained-release pellet formulations in development for cryptococcal meningitis, presentation by Dr Tadesse T. Mekonen, ICCC – Kampala, Uganda, 12 Jan 2023 • Pharmacokinetics & safety of sustained-release flucytosine pellet formulation, Poster Presentation, 30th CROI, Summit Convention Center in Seattle, Washington, USA, 19-22 Feb 2023	
Study Period	**First subject first visit:**	17 Jan 2022 *(first signing of Informed Consent)*
	Last subject last visit:	22 Apr 2022 *(post-study visit)*

Study Objectives

Primary Objective

- To assess and compare the relative bioavailability of each of the three test products (Test 1, Test 2, and Test 3), flucytosine sustained-release (5-FC SR) pellets (single dose: 1 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 fasting conditions.

Secondary Objective

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

Study Design

This was an open-label, bioanalytical laboratory-blind, randomized, four period crossover study with orally administered flucytosine IR tablets and SR pellets conducted under fasting conditions in at least 32 evaluable healthy males and females at a single study center.

Subjects received the following treatments:

- **Reference (Treatment A):** Ancotil® 500 mg IR tablets (twice daily [b.i.d] dose: 3 x 500 mg [0 hours] and 3 x 500 mg [6 hours])
- **Test 1 (Treatment B):** Flucytosine 3000 mg SR pellets (single dose: 1 x 3000 mg [0 hours])

- **Test 2 (Treatment C):** Flucytosine 3000 mg SR pellets (single dose: 1 x 3000 mg [0 hours])
- **Test 3 (Treatment D):** Flucytosine 3000 mg SR pellets (single dose: 1 x 3000 mg [0 hours])

The study comprised:

- a screening period of maximum 21 days,
- four 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 immediate-release formulation) to 14 calendar days (maximum number of days based on logistical arrangements) between consecutive administrations of the investigational medicinal product (IMP). 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, 2, 3 and 4, and 5 days after administration of IMP in Treatment Periods 1, 2 and 3, and
- a post-study visit, 1 week after completion of the last treatment period of the study.
- 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 treatment sequence before the first administration of IMPs.

Study Subjects	
Planned for inclusion	36 subjects, to ensure that at least 32 evaluable subjects complete the study
Enrolled and randomized	42 subjects (36 subjects were initially enrolled and randomized; 6 additional subjects were enrolled and randomized after early withdrawal of 6 initially enrolled subjects, to ensure that at least 32 evaluable subjects complete the study)
Withdrawals	7 subjects
Completed as per protocol	35 subjects
Analyzed	Safety: 42 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:	Viatris (previously known as Mylan Medical SAS [France])
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:	80196184
Batch size	939 bottles, each bottle contained 100 tablets
Expiry date:	Jan 2023

Test Products 1, 2, and 3 (Treatments B, C, and D), Dose and Mode of Administration, Batch Numbers	
Generic name:	Flucytosine
Manufacturer:	Viatris (previously known as Mylan)
Country of origin:	India
Dosage form and strength:	3000 mg SR pellets
Study dose:	3000 mg (single dose: 1 x 3000 mg [0 hours])
Route of administration:	Oral
Batch number:	Treatment B, Test 1: EX03022021 Treatment C, Test 2: EX03032021 Treatment D, Test 3: EX03042021
Batch size:	Treatment B, Test 1: 57.333 kg Treatment C, Test 2: 55.045 kg Treatment D, Test 3: 54.201 kg
Expiry date:	Treatment B, Test 1: Nov 2023 Treatment C, Test 2: Oct 2023 Treatment D, Test 3: Oct 2023
Assayed product content:	Treatment B, Test 1: 100.1% Treatment C, Test 2: 99.3% Treatment D, Test 3: 99.0%

Duration of Treatment

The study consisted of four 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 each of the test products once (a single dose of 3000 mg 5-FC SR pellets in the morning) in a crossover manner, according to the randomization schedule.

Administration of Investigational Medicinal Products

The subjects received either the reference product or one of the test products according to the randomization schedule, under fasting 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 amended version of the protocol was adhered to except for the following deviations.

Minor

- Thirty-eight subjects had at least 1 post-dose PK blood sample collected outside of the agreed time window during the study (of the 38 deviations: 25 samples were delayed between 3 and 5 minutes [1 at 0.5 hours, 1 at 1 hour, 1 at 1.5 hours, 1 at 2 hours, 1 at 3 hours, 5 at 4 hours, 2 at 6 hours, 2 at 6.5 hours, 3 at 7.5 hours, 1 at 8 hours, 1 at 9 hours, 2 at 10 hours, and 4 at 12 hours]; 8 samples were delayed between 6 and 10 minutes [1 at 1.5 hours, 1 at 4 hours, 1 at 6 hours, 1 at 7.5 hours, 2 at 8 hours, 1 at 10 hours, and 1 at 36 hours]; 4 samples were delayed between 11 and 20 minutes [1 at 6 hours, 1 at 6.5 hours, 1 at 20 hours, and 1 at 30 hours]; 1 sample was delayed for more than 21 minutes [1 at 20 hours]). As actual blood sampling times were used during PK analysis, these deviations did not influence the PK analysis.
- The pre-dose PK blood sample of Subject 019 in Treatment Period 4 was drawn 4 minutes early and dosing was performed 4 minutes later for logistical reasons.
- The interim safety blood sample (for hematology) of Subject 006 at 30 hours post-dose in Treatment Period 2

was clotted and a repeat blood sample was drawn 2 hours 16 minutes later and re-tested.

- It was reported that the vital signs measurement of Subject 008 at 48 hours post-dose in Treatment Period 1 was performed late due to difficult blood sampling, however, this deviation was reported in error, and no protocol deviation actually occurred.
- The 4-hour post-dose ECG of Subject 028 in Treatment Period 1 was performed 2 seconds outside of the agreed time window.

Major

- The 48-hour post-dose ECGs in Treatment Period 1 were not performed for the initially enrolled 36 subjects. An ECG was performed for these subjects at the following interim safety visit (5 days post-dose), before dosing in Treatment Period 2.
- The 36-hour PK blood sample of 1 subject (Subject 003) in Treatment Period 3 was not collected (due to difficult blood sampling) and thus considered missing.
- One subject (Subject 013) used medication (Acurate® [a combination pain tablet containing paracetamol 450 mg, doxylamine succinate 5 mg, caffeine 30 mg and codeine phosphate 10 mg] 11 days before dosing in Treatment Period 1.

In the opinion of the investigator and the sponsor, these deviations were not considered to have compromised subject safety or the integrity of the study data. During the blinded data review meeting it was decided if any subjects needed to be excluded from the PK population due to major protocol deviations thought to impact the PK analysis. No subjects were excluded from the PK population for this reason.

Pharmacokinetic Parameters

Primary PK parameters for flucytosine and 5-FU:

- 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:

- 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 ($t_{½}$)
- Evaluation of unexpected release characteristic (i.e., dose-dumping) in 8 selected PK samples of all subjects at the end of Treatment Period 1. No additional blood samples were collected for these analyses.

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.
- Frequency and incidence of AEs in all subjects were analyzed at the end of Treatment Period 1 to evaluate potential for significant dose dumping.

Statistical Methods

Sample Size

Thirty-two subjects were required as completers in this clinical study. Sample size considerations were driven by the primary pharmacokinetic evaluation and planned pairwise comparison among Treatments B, C, and D (Tests 1, 2, and 3) versus Treatment A (Reference).

Assuming the intra-subject coefficient of variation (CV) being no more than 17%, with 32 subjects in total (i.e. 8 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 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, MSE (in scale) was 0.17 (the SD differences, σ [ln scale]) was 0.24), 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 1.7% level. CV was calculated with the ANOVA final analysis. If the test was significant, the power of the analysis was calculated

based on the final outputted CV%.

It was planned in the protocol to enroll a total of 36 eligible subjects in the study to complete the study with at least 32 evaluable subjects. It was also planned in the protocol that subjects who withdrew or were withdrawn from the study were not to be replaced, unless fewer completed the study than the estimated number of evaluable subjects (i.e., 32).

After Treatment Period 4, the study team noted that only 30 randomized subjects were completers of the study. The sponsor, in collaboration with the investigator, decided to implement the subject replacement as described in the protocol. Six (6) replacement subjects were enrolled and received the same treatment sequence as the withdrawn subjects to maintain the sequence balance. In total, thirty-five (35) subjects completed the study.

Randomization

A randomization schedule was provided by Luxembourg Institute of Health, Competence Center for Methodology and Statistics. The randomization schedule was generated utilizing the PROC PLAN procedure of SAS® software. The replacement subjects were randomized using a firewall process describing the random allocation of identification numbers and it had been documented and signed by the sponsor.

Pharmacokinetic Analysis

Pharmacokinetic population:

All subjects who completed the PK sampling in all periods and for whom primary PK parameters could be calculated for all 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.

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 by the acceptance limit range of 80.00% to 125.00% to both C_{max} and the $AUC_{(0-t)}$ 90% CIs lower and upper limit, respectively. PK data of 5-FU (metabolite) served as supportive data only.

Interim safety analysis:

An interim safety analysis was performed in Feb 2022 (after Treatment Period 1). Data reviewed during this interim analysis were flucytosine plasma concentrations, time of IMP administration, time of PK blood sampling, safety data (i.e., AEs and laboratory test results), and subject number (randomization number). Eight (8) flucytosine PK samples per subject were analyzed for safety reasons to identify any potential dose dumping before commencement of Treatment Period 2. The PK parameters C_{max}, t_{max}, and $AUC_{(0-t)}$ were calculated to study dose dumping. No formal statistical test was performed and therefore there was no impact on the overall risk alpha level of the study.

The data and interim safety report were reviewed and discussed by the Data Monitoring Committee (DMC) on 08 Feb 2022. The DMC members had no substantive safety concerns and confirmed that IMP-administration in Treatment Period 2 could continue.

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. 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 by the acceptance limit range of 80.00% to 125.00% to both C_{max} and the $AUC_{(0-t)}$ 90% CIs lower and upper limit, respectively. PK data of 5-FU (metabolite) served as supportive data only.

Summary of Statistical Analyses of Plasma Flucytosine (5-FC) Pharmacokinetic Parameters (PK Population) – Test 1 vs Reference

Parameter (unit)	LS Geometric Mean		Mean Ratio (%)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Test 1 n = 35	Reference n = 35			
C_{max} (µg/mL)	10.55	40.04	26.35	23.41 ; 29.65	34.90
$AUC_{(0-t)}$ (h•µg/mL)	166.34	465.79	35.71	32.81 ; 38.88	23.37
$AUC_{(0-\infty)}$ (h•µg/mL)	216.04	472.49	45.75	41.65 ; 50.20	NC
t_{max} (h) (median)	6.0	7.5	p-value: < 0.0001		

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

Reference (Treatment A): Ancotil® 500 mg IR tablets (twice daily dose: 3 x 500 mg [0 hours] and 3 x 500 mg [6 hours])

Test 1 (Treatment B): Flucytosine 3000 mg SR pellets (single dose: 1 x 3000 mg [0 hours])

Summary of Statistical Analyses of Plasma Flucytosine (5-FC) Pharmacokinetic Parameters (PK Population) – Test 2 vs Reference

Parameter (unit)	LS Geometric Mean		Mean Ratio (%)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Test 2 n = 35	Reference n = 35			
C_{max} (µg/mL)	16.35	40.04	40.84	36.29 ; 45.97	19.65
$AUC_{(0-t)}$ (h•µg/mL)	219.35	465.79	47.09	43.26 ; 51.26	13.27
$AUC_{(0-\infty)}$ (h•µg/mL)	248.14	472.49	52.52	47.87 ; 57.61	NC
t_{max} (h) (median)	4.0	7.5	p-value: < 0.0001		

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

Reference (Treatment A): Ancotil® 500 mg IR tablets (twice daily dose: 3 x 500 mg [0 hours] and 3 x 500 mg [6 hours])

Test 2 (Treatment C): Flucytosine 3000 mg SR pellets (single dose: 1 x 3000 mg [0 hours])

Summary of Statistical Analyses of Plasma Flucytosine (5-FC) Pharmacokinetic Parameters (PK Population) – Test 3 vs Reference

Parameter (unit)	LS Geometric Mean		Mean Ratio (%)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Test 3 n = 35	Reference n = 35			
C_{max} (µg/mL)	19.61	40.04	48.99	43.53 ; 55.14	22.48
$AUC_{(0-t)}$ (h•µg/mL)	249.43	465.79	53.55	49.19 ; 58.29	16.72
$AUC_{(0-\infty)}$ (h•µg/mL)	268.40	472.49	56.81	51.78 ; 62.32	NC
t_{max} (h) (median)	4.0	7.5	p-value: < 0.0001		

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

Reference (Treatment A): Ancotil® 500 mg IR tablets (twice daily dose: 3 x 500 mg [0 hours] and 3 x 500 mg [6 hours])

Test 3 (Treatment D): Flucytosine 3000 mg SR pellets (single dose: 1 x 3000 mg [0 hours])

Test 1 vs Reference

The 90% CIs for the primary PK parameters (C_{max} and $AUC_{(0-t)}$) for flucytosine (5-FC) for Test 1 (Treatment B): Flucytosine 3000 mg SR pellets (single dose: 1 x 3000 mg [0 hours]) compared to the Reference (Treatment A): Ancotil® 500 mg IR tablets (twice daily dose: 3 x 500 mg [0 hours] and 3 x 500 mg [6 hours]) fell below the conventional acceptance range (i.e., 80.0% to 125.00%) to establish comparable bioavailability.

Test 2 vs Reference

The 90% CIs for the primary PK parameters (C_{max} and $AUC_{(0-t)}$) for flucytosine (5-FC) for Test 2 (Treatment C): Flucytosine 3000 mg SR pellets (single dose: 1 x 3000 mg [0 hours]) compared to the Reference (Treatment A): Ancotil® 500 mg IR tablets (twice daily dose: 3 x 500 mg [0 hours] and 3 x 500 mg [6 hours]) fell below the conventional acceptance range (i.e., 80.0% to 125.00%) to establish comparable bioavailability.

Test 3 vs Reference

The 90% CIs for the primary PK parameters (C_{max} and $AUC_{(0-t)}$) for flucytosine (5-FC) for Test 3 (Treatment D): Flucytosine 3000 mg SR pellets (single dose: 1 x 3000 mg [0 hours]) compared to the Reference (Treatment A): Ancotil® 500 mg IR tablets (twice daily dose: 3 x 500 mg [0 hours] and 3 x 500 mg [6 hours]) fell below the conventional acceptance range (i.e., 80.0% to 125.00%) to establish comparable bioavailability.

Based on the results of the study and data obtained from physiologically based pharmacokinetic (PBPK) modeling performed using the study data, Test 3 (Treatment D) was identified as the product to utilize for further development and testing. In order to reach the therapeutic target plasma flucytosine (5-FC) concentrations, the DMC recommended that the dose be increased in the fed study performed after this fasted study.

As described in the protocol, the PK data of 5-FU (metabolite) were to serve as supportive data, however, as 5-FU concentrations were not quantifiable in over 90% of 5-FU samples in the PK population, even when using a more sensitive calibration range, no interpretation of data was possible.

Safety Results and Conclusions

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.

During the interim clinical chemistry evaluation at 30 hours post-dose in Treatment Period 2, it was observed that one subject (Subject 024) had an elevated AST concentration of 156 U/L (> 3.4 x ULN; clinically significant), ALT concentration of 67 U/L (1.2 x ULN) without other associated liver abnormalities. This was reported as an AE of moderate intensity (considered as possibly related to the IMP [Test 2 (Treatment C): Flucytosine 3000 mg SR pellets, a single dose: 1 x 3000 mg at 0 hours]) and the subject was subsequently withdrawn from the study. Both AST and ALT concentrations returned to normal within 4 days after IMP administration.

Twenty (20) subjects had a total of 36 AEs during the study. Eight (8) of these events were considered by the investigator as possibly related to the IMP, and 1 event as probably related to the IMP (2 events related to the reference product and 7 events related to the test products). Twenty-eight (28) of the reported events were of mild intensity and 8 events were of moderate intensity (3 events after reference product, 1 event after Test 1 [Treatment B], 3 events after Test 2 [Treatment C], and 1 event after Test 3 [Treatment D]. All AEs reported during the study were as expected based on the known safety profile of Ancotil®.

There were no clinically significant electrocardiogram abnormalities in the healthy male and female study population.

There were no clinically significant and/or consistent IMP-related changes in vital signs or physical findings after administration of the IMPs.

With the exception of the above-mentioned AE (clinically significant elevated AST concentration of 156 U/L [> 3.4 x ULN]), no other AEs related to laboratory investigations were reported.

Discussion and Overall Conclusions

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

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 90% CIs for estimates of the geometric mean ratios between the primary PK parameters of the test and reference products for flucytosine. PK data of 5-FU (metabolite) served as supportive data only.

Pharmacokinetics

Flucytosine (5-FC)

Based on the results of the study and data obtained from physiologically based pharmacokinetic (PBPK) modeling performed using the study data, Test 3 (Treatment D) was identified as the product to utilize for further development and testing. In order to reach the therapeutic target plasma flucytosine (5-FC) concentrations, the DMC recommended that the dose be increased in the fed study performed after this fasted study.

Metabolite (5-FU)

As described in the protocol, the PK data of 5-FU (metabolite) were to serve as supportive data, however, as 5-FU concentrations were not quantifiable in over 90% of 5-FU samples in the PK population, even when using a more sensitive calibration range, no interpretation of data was possible.

Safety

In general, all the IMPs were well tolerated by healthy subjects in this study.

As Test 3 will be developed further, data confirming a comparable safety profile to that of Ancotil® is required, as was observed in this study. Of note, however, is that the exposure to flucytosine in this study was lower for Test 3 compared to Ancotil®. Further research is required to confirm the similar safety profile of Test 3 at the same exposure as Ancotil®.

Date of Report: Final 1.0, 31 Mar 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.