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Sub-track: B5. Co-infections (TB, hepatitis, STIs, cryptococcus, bacterial diseases, leishmaniasis, malaria, and others)

A Phase 1 bioavailability study of sustained-release oral flucytosine in healthy, fed participants

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BACKGROUND

5-flucytosine (5-FC) is used to treat cryptococcal meningoencephalitis (CM), often associated with advanced HIV disease. Current dosing of 5-FC immediate-release (IR) tablets, in patients, is four times a day, which risks low treatment adherence. To address this, DNDi and its partners are developing a 5-FC sustained-release (SR) formulation. A Phase I pharmacokinetics (PK) study in healthy participants under fasted conditions was completed previously to select a formulation suitable for twice-daily oral and naso-gastric administration – the only route of administration when patients with CM are unconscious. The Phase I study presented here was conducted to assess the SR formulation absorption under fed conditions. It evaluated the PK and safety of the selected SR formulation at twice the dose (adapted based on fasted PBPK modeling data) used in the fasted study, compared to IR formulation.

METHODS

Trial design: A Phase I, open-label, laboratory-blind, randomized, single-dose, two-period crossover study with orally administered flucytosine IR and SR products was conducted under fed conditions in 35 evaluable healthy males and females at a single study centre.

Participants received: Reference (Treatment A): Ancotil 500 mg IR tablets (3000 mg, administered BID: 3 x 500 mg at 0 hours and 3 x 500 mg at 6 hours) and Test (Treatment B): Flucytosine 3000 mg SR pellets (6000 mg, administered as a single dose: 2 x 3000 mg at 0 hours).

The primary objective was to assess and compare the relative bioavailability of the SR and IR products administered under fed conditions. The secondary objective was to evaluate the safety and tolerability of the IR and SR products.

The primary endpoints were plasma C_{max} and $AUC_{0\text{-}t}$. Physiologically based pharmacokinetic (PBPK) modelling was performed. Safety was monitored by recording adverse events (AEs), blood chemistry, hematology, urinalysis, and ECG.

Participants: 35 healthy male and female participants, recruited between Nov. 2022 and May 2023 at a single site (Phase I unit) in South Africa.

Treatments:

- Treatment B: Flucytosine Treatment A: Ancotil 500 mg IR tablets (twice daily [BID] dose: 3 x 500 mg [0 hours and 6 hours])
- 3000 mg SR pellets (6000 mg, administered as a single dose: 2 x 3000 mg

RESULTS

35/36 randomized healthy participants (30 males, 6 females) completed the two study treatment periods. 1 participant dropped-out due to a drug positive test.

There were no significant safety concerns with the SR formulation.

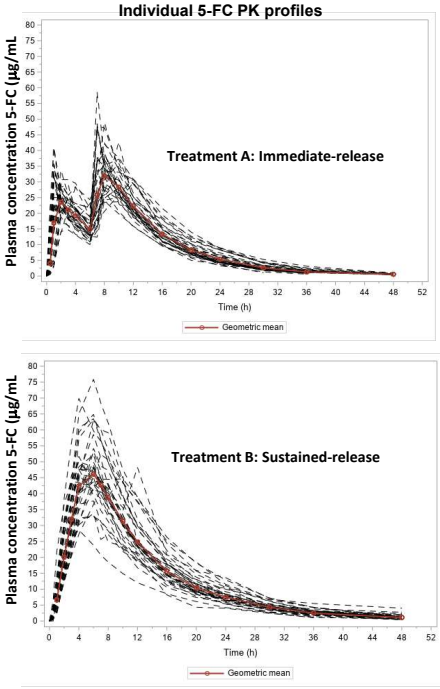
Characteristics	Treatment A (N = 35)	Treatment B (N = 36)
Subjects with TEAEs n (%)	2 (5.7)	4 (11.1)
Subjects with SAEs n (%)	0	0
Subjects with related TEAEs n (%)	1 (2.9)	2 (5.6)
Subjects with TEAEs leading to withdrawal	0	0
Subjects with mild TEAEs n (%)	1 (2.9)	4 (11.1)
Subjects with moderate TEAEs n (%)	1 (2.9)	0
Subjects with severe TEAEs n (%)	0	0

TEAE = treatment-emergent adverse events
SAE = severe adverse events

No deaths or serious adverse events were reported, and all adverse events (AEs) were mild or moderate. Six participants had a total of 9 AEs, of which 3 (mild to moderate) were related to treatment (1 related to IR product and 2 related to SR product). All AEs were reversible without sequalae.

Single-dose sustained-release pellets were shown to be safe in healthy participants at a higher nominal dose in a Phase 1 food effect study and will be further assessed and developed in a Phase 2 study in cryptococcal meningitis patients.

Individual 5-FC PK profiles

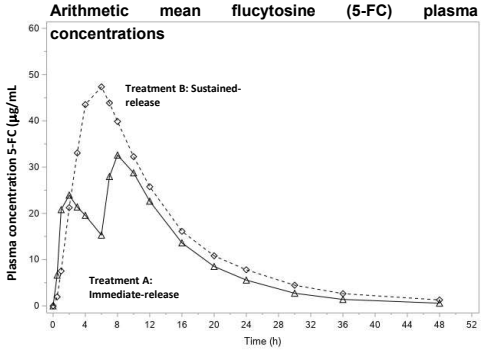


The plasma profile following IR tablet administration was characterized by the presence of two relatively sharp peaks 6 hours apart (explained by the two dosing for the IR treatment) followed by a gradual decline. On the other hand, the plasma concentration-time profile of the SR pellets was characterized by a gradual increase to a single peak between 3.0 and 7.0 hours, followed by a

PK Parameters	Treatment A (N = 35)	Treatment B (N = 36)
C_{max} (µg/mL)*	36.8 ± 7.6	49.2 ± 10.5
$AUC_{(0\text{-}t)}$ (h•µg/mL)*	456.6 ± 72.8	640.4 ± 126.4
T_{max} (h) (median and range)	8.0 (1.0 -12.0)	6.0 (3.0 – 7.0)

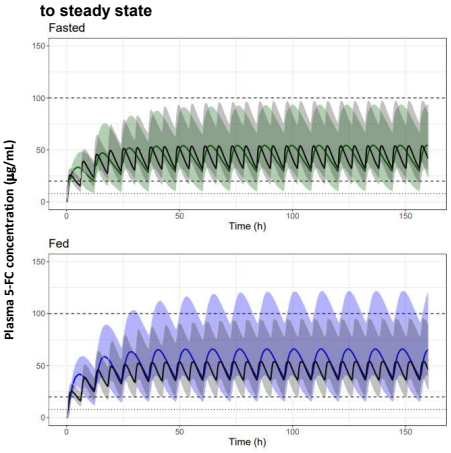
**Arithmetic mean ± Standard Deviation*

Arithmetic mean flucytosine (5-FC) plasma concentrations



The bioavailability of flucytosine from the SR product exceeded the bioavailability of flucytosine from the IR product at the doses administered in the study in fed conditions. 5-FC bioavailability (as a mean ratio of $AUC_{(0\text{-}t)}$) was 1.4-fold higher for the SR product (640.4 ± 126.4 h•µg/mL) than the IR product (456.6 ± 72.8 h•µg/mL). Similarly, mean ratio of C_{max} was 1.3-fold higher for the SR product (49.2 ± 10.49 mg/ml) compared to the IR product (36.8 ± 7.61 mg/ml).

Simulated 5-FC plasma concentration-time profiles up to steady state



Black (immediate-release treatment) and coloured (sustained-release treatment) lines and shaded areas represent the median and 5-95% range of the simulations, respectively. Immediate-release formulation dosing was 1500 mg 4 times per day and Sustained-release formulation dosing was 6000 mg bid. The dashed lines represent the therapeutic interval and the dotted line represent 5-FC MIC_{90}.

A physiologically based PK model used to select study doses predicted that 6000 mg SR pellets twice daily would result in higher exposure under fed conditions in healthy participants, compared to IR tablets (1500 mg administered 4 times per day). Based on this PBPK modelling, SR formulation should be administered at 6000 mg BID in fasting condition, to avoid overexposure. Furthermore, the C_{trough} after the first dose (at 12 hours) for some participants receiving treatment B (SR formulation) was either at or below the lower therapeutic level of 20 mg/L. The MIC_{90} for 5-FC was determined between 4.0-8.0 µg/mL. In this simulation, after the first dose, the 5th percentile of simulated C_{trough} is slightly below the MIC_{90} of 8 mg/L, but above 4 mg/L. From the second administration of the SR, the 5th percentile of simulated C_{trough} is above the MIC_{90} of 8 mg/L.

CONCLUSIONS

Switching from IR to SR 5-FC to treat CM is not predicted to cause additional safety concerns for patients. A PBPK model used to select study doses predicted that 6000 mg SR pellets would result in higher exposure under fed conditions in healthy participants, compared to IR tablets (3000 mg administered BID). It predicted that under fasting conditions, the same doses will show a good overlap with the IR product, so 6000 mg SR 5-FC BID in fasting conditions is recommended and will be explored in a Phase II study in adults living with HIV-associated CM.

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