BACKGROUND
5-flucytosine (5-FC) is used to treat cryptococcal meningiopencephalitis (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-blinded, 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 as a single dose: 2 x 3000 mg at 0 hours).

Test (Treatment B): Flucytosine 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 Cmax and AUC0-t. Physiologically based pharmacokinetic (PBPK) modeling 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 1 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.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment A</th>
<th>Treatment B</th>
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<tr>
<td>Cmax (µg/mL)</td>
<td>36.6 (7.6)</td>
<td>49.2 (10.5)</td>
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<tr>
<td>AUC0-t (µg·h/mL)</td>
<td>456.6 (72.8)</td>
<td>640.4 (126.4)</td>
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<tr>
<td>Tmax (h) (median and range)</td>
<td>8.0 (1.0–12.0)</td>
<td>6.0 (3.0–7.0)</td>
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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 dotted line representing the therapeutic interval and the dotted line representing IR product.

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 placebo product). All AEs were reversible without sequelae.

ACKNOWLEDGMENTS
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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 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 Cmin 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 MIC90 for 5-FC was determined between 4.0–8.0 µg/mL. In this simulation, after the first dose, the 5th percentile of the simulated Cmin was slightly below the MIC90 of 8 mg/L, but above 4 mg/L. From the second administration of the SR, the 5th percentile of simulated Cmin is above the MIC90 of 8 mg/L.