Poster No: 594

# An Open-Label Study in Healthy Volunteers to Determine the Absolute Bioavailability of, the Effect of Food and Dosing by Nasogastric Tube upon the Pharmacokinetics of a Single Oral Dose of Olorofim (OLO)

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## INTRODUCTION

Olorofim, a selective fungal pyrimidine biosynthesis inhibitor, is currently in Phase II clinical development in patients with invasive fungal disease (IFD) who have limited or no treatment options. Information on absolute bioavailability and effect of food upon the pharmacokinetics (PK) of OLO when administered as a 30 mg tablet is required for appropriate guidance on dosing. Furthermore, as critically ill IFD patients may not always be able to swallow intact tablets, evaluation of an alternative enteral formulation is likely to be of great value to this target population.

## AIMS

- To determine the absolute bioavailability ($F_{abs}$) of and the impact of food upon the 30-mg oral tablet of olorofim in healthy subjects
- To determine the relative bioavailability ($F_{rel}$) of a "tablet-in-water" preparation of olorofim in healthy subjects
- To further evaluate the safety and tolerability of single IV and oral doses of olorofim in healthy subjects.
- To assess whether the composition of a meal impacts the meal driven increase in plasma levels of olorofim (the "PK surge").

## METHODS

Cohorts A and B (*randomised 3-way crossover design*)

12 healthy male and female subjects (6/cohort, aged 18 to 55 years; BMI of 18-30 kg/m$^2$) received single doses of 150 mg olorofim on Days 1, 12 and 23 in accordance with a master randomisation plan. Treatments were:

- IV: 2-hour intravenous infusion
- Oral (fasted): 30 mg tablets given after an overnight fast
- Oral (fed): 30 mg tablets given 30 min after starting a high fat breakfast
- At 8 h and 24 h post-dose, Cohort A subjects received high carbohydrate/low fat meals; Cohort B received low carbohydrate/high fat meals
- PK sampling for olorofim occurred for 120 h postdose, with safety assessments occurring up to approximately 10 days post last dose.

Cohort C *(randomised 2-way crossover design)*

12 healthy male and female subjects (aged 18 to 55 years; BMI of 18-30 kg/m$^2$) received single doses of 150 mg olorofim on Days 1 and 12 in accordance with a master randomisation plan. Treatments were:

- Oral (intact tablets): 30 mg tablets given after an overnight fast
- Oral (tablet-in-water): 30 mg tablets dispersed in water and administered via NG tube after an overnight fast
- PK sampling for olorofim occurred for 120 h postdose, with safety assessments occurring up to approximately 10 days post last dose.

Analysis

- Plasma levels of olorofim were quantitatively measured using a validated liquid chromatography dual mass spectrometry (LC-MS/MS ) assay.

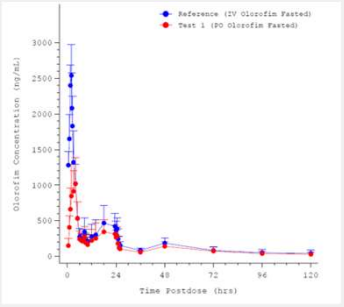
## RESULTS (Cohorts A and B)

- The absolute bioavailability of a single oral dose of olorofim (administered as 30 mg tablets) = 67.8% (90%CI: 61.4, 75.0)
- Food had little effect upon overall systemic exposure of olorofim (based upon $AUC_{0\text{-}t}$ )
  - $F_{rel}$ = 88.0% (90% CI: 79.6, 97.3)
- $C_{max}$ was lower when olorofim was dosed in the fed state
  - $F_{rel}$ = 41.7% (90% CI: 34.9, 49.9)
- All subjects showed secondary peaks in plasma levels of olorofim which were closely associated with meal times
  - Meal composition (high carbohydrate or high fat) had no major impact upon magnitude of secondary peaks
- All doses were safe and generally well tolerated
  - There were 2 cases of reversible increases in ALT above 3xULN (both CTCAE grade 2)
  - All other liver enzymes were either not elevated or were at most a grade 1 increase; bilirubin was not elevated

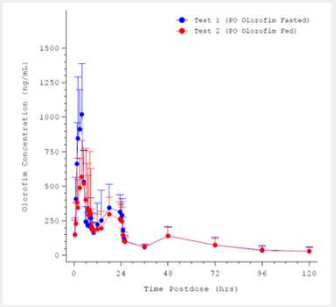
*Table 1: Systemic exposure of olorofim after single oral and IV dosing*

| Parameter | Statistic | IV OLO | Oral OLO (fasted) | Oral OLO (fed) |
|---|---|---|---|---|
| $C_{max}$ (µg/mL) | N | 12 | 12 | 12 |
| | Geo mean (CV%) | 2.67 (16.6%) | 1.11 (28.9%) | 0.77 (39.9%) |
| $T_{max}$ (h) | N | 12 | 12 | 12 |
| | Median (min,max) | 2 (1.5 – 2.25) | 4.0 (2.0 – 4.0) | 3.5 (1.5 – 23.5) |
| $AUC_{0\text{-tlast}}$ (µg·h/mL) | N | 12 | 12 | 12 |
| | Geo mean (CV%) | 21.7 (30.2%) | 14.7 (34.4%) | 12.9 (33.3%) |
| $AUC_{0\text{-}\infty}$ (µg·h/mL) | N | 7 | 8 | 6 |
| | Geo mean (CV%) | 23.9 (14.4%) | 15.3 (40.9%) | 12.5 (19.7%) |
| $t_{½}$ (h) | N | 7 | 8 | 7 |
| | Geo mean (CV%) | 19.7 (27.7%) | 21.2 (25.9%) | 25.9 (51.1%) |

*Mean plasma concentrations of olorofim following a single IV and oral dose of OLO*




*Mean plasma concentrations of olorofim following a single oral dose of OLO in the fed and fasted state*



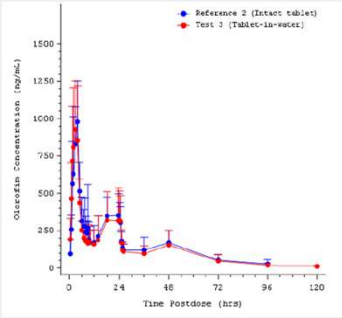

## RESULTS (Cohort C)

### Tablet in water preparation

- Intact tablets were placed into the barrel of a syringe
- Potable water added (10 mL/tablet)
  - Water can be ambient temperature up to 37°C
- Syringe capped, shaken by hand for a few minutes prior to dosing through NG tube
  - opaque liquid prepared (yellow to deep orange depending upon colour of film-coating)
- Syringe and NG tube were flushed with same volume of water (ie 10 mL/tablet)
  - Minimal amounts of coloured liquid visible in either syringe or NG tube after flushing

### Relative Bioavailability of Tablet in Water

*Mean plasma concentrations of olorofim following a single oral dose of OLO given via NG tube or intact tablet*




- The relative bioavailability of a single oral dose of olorofim when administered as tablet in water via NG tube = 87.6% (90%CI: 72.3, 106.2)
- $T_{max}$ and $C_{max}$ were similar when olorofim was dosed as either tablet in water via NG tube or as intact tablet.
- All doses were safe and well tolerated

*Table 2: Systemic exposure of olorofim after dosing tablet-in-water via NG tube and intact tablet*

| Parameter | Statistic | Tablet-in-water | Intact tablet |
|---|---|---|---|
| $C_{max}$ (µg/mL) | N | 10 | 11 |
| | Geo mean (CV%) | 0.94 (28.7%) | 1.05 (23.9%) |
| $T_{max}$ (h) | N | 10 | 11 |
| | Median (min,max) | 3.0 (1.5 – 4.0) | 4.0 (2.0–9.0) |
| $AUC_{0\text{-tlast}}$ (µg·h/mL) | N | 10 | 11 |
| | Geo mean (CV%) | 12.5 (47.6%) | 14.3 (35.3%) |
| $AUC_{0\text{-}\infty}$ (µg·h/mL) | N | 8 | 9 |
| | Geo mean (CV%) | 13.5 (46.2%) | 14.7 (30.6%) |
| $t_{½}$ (h) | N | 8 | 10 |
| | Geo mean (CV%) | 20.9 (36.3%) | 21.7 (65.0%) |

## CONCLUSIONS

- Olorofim has good oral bioavailability when given as 30 mg tablets
- As high fat breakfast has minimal impact upon overall systemic exposure, olorofim can be administered with or without food
  - Decrease in $C_{max}$ is of no clinical significance as efficacy is driven by $C_{min}$
- Dosing of tablet-in-water formulation via NG tube is a suitable dosing approach if swallowing intact tablets is not possible
  - Doses must remain multiples of 30 mg tablet strengths
  - No dose adjustment needed upon switching from intact tablets to NG dosing
- Olorofim was generally well tolerated – incidence and severity of treatment-related AEs are similar to Phase 2 ; See abstract #1265672 for details of safety of olorofim during extended dosing