Poster No: 595

Olorofim (OLO) for treatment of invasive mould infections in patients with limited or no treatment options: PK data from a Phase 2b open-label study (NCT03583164, Study 32)

Cornelissen K[1], Wright J[2], Cristinacce A[2], Galbraith, H[3], Brüggemann R[4], Maertens J[5], Thompson GR[6]; Chen SC-A[7], Rex J[1]

[1] F2G Ltd, Manchester, UK; [2] WrightDose Manchester UK; [3] IQVIA Kansas City USA; [4] Radboudumc, Nijmegen, Netherlands; [5] KU Leuven, Leuven, Belgium [6] University of California-Davis, California, USA; [7] Westmead Hospital, NSW, Australia

Corresponding author:
Karen Cornelissen PhD
F2G Ltd, Lankro Way, Eccles, Manchester, M30 0LX, UK
kcornelissen@f2g.com

INTRODUCTION

Olorofim is the first of a new class of antifungal agents (the orotomides) and has a novel, well defined and selective mechanism of action, inhibiting a rate limiting enzyme of fungal pyrimidine biosynthesis, DHODH. *In vitro* and non-clinical *in vivo* studies have shown that olorofim is active against *Aspergillus* (including azole-resistant strains), resistant moulds such as *Scedosporium* and *Lomentospora* prolificans, and dimorphic moulds such as *Coccidioides*. Non-clinical PKPD studies have demonstrated that efficacy is seen when plasma levels exceed 0.1 to 0.2 µg/mL.

Study 32 (an open-label Phase IIb study) was designed to assess safety , tolerability, efficacy and PK of olorofim in patients with Invasive Fungal Infection (IFI) caused by resistant moulds for which there are no or limited treatment options.

The PK data from Study 32 were collected to characterized olorofim pharmacokinetics in the target population, evaluate attainment of efficacy targets with the proposed dosing regimens and investigate exposure-response relationships.

METHODS

Study design

- Study 32 was a multi-centre, open-label, single arm , Phase IIb study in patients with IFI aged 18 and over
- Patients received olorofim (OLO; 30 mg tablets) for 90 days as:
  - Either: Adjusted dose: therapeutic drug monitoring (TDM) based on baseline bodyweight and olorofim pre-dose plasma levels
    - *< 60 kg*: 1-day loading dose 90 mg BID then maintenance dose of 60 mg BID
    - *60 to 85 kg*: 1-day loading dose of 90 mg TID then maintenance dose of 60 mg TID
    - *> 85 kg*: 1-day loading dose of 150 mg BID then maintenance dose of 120 mg BID
  - Or: Fixed dose: 1-day loading dose of 150 mg BID then maintenance dose of 90 mg BID
  - For each subject, doses could also be adjusted due to potential drug interactions or clinical observations (safety concerns or sub-optimal efficacy)
  - Dosing could continue beyond 90 days if subjects were likely to benefit from extend therapy
  - Food intake around time of dosing was not constrained.
- Olorofim PK profiles were determined on 1 or 2 sampling days, with 7 to 9 samples taken over each 8 or 12 hour dosing interval
- 8 to 9 scheduled pre-dose samples were also taken during 90-day main phase of the study

Sample Analysis

- Plasma levels of olorofim were quantitatively measured using a validated liquid chromatography dual mass spectrometry (LC-MS/MS) assay at a central bioanalytical laboratory .
  - Data presented are from the central bioanalytical laboratory
- For the adjusted dose subjects, TDM data was obtained from 3 regional hubs (EU, USA and NZ-based)
  - Regional hubs using a qualified LC-MS/MS assay with annual cross-validation performed with the central laboratory.
  - Data were typically provided to F2G within 3 to 4 working days of sample collection

PK analysis

- Non-compartmental PK analysis was performed on samples collected over a dosing interval
- A multi-compartment PopPK model was developed using NonMem to describe olorofim PK
  - All available plasma concentration data (ie both pre-dose samples and those collected over a dosing interval) were utilised in the model

RESULTS (PK over a dosing interval)

- Olorofim C_{max}, C_{min}, and $AUC_{0\text{-}24}$ were similar between the adjusted and fixed dosing groups (*Table 1*)
  - To normalise for dosing interval, $AUC_{0\text{-}24}$ calculated as AUC_{tau} multiplied by a factor of 2 or 3 for BID and TID dosing
- For those adjusted dose group patients who had 2 intensive PK days on Days 6 and 14, olorofim systemic exposure was similar between days
- Systemic exposure in patients with IFI was similar to healthy subjects receiving a maintenance dose of 90 mg BID for 10 days (*Table 1*)

Table 1: Olorofim Systemic Exposure at Steady State

Population; Dosing type	Geometric Mean (5th - 95th percentile)				
	C_{max} (µg/mL)	C_{min} (µg/mL)	C_0 (µg/mL)	Ratio of C_0:C_{min}	$AUC_{0\text{-}24}$ (µg·h/mL)
IFI patients: Adjusted dose (N=56)	1.37 (0.42 - 4.3)	0.38 (0.10 - 1.18)	0.70 (0.20 - 2.79)	1.82 (1.0- 6.17)	18.1 (5.6 - 51.8)
IFI patients: Fixed dose (N=34)	1.66 (0.53 - 3.75)	0.41 (0.11 - 0.93)	0.75 (0.22 - 2.37)	1.84 (1.0 - 4.04)	20.7 (7.59 - 52.5)
Healthy subjects: 90 mg BID (N=12)	2.21 (1.50 – 3.23) #	0.43 (0.29 -0.61) #	0.52 (0.35 -1.18) #	1.21 (1.00-2.89) #	23.8 (16.6 – 31.4) #

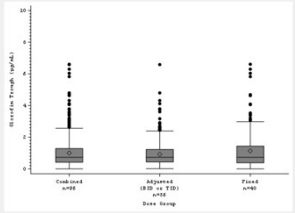
Geometric mean (range)

- In IFI patients, meal times were not controlled and a temporal dependency between food intake and secondary peaks in olorofim plasma levels was evident (*example shown in Figure 3*)
- For most patients (73%), C_{min} was lower than pre-dose trough concentrations (C_0) taken on the PK dosing interval day
  - Ratio of C_0 : C_{min} ranged from 1.0 to 15.8

RESULTS (Pre-dose levels)

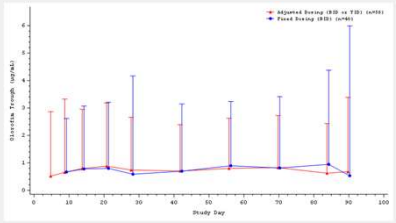
- Mean OLO pre-dose concentrations were stable over time for all 100 patients
- Range of geometric mean pre-dose plasma levels over 90 days:
  - Adjusted dose = 0.66 to 0.88 µg/mL
  - Fixed dose = 0.59 to 0.92 µg/mL

Figure 2: Distribution of olorofim pre-dose (trough) concentrations



Error bars: 5th to 95th percentiles; Shaded box: 25th to 75th percentiles
Horizontal line: median; ◊: mean

Figure 1: Geometric Mean (+SD) Olorofim Pre-Dose (trough) Concentrations by Scheduled Study Day



- Variability in pre-dose levels was slightly greater when TDM was not utilized
- Pre-dose concentrations based on regional hub data were similar to central laboratory data
  - Geometric mean data for central laboratory and regional hub varied by < 10% across all sampling points

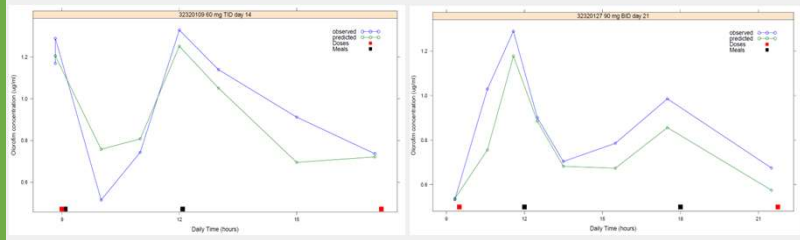
RESULTS (Population PK modelling)

- The PopPK model provides a good description of the Phase II dataset with relatively low residual noise (median of 30% and a between-subject variation in residual noise magnitude of 9%).
- Systemic exposure predicted by Population PK modelling was in reasonable agreement with observed exposure (*Table 2*)
  - PopPK model was able to predict food- triggered surges in plasma levels (*example shown in Figure 3*)

Table 2: Observed and predicted exposure of olorofim in IFI patients

	Median (5th - 95th percentile)		
	C_{max} (µg/mL)	C_{min} (µg/mL)	$AUC_{0\text{-}24}$ (µg·h/mL)
Observed PK (fixed dose; N=34)	1.89 (0.53 -3.75)	0.39 (0.11 - 0.93)	20.1 (7.59 - 52.5)
Predicted PK (90 mg BID)	1.65 (0.61 - 5.16)	0.60 (0.12 - 2.21)	20.6 (6.20 - 68.5)

Figure 3: typical plasma concentration profiles (observed and predicted) showing food-triggered surges



CONCLUSIONS

- Systemic exposure of olorofim in IFI patients was similar to that observed in healthy subjects
  - Invasive fungal infection and serious co-morbidities present in many patients did not have an important impact upon olorofim disposition
- Plasma levels of olorofim (determined both pre-dose and over a dosing interval) were similar for TDM-adjusted dosing and fixed dosing
  - Regardless of dosing approach, plasma levels exceeded the threshold necessary for efficacy
- Multiple peaks in olorofim plasma levels observed in most subjects across a dosing interval were considered to be due to food-triggered surges from a deep compartment back into plasma
  - Food-triggered redistribution of olorofim limits the appropriateness of pre-dose levels to monitor exposure and helps maintain plasma levels above the therapeutic target.

When olorofim is administered as a fixed dose (90 mg BID) adequate exposure for efficacy against invasive mycoses is achieved without the need to confirm by TDM