Clinical Safety, Efficacy and Pharmacokinetics of Fosmanogepix, a Novel First-in-class Antifungal, in Patients with Renal Insufficiency: Subset Analysis from a Phase 2 Candidemia Trial

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Background

Candidemia and Renal Impairment

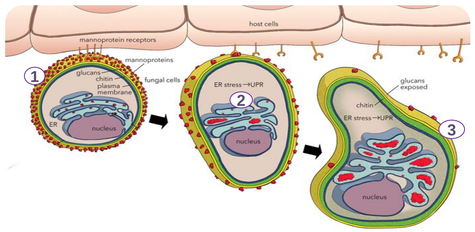
- Patients with candidemia often have underlying renal insufficiency or are receiving medications that affect renal function.
- Clinical outcomes are universally poor in patients with organ failure and septicemia
- Standard of care therapies (amphotericin B and voriconazole) can cause renal toxicity

Fosmanogepix

Fosmanogepix (FMGX) is a prodrug that is rapidly converted *in vivo* by systemic phosphatases to the microbiologically-active moiety manogepix (MGX).

- First in a new class of antifungals with a novel mechanism of action
- Demonstrates broad-spectrum in vivo antifungal efficacy in yeasts and molds, including rare and resistant strains
- Exhibits a wide tissue distribution including brain, lung, kidney and eye
- Has a favorable safety profile, low potential for drug-drug interactions, and both oral and IV formulations are in clinical development

Figure 1. Fosmanogepix Mechanism of Action: Gwt1 inhibitor

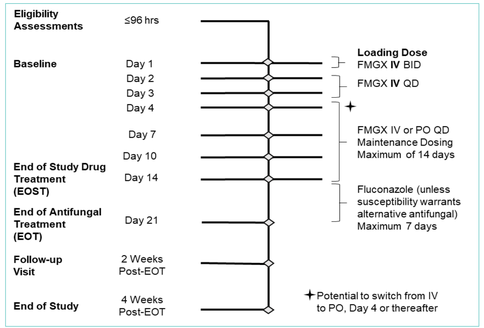


1. Gwt1 protein exists only in fungal cells
2. Gwt1 inhibition blocks mannoprotein transport
3. Lack of mannoproteins on cell wall and stress response lead to fungal cell death

Methods

- This global, multicenter, open-label, non-comparative study evaluated the safety and efficacy of FMGX for first-line treatment of candidemia.
- Patients with a recent diagnosis of candidemia defined as positive blood culture for *Candida* spp. within 96 hrs prior to study entry with ≤ 2 days of prior antifungal treatment were eligible, including those with renal insufficiency and/or with isolates resistant to standard of care therapies
- Patients with neutropenia, *C. krusei* infection, deep-seated *Candida* infections or receiving hemodialysis were excluded

Study design



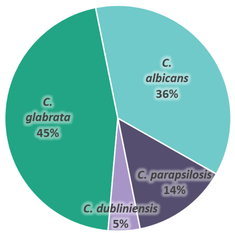
Study Endpoints

- Primary: End of Study Treatment Success by Data Review Committee (DRC)
  - Clearance of infection
  - No additional antifungal therapy required
  - Survival
- Secondary: Survival at Day 30
- Others: Time to first negative blood culture, mycological outcomes, safety, PK/PD

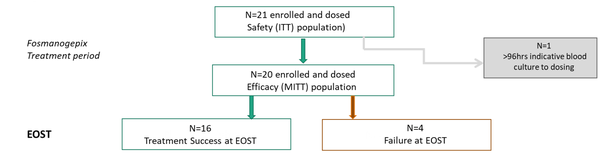
Results

- Demographics, underlying disease and disease severity similar to recent Phase 2/3 candidemia trials
- Average age 63
- 14 Males, 7 Females in ITT population
- Underlying disease - GI surgery, GI disease, malignancies, diabetes, CVC line, TPN, prolonged hospitalization/ ICU, antibiotics, obesity
- Mean APACHE score 13.3 (range 2-27)
- 20 subjects (MITT) with 23 Candida isolates

Baseline pathogens in MITT population N=23 isolates



Disposition and Outcomes



EOST= End of Study Treatment, ITT= Intent to treat, MITT=modified intent to treat

Results

Overall Efficacy

Primary Efficacy Endpoint: Response at EOST	n/N (%)
Treatment Success[1]	**16/20 (80%)**
Treatment Failure	4/20
Reasons for treatment failure:	
• Persistent *Candida* in blood cultures[2]	3/20
• Death (gram-negative *Acinetobacter* sepsis)[3]	1/20

Secondary Efficacy Endpoint: Survival at Day 30	n/N (%)
Patient Survival at Day 30	**17/20 (85%)**
All-Cause Mortality (none drug related)	3/20
Reasons for mortality[3]:	
• Gram-negative *Acinetobacter* sepsis	Day 12
• Progression of underlying cancers	Day 15
• Worsening of interstitial pneumonia	Day 30

1. Treatment Success at EOST = eradication of *Candida* spp. from blood + no use of other systemic antifungal through EOST + alive at EOST
2. Candida spp.: *C. glabrata* (n=1), *C. albicans* + *C. glabrata* (n=1), *C. parapsilosis* (n=1)
3. Patient deaths not drug-related

- 2/20 (10%) assessed as Treatment Success EOST by DRC then relapsed
- Median exposure to study drug was 14 days (range 5-14 days) (ITT)
- 10/21 subjects switched from IV to oral treatment (range 4-11 days), with no apparent decrease in PK observed

Patients with Resistant Candida Isolates (Safety Population)

Subpopulation	Patient Summary Resistant Isolates	Treatment Success	Day 30 Survival
14/21 pts	Patients with *glabrata*, *albicans*, or *parapsilosis* infections resistant to anidulafungin, amphotericin B, or both	**71%** 10/14 pts	**93%** 13/14 pts

- Resistant Candida isolates were identified in 66% of the study population

Overall Safety

- Overall, FMGX was safe and well tolerated
- The most common TEAEs were diarrhea, vomiting, edema peripheral, and pleural effusion, all considered not related to FMGX
- One adverse event of transient moderate thrombocytopenia considered possibly related to FMGX
- No FMGX-related discontinuations
  - 3 discontinued treatment before completion of 14 days of treatment due to inadequate response or deteriorating condition
- No treatment-related SAEs
  - 19 unrelated SAEs observed in 9 patients

Incidence of Treatment-emergent Adverse Events (Safety Population)

	TEAE CTCAE Grade	Total (n=21) n	%
Patients with any TEAE		20	95.2
Mild	1	4	19.0
Moderate	2	3	14.3
Severe	3	5	23.8
Life-threatening	4	3	14.3
Death[1]	5	5	23.8
Patients with related TEAE	**2**	**1**	**4.8**

[1] Patient deaths not drug-related. Deaths after Day 30 included voluntary euthanasia (Day 39) and general physical health deterioration (Day 42)

Summary of TEAEs in >2 Patients by Preferred term

System Organ Class Preferred Term	Total (N=21) n (%)
Patients with any TEAEs	20 (95.2)
Gastrointestinal disorders	10 (47.6)
Diarrhea	3 (14.3)
Vomiting	3 (14.3)
General disorders and administration site conditions	8 (38.1)
Edema peripheral	3 (14.3)
Respiratory, thoracic, and mediastinal disorders	7 (33.3)
Pleural effusion	3 (14.3)

Efficacy in Patients with Renal Impairment (Safety Population)

Subpopulation	Patient Summary Renal Impairment	Treatment Success	Day 30 Survival
14/21 pts	Patients with mild to severe renal impairment (GFR from 86 – 22)	**86%** 12/14 pts	**79%** 11/14 pts

- 14/21 (66%) subjects had some degree of renal impairment at time of study entry:
  - 5 subjects had moderate renal impairment (GFR 30-59)
  - 2 subjects had severe renal impairment (GFR 15-29)
- 4/21 renal function decreased during follow-up period, not related to study drug
  - None required dialysis
- 12/14 (86%) completed study treatment
- 6/7 with moderate or severe renal impairment showed treatment successes per DRC at EOST
- From sparse pharmacokinetic sampling, there were no significant difference in MGX exposure in subjects with and without renal impairment

Baseline GFR	Baseline Renal Impairment	Change in renal function during study treatment	EOST Efficacy (DRC)
43	Moderate	No change	Success
82	Mild	No change	Success
22	Severe	No change	Success
73	Mild	No change	Success
40	Moderate	No change	Success
79	Mild	No change	Success
86	Mild	No change	Success
80	Mild	Mild to normal	Success
50	Moderate	No change	Success
85	Mild	Mild to normal	Success
45	Moderate	Mod to severe to mod	Success
44	Moderate	Moderate to mild	Success
77	Mild	No change	Failure
25	Severe	Severe to moderate	Failure

Conclusions

- Similar to other published candidemia studies, the majority of subjects in this study had some degree of renal impairment at study entry. Most completed a full course of treatment with FMGX with no evidence of worsening in renal function at end of study treatment.
- Rates of Treatment Success at EOST and Survival at Day 30 were high in patients with renal impairment and comparable to the overall population
- None of the patients with renal insufficiency had unexpectantly increased blood levels of FMGX.
- FMGX was safe and well tolerated
- FMGX demonstrated a high level of efficacy in the treatment of candidemia in patients with mild moderate or severe renal impairment with no evidence of drug-related renal toxicity.
- These preliminary data support the continued evaluation of FMGX in patients with candidemia and renal dysfunction as an alternative to potentially nephrotoxic antifungal agents.

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