Design of a Phase 2 Study to Evaluate Fosmanogepix (FMGX, APX001), a Novel Antifungal Agent, for the Treatment of Patients with Invasive Mold Infections (IMIs) Caused by Aspergillus Species or Rare Molds

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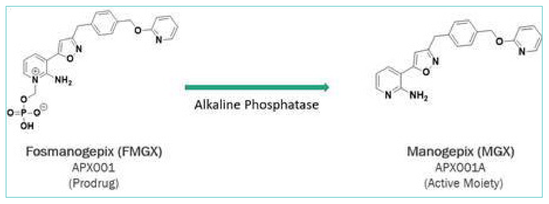
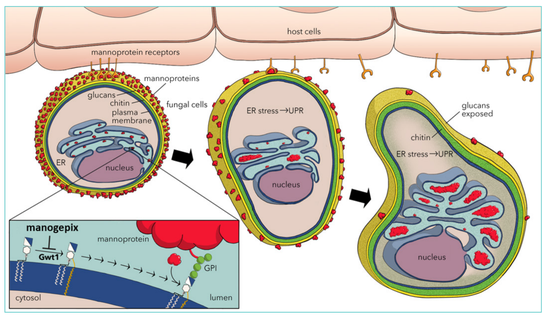
Fosmanogepix - A Novel, First-in-Class Antifungal

- Fosmanogepix is a novel drug candidate in a new class of antifungal agents.
- Fosmanogepix is currently in Phase 2 clinical trials evaluating the efficacy and safety of both IV and oral formulations for the treatment of patients with invasive fungal infections.

Novel Mechanism of Action, Distinct from All Other Available Antifungal Therapies



- After administration, fosmanogepix is rapidly converted to manogepix, the active moiety, which has a unique mechanism of action – inhibition of the fungal enzyme Gwt1, a highly conserved inositol acylase, which catalyzes an early step in the GPI-anchored biosynthesis pathway.
- This inhibition has pleiotropic effects on the fungal cell due to inhibition of cell wall mannoprotein localization, which compromises cell wall integrity, biofilm formation, germ tube formation, and fungal growth.
- Fosmanogepix does not inhibit the phosphatidylinositol glycan anchor biosynthesis class W (PIGW) protein, the closest mammalian ortholog of the fungal GWT1 protein. Thus, no on-target toxicity is expected.



Fosmanogepix - Broad-Spectrum Antifungal Activity

- Fosmanogepix has broad-spectrum antifungal activity, covering most yeasts, *Aspergillus* spp. and rare molds, including species that are resistant to the current standard of care (SOC) antifungal agents.
- *In vitro* testing demonstrates that Fosmanogepix has broad antifungal activity against *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., *Scedosporium* spp., *Fusarium* spp., and Mucorales, including azole- and echinocandin-resistant strains.
- In immunosuppressed mice with IMIs (A. *fumigatus*, S. *prolificans*, F. *solani*, *Rhizopus* spp.), fosmanogepix was associated with improved survival rates and reduced pulmonary fungal burden.
- Fosmanogepix has the potential to treat infections caused by a broad-spectrum of fungal pathogens, with low risk of hepatic and renal toxicities associated with the currently available antifungal agents.

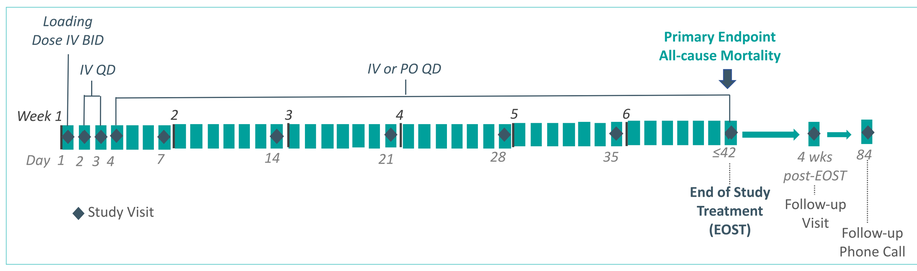
The AEGIS Study – Designed to Address an Unmet Medical Need

- There is an urgent need for new and more effective antifungal drugs to treat the life-threatening IMIs that can develop in severely immunocompromised patients. Although *Aspergillus* spp. is the major cause of IMIs in these patients, infections caused by other fungi, such as *Fusarium* spp., *Scedosporium* spp., and Mucorales fungi are becoming more important. These emerging fungal pathogens may be resistant to the currently available antifungal agents.
- There is also a need for a new antifungal agent that is safe and well-tolerated in patients with complicated medical conditions including renal or hepatic insufficiency, and can be used in patients receiving concomitant medications that may cause drug interactions with the currently available antifungal agents.
- This proof of concept Phase 2 study was designed to evaluate the safety and efficacy of fosmanogepix for the treatment of IMIs in patients with limited treatment options due to antifungal resistance, drug-drug interactions, toxicity and/or intolerance to one of the currently recommended SOC antifungal agents. This study will include 50 patients from up to 40 global sites experienced in conducting similar studies.
- This study will include 50 patients from up to 40 global sites.
- The study design was based on prior studies with updates based on current regulatory guidance, expert opinions and new approaches for the diagnosis and treatment of IMIs.

Study Population

- Immunocompromised adult patients with a diagnosis of invasive mold infection (eg, *Aspergillus* spp., *Scedosporium* spp., *Fusarium* spp., and Mucorales fungi).
  - Proven or probable IMI will be defined in accordance with a modified version of the 2008 EORTC/MSG Revised Definitions of Invasive Fungal Disease
- Patients must also have limited or no treatment options for the IMI. Examples of limited treatment options include: documented/ anticipated resistance, contraindication, and/or intolerance to the currently available antifungal agents.
- There must be a potential advantage of using fosmanogepix over current SOC in terms of spectrum of activity, available IV and PO formulations, favorable DDI profile, favorable hepatic and renal safety profile, and/or wide tissue distribution.
- Patients with poor prognoses due to refractory hematologic malignancy, significant hepatic dysfunction, neurological disorders or receiving palliative care will be excluded.
- Duration of prior antifungal treatment will be limited to 5 days in most cases. An exception is antifungal prophylaxis, which is allowed but must be discontinued at time of study entry.

Study Treatment and Procedures



- After a screening period for study eligibility, patients will receive fosmanogepix intravenously with a potential to step down to the oral formulation to complete up to six weeks of treatment.
- There will be a follow-up study visit 4 weeks after the end of study treatment, and a follow-up telephone contact at Day 84.
- Radiological assessments (including computed tomography scans of the chest, sinuses, and abdomen) will be performed at study entry, on Day 14, at end-of-study-treatment, and at other times if clinically indicated.
- Safety and tolerability of fosmanogepix will be evaluated through physical examination findings, vital signs and changes in clinical laboratory tests.
- Serum samples for galactomannan and β-D-glucan will be collected at baseline, and throughout the study.
- Interested sites will be provided with supplies to perform on-site evaluation of GM using IMMY's sōna *Aspergillus* galactomannan LFA (serum or BAL fluid)Samples will also be sent for investigational diagnostic testing including:
  - MycoMEIA- *Aspergillus* diagnostic lateral flow device (urine)
  - Karius – next-generation sequencing of microbial cell-free DNA for fungal identification (serum samples)
- All fungal isolates will be sent to the central mycology reference laboratory for confirmation of identification and susceptibility testing.
- Plasma samples will be collected and analyzed to derive the population mean (and variance) values of specific PK parameters.

Study Endpoints

- The primary endpoint of the study is the all-cause mortality at Day 42.
- If at least 50% of patients in this study are evaluable, there will be an adequate number of patients to test the hypothesis that the FMGX all-cause mortality is not equal to the all-cause mortality historically associated with amphotericin, which is considered to be sub-optimal for the treatment of IMIs.
- Secondary and exploratory endpoints include:
  - Global Response at end-of-study-treatment
  - All-cause mortality at Day 84
  - Changes from baseline in galactomannan and β-d-glucan.

Review Committees

- A Data Review Committee of infectious disease experts will review and adjudicate the following:
  - Diagnosis of IMI at study entry
  - Global Response, incorporating clinical, mycological and radiological responses, at end-of-study-treatment.
    - Global Response will be classified as complete, partial, stable or progression of disease according to prespecified criteria. A complete or partial global response will be categorized as a success; stable global response or progression of disease will be categorized as a failure.
- A Data and Safety Monitoring Board will be responsible for the periodic review of cumulative data from the study.

Potential Advantages of FMGX Over Current SOC Antifungal Agents

- **Examples of clinical situations in which there may be a potential advantage of FMGX over one of the mold-active azoles (voriconazole, isavuconazole, posaconazole):**
  - Infection with rare mold or A. *fumigatus* suspected or confirmed to be azole-resistant - especially at centers with >10% incidence
  - Breakthrough IFI despite mold-active prophylaxis
  - Advanced GvHD, underlying liver disease, and/or receiving hepatotoxic medications where azoles may worsen hepatic dysfunction
  - Receiving medications with potential for clinically significant drug interactions with azoles (e.g. CYP3A4 substrates including tacrolimus, sirolimus, cyclosporine, vincristine, tyrosine kinase inhibitors)
  - Receiving medications that could prolong QT interval
  - History of hypersensitivity/intolerance to azoles, including visual or neurological side effects
- **Examples of clinical situations in which there may be a potential advantage of FMGX over a polyene (e.g. liposomal amphotericin B):**
  - Clinical situations in which polyenes may worsen renal dysfunction (e.g. older age, sepsis/ hypotension, underlying renal disease, receiving nephrotoxic medications)
  - Suspected or confirmed infection with polyene-resistant mold
  - Receiving concomitant medications (e.g. corticosteroid/ACTH) which may potentiate polyene-induced hypokalemia or which may be affected by polyene-induced hypokalemia (e.g. digitalis, skeletal muscle relaxants)
  - Receiving neoplastic agents which may increase the potential for polyene-induced toxicities including bronchospasm, hypotension, and renal toxicity
  - Receiving white cell transfusions
  - History of hypersensitivity/intolerance to polyenes
  - Clinical situations that require switch from PO to IV formulations (e.g. gastrointestinal GvHD, malabsorption, mechanical ventilation, altered mental status)

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