Clinical Safety and Efficacy of Novel Antifungal, Fosmanogepix, in the Treatment of Candidemia: Results from a Phase 2 Proof of Concept Trial

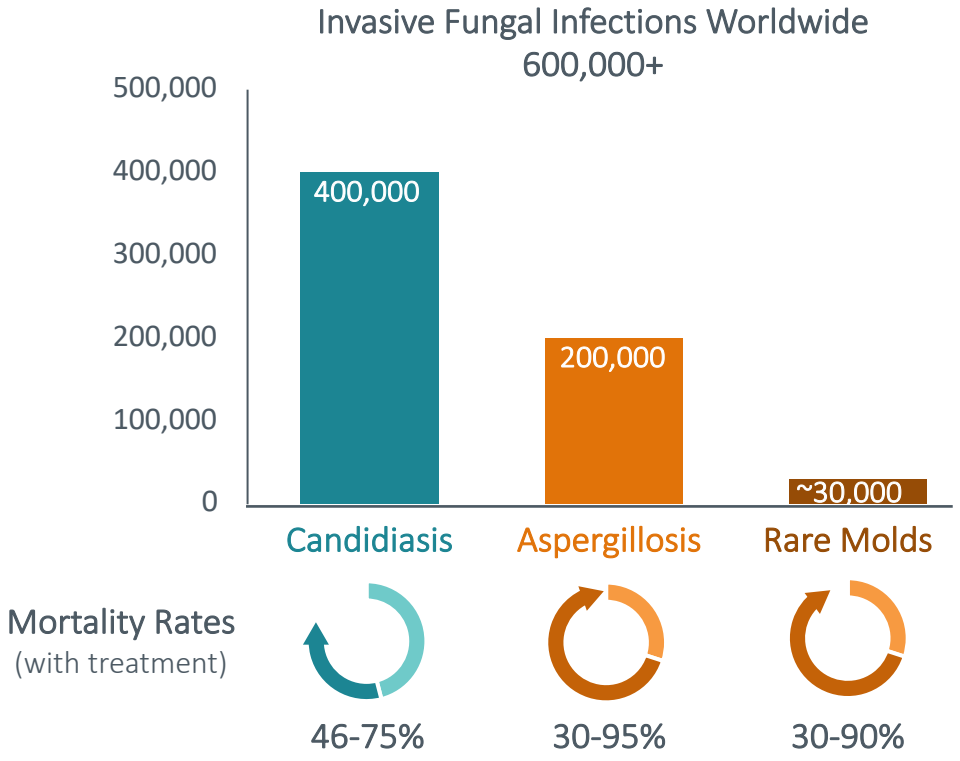
Peter G. Pappas[1], Bart Jan Kullberg[2], Jose A. Vazquez[3], Ilana Oren[4], Galia Rahav[5], Mickaël Aoun[6], Pierre Bulpa[7], Ronen Ben-Ami[8], Ricard Ferrer[9], Todd McCarty[1], George R. Thompson III[10], Sara H. Barbat[11], Pamela Wedel[11], Iwonka Oborska[11], Haran Schlamm[11], and Michael R. Hodges[11]

[1] University of Alabama at Birmingham, Birmingham, Alabama, USA; [2] Radboud Center for Infectious Diseases, and Department of Medicine, Radboud University Medical Center, Nijmegen, The Netherlands; [3] Medical College of Georgia/Augusta University, Augusta, GA, USA; [4] Rambam Health Care Campus, Haifa, Israel; [5] Sheba Medical Center, Ramat Gan, Israel; [6] Institut Jules Bordet, Brussels, Belgium; [7] University Hospital Mont-Godinne, Yvoir, Belgium; [8]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel and Sackler School of Medicine, Tel Aviv University, Israel; [9] Vall d'Hebron University Hospital, Barcelona, Spain, [10] University of California Davis, Sacramento, CA, USA; [11] Amplyx Pharmaceuticals Inc., San Diego, CA, USA

New Antifungal Agents Needed For Candidemia

- In the US, there were an estimated 23,000 cases of candidemia and 3,400 deaths in 2017
- Approximately 50% of isolates identified in healthcare-associated bloodstream infections are non-*Candida albicans*
  - *C. auris* and *C. glabrata* are more likely to be resistant to standard of care therapies
- The unmet medical need of candidemia and invasive candidiasis remains high, especially for high-risk patients
  - Treatment can be complex in critically ill patients in the ICU
  - Existing antifungal agents can be difficult to use, poorly tolerated, or ineffective due to resistance

Candidiasis is the most common invasive fungal infection worldwide, with high mortality rates



Sources: www.bccresearch.com; Stanzani, 2007 Therap & Clin Risk Mgmt; Brown, 2012 Science & Translational Med; Harpaz, 2016 JAMA

Fosmanogepix: First-in-Class, Potent and Selective Gwt1 Inhibitor

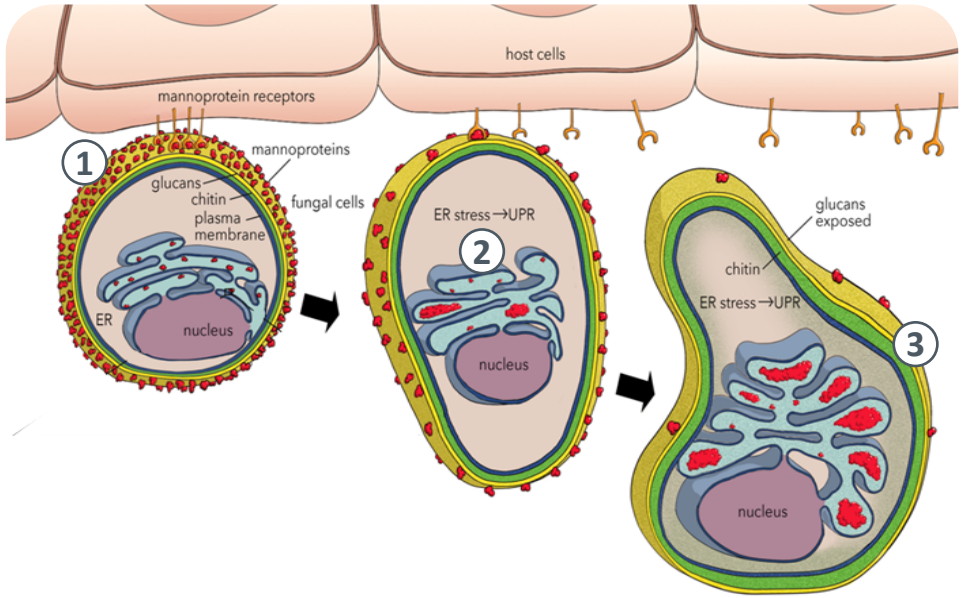
- ✓ **Novel Targeted Mechanism:** Inhibits Gwt1, a target specific to fungal cells that triggers two distinct cellular vulnerabilities
- ✓ **Broad Spectrum:** Demonstrates *in vivo* antifungal efficacy in yeasts and molds, including rare and resistant strains
- ✓ **Wide Tissue Distribution:** Reaches hard-to-access compartments in brain, lung, kidney, and eye
- ✓ **Favorable Safety Profile:** Minimizes additional toxicity burden for very sick patients
- ✓ **Favorable DDI Profile:** Low potential for CYP3A4 inhibition, simplifies co-administration
- ✓ **IV and Oral Formulations:** Supports continuation of care outside of the hospital

Fosmanogepix Inhibits Gwt1

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



GWT1= Glycosylphosphatidylinositol-anchored wall transfer protein 1, DDI=drug-drug interaction, IV=intravenous, CYP=cytochrome p450

Phase 2 Trial of Fosmanogepix in Patients with Candidemia

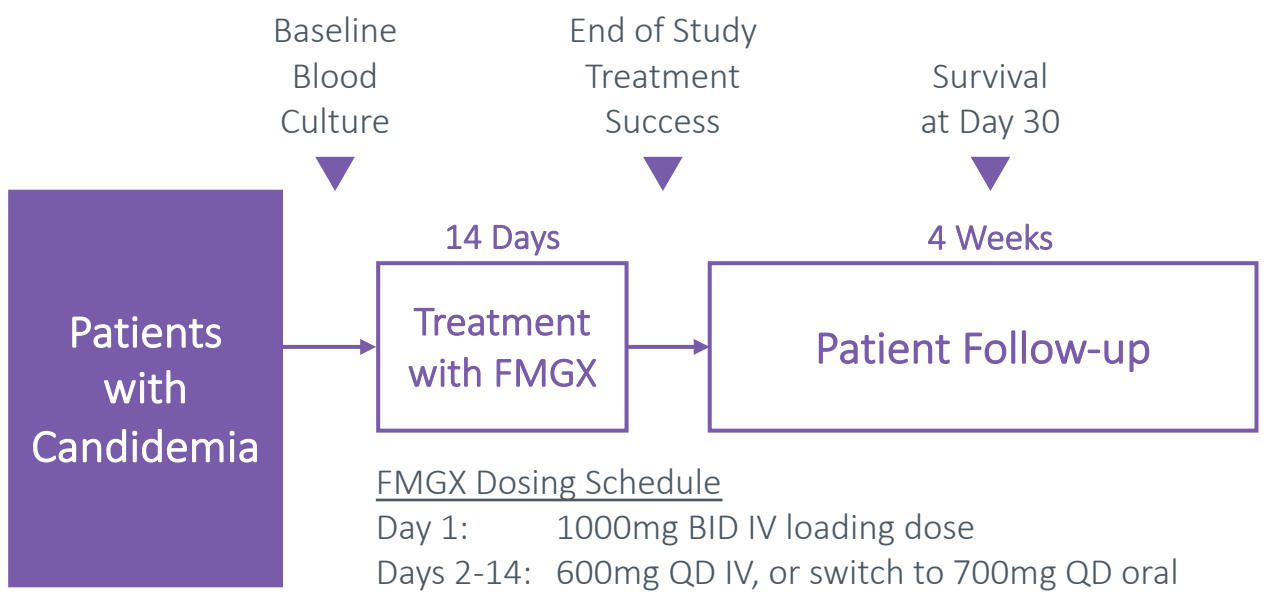
- **Study Objectives: Demonstrate safety and efficacy of FMGX in target patient population**

Study Population

- Non-neutropenic with candidemia
- May have isolates resistant to SOC antifungals
- Positive blood culture required within 96 hours of first FMGX dose
- May not have more than 48 hours of prior antifungal therapy for current infection

Study Endpoints

- Primary: End of Study Treatment Success by 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



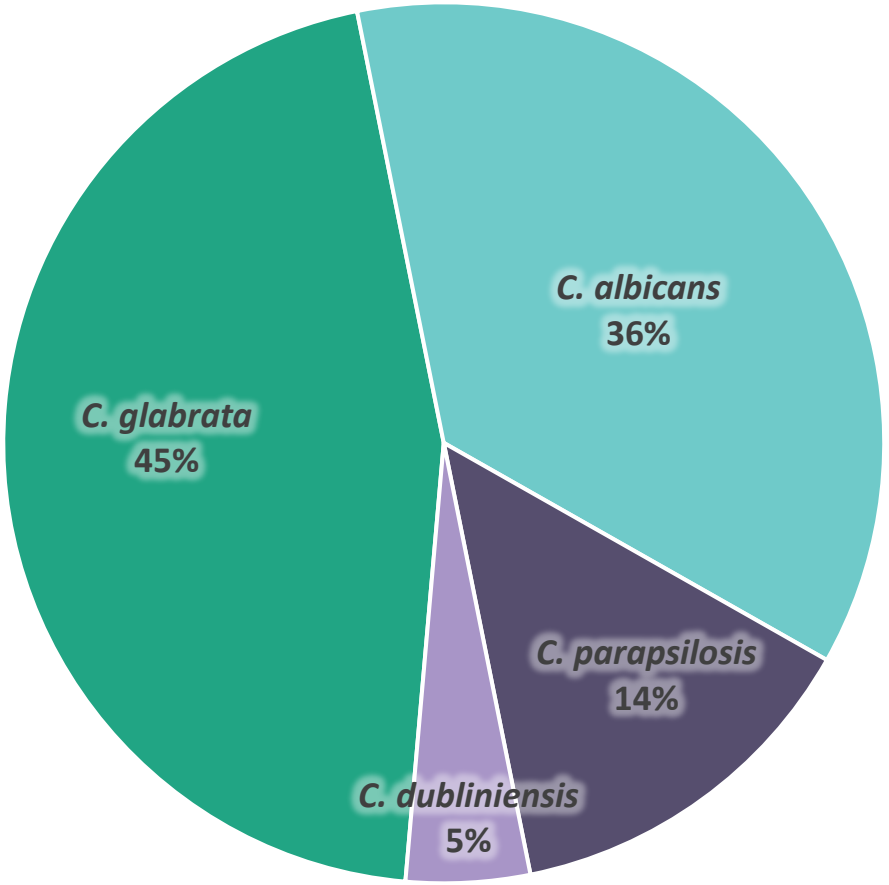
20 sites in Belgium, Germany, Israel, Spain and US

Clinicaltrials.gov Identifier: NCT03604705. EOST= End of Study Treatment, FMGX=fosmanogepix, DRC= Data review committee, BID= twice daily, QD= once daily, PK/PD=pharmacokinetics/pharmacodynamics, SOC=standard of care, IV=intravenous

Patient Demographics and Mycology

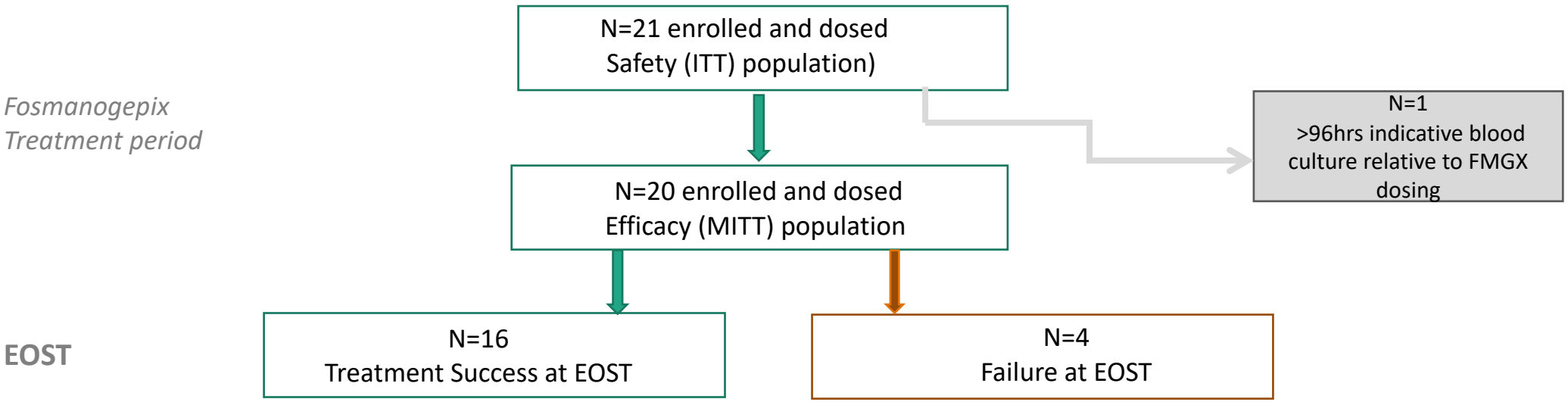
- Demographics, underlying disease and disease severity similar to recent Phase 2/3 candidemia trials
  - Average age 63
  - 14 Males, 7 Females in ITT population
  - Underlying disease:
    - GI surgery
    - GI disease
    - malignancies
    - Diabetes
    - CVC line
    - Total parenteral nutrition
    - Prolonged hospitalization/ ICU
    - Antibiotics
    - Obesity
  - Mean APACHE score 13.3 (range 2-27)
- 20 subjects in MITT population with 23 *Candida* isolates

Baseline pathogens in MITT population
N=23 isolates



ITT= Intent to treat, MITT=modified intent to treat, APACHE= Acute Physiology And Chronic Health Evaluation, ICU=intensive care unit, CVC=central venous catheter

Patient Disposition and Treatment Outcomes



- Treatment Success at EOST = eradication of *Candida* spp. from blood + no use of other systemic antifungal through EOST + alive at EOST
- 2/20 (10%) relapsed – both patients had pancreatic cancer with potential for disruption of the gut/blood interface
- Median exposure to study drug was 14 days (range 5-14 days) (ITT population)
- **10/21 subjects switched from IV to oral treatment (range 4-11 days), with no apparent decrease in PK observed**

EOST= End of Study Treatment, FMGX=fosmanogepix, ITT= Intent to treat, MITT=modified intent to treat, IV=intravenous, PK=pharmacokinetic

Efficacy: Response at End of Study Treatment and Survival at Day 30 (MITT population)

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] • Death (gram-negative *Acinetobacter* sepsis)[3]	 3/20 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 • Progression of underlying cancers • Worsening of interstitial pneumonia	 Day 12 Day 15 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

EOST= End of Study Treatment

Efficacy: Patients with Isolates Non-Susceptible to SOC Therapies

- 14/21 (66%) patients were infected with *Candida* spp. resistant to AmB and/or anidulafungin (EUCAST method) [+/- intermediate resistance to fluconazole]

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

PID	Candida spp.	Resistance/[intermediate susceptibility]	MIC (EUCAST)	Manogepix MIC ug/mL[1]	Day(s) with Positive Blood Culture Relative to Baseline	Efficacy (DRC)	Day 30 Survival
103001	*parapsilosis*	AmB	≥ 2 µg/mL	0.016	D -3	Success	Alive
202002	*glabrata*	Anid, [Flu]	≥ 0.12 µg/mL,[1 µg/mL Flu]	0.008	D -3	Success	Alive
202003	*glabrata*	AmB, Anid, [Flu]	≥ 2 µg/mL (AmB), ≥ 0.12 µg/mL (Anid); [1 µg/mL Flu]	0.008	D -3, D 1	Success	Alive
502002	*albicans*	AmB	≥ 2 µg/mL (AmB), ≥ 0.06 µg/mL (Anid*)	0.004	D -2, D -1, D1	Success	Alive
103002	*glabrata*	AmB, [Flu]	≥ 2 µg/mL(AmB), [≥2 µg/mL Flu]	0.016	D -4, D3	Success	Alive
201003	*glabrata*	AmB, [Flu]	≥ 2 µg/mL; [≥ 2 µg/mL Flu]	0.016	D-3, D 1	Success	Alive
202004	*parapsilosis*	AmB, [Flu]	≥ 2 µg/mL; [4µg/mL Flu]	0.004	D -4	Success	Alive
202005	*glabrata*	AmB, Anid, [Flu]	≥ 2 µg/mL (AmB), ≥ 0.12 µg/mL (Anid), [2 µg/mL Flu]	0.008	D -3	Success	Alive
502003	*albicans*	AmB	≥ 2 µg/mL	0.008	D -4	Success	Alive
502004	*albicans*	AmB	≥ 2 µg/mL	0.004	D -4	Success	Alive
503003	*glabrata*	AmB, Anid, [Flu]	≥ 2 µg/mL (AmB), ≥ 0.12 µg/mL (Anid), [≥ 1 µg/mL Flu]	0.004	D -3, D -2, D 2, D 4 - 9, D 12, D 13	Failure	Alive
101001	*parapsilosis*	AmB	≥ 2 µg/mL	0.008	D -4, D 1- 5	Failure	Alive
201004	*glabrata*	AmB, Anid, [Flu]	≥ 2 µg/mL (AmB), ≥ 0.12 µg/mL (Anid), [≥ 1 µg/mL Flu]	0.016	D -4	Failure	Dead
301002	*albicans*	AmB	≥ 2 µg/mL	0.004	D-4, D -1, D 1- 3, D 5-7	Failure	Alive

* Single anidulafungin-resistant isolate with multiple susceptible isolates, [1] Low manogepix MICs (EUCAST) as expected.
Note: an additional 3 patients had baseline *C. glabrata* blood isolates with intermediate resistance to fluconazole (201001, 203001, 203002)
All isolates testing was conducted by NTS Ventures (new technology systems) central laboratory

Efficacy in Patients with Renal Impairment (ITT population)

- 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
- Treatment successes per DRC at EOST
  - 6/7 with moderate or severe renal impairment

Subpopulation	Patient Summary Renal Impairment	Treatment Success[2]	Survival at Day 30
14/21 pts	Patients with mild to severe renal impairment (GFR from 86 – 22)	86% 12/14 pts	79% 11/14 pts

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

GFR= Glomerular filtration rate, EOST= End of Study Treatment, DRC= Data review committee

Safety Summary

Fosmanogepix was safe and well tolerated

- 1/21 patients had a possibly drug-related adverse event:
  - Transient moderate thrombocytopenia
- The most common TEAEs were diarrhea, vomiting, edema peripheral, and pleural effusion
- 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/ITT 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**

Summary of TEAEs in >2 Patients by Preferred term

System Organ Class Preferred Term	Total (N=21) n (%)
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)

FMGX=fosmanogepix, ITT= Intent to treat, TEAE=treatment emergent adverse event, CTCAE=Common Terminology Criteria for Adverse Events, SAE=severe adverse event

Summary of Clinical Outcomes in *Candida*

Study Objectives met

- High rates of Treatment Success and Day-30 survival
  - DRC assessed Treatment Success at end of study drug treatment: 16/20 (80%)
  - Survival at Day 30: 17/20 (85%)
  - Low rate of relapse
- Efficacy seen in hard-to-treat subpopulations
  - Patients with amphotericin-resistant and/or anidulafungin-resistant *Candida* spp.
  - Patients with renal impairment
- Approximately 50% of patients transitioned from IV to oral, with no apparent decrease in PK
- Safe and well tolerated
- Limitations of study include single arm design and relatively small size
- Trial results inform design of the Phase 3 clinical studies

Fosmanogepix Clinical Development

Next Steps

- Phase 3 Candidemia and invasive candidiasis study planned
- Phase 2 studies ongoing in other invasive fungal infections:
  - Resistant *Candida auris* (IV and oral)- *enrolling*
  - Aspergillosis and Rare molds (IV and oral)- *enrolling*
- Expanded Access Program available for patients with invasive fungal infections either resistant to or intolerant of standard antifungal agents

Acknowledgements

We thank the investigators, study personnel, monitoring staff, and patients from our study sites

Investigator/Medical Monitor	Institution
George Thompson	University of California - Davis
Luis Ostrosky	The University of Texas Health Science Center at Houston
Todd McCarty	University of Alabama at Birmingham (UAB)
Kathleen Mullane	University of Chicago
John Perfect	Duke University Medical Center (DUMC) - Division of Infectious Diseases
Andrew Chao	Augusta University Medical Center
Andrej Spec	Washington University School of Medicine - Division of Infectious Diseases
Galia Rahav	Sheba Medical Center
Ilana Oren	Rambam Health Care Campus
Ronen Ben-Ami	Tel Aviv Sourasky Medical Center
Ricard Ferrer Roca	Hospital Universitario Vall D Hebron
Esperanza Merino de Lucas	Hospital General Universitario de Alicante
Esther Calbo Sebastian	Mutua de Terrassa - Servicio de enfermedades infecciosas
Oliver Cornely	Universitaetsklinikum Koeln Klinik I fur Innere Medizin ~~Uniklinik Koln~~
Daniel Teschner	Universitaetsmedizin der Johannes Gutenberg-Universitaet Mainz - III. Medizinische Klinik Haematologie/Onkologie
Johann Motsch	Universitaetsklinikum Heidelberg Klinisches Studienzentrum Chirurgie
Patrick Biston	CHU de Charleroi - Hopital Civil Marie Curie
Pierre Bulpa	University Hospital Mont-Godinne
Mickael Aoun	Institut Jules Bordet
Maya Hites	Clinique Universitaire de Bruxelles - Hopital Erasme