New Kids on the Block: Antimicrobials to Watch in Clinical Practice

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Allina Health

Antimicrobial Stewardship | SUMMIT

Objectives

- Upon completion of this lecture, participants should be able to:
  - Understand the process for FDA approval of new antimicrobials
  - Describe newly approved antimicrobials and their niche in the current infectious diseases landscape.
  - Identify what antimicrobials may be coming to market soon.

Disclosures

- We have no disclosures to provide

WHO data

97 products (57 antibiotics and 40 non-traditional antibacterial agents) in clinical development

32 of these antibiotics active against WHO bacterial priority pathogens

19 against *M. tuberculosis*

5 against *C. difficile*

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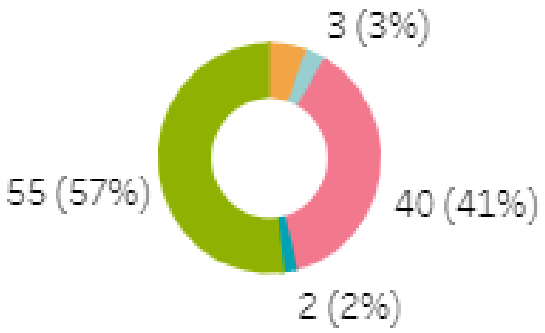
Antibacterial products in clinical development for priority pathogens (who.int)

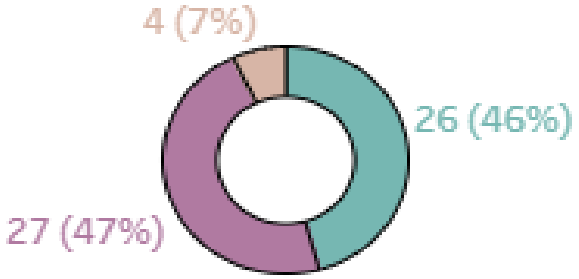
C.1. Route of administration



N=97

Route of administration
- Inhalation
- Intra-articular
- Intravenous
- Irrigation
- Oral

C.2. Innovative?



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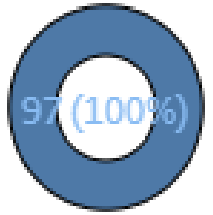
Innovative?
- Yes
- No
- Inconclusive

C.3. New chemical entity (NCE)?



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NCE?
- Yes

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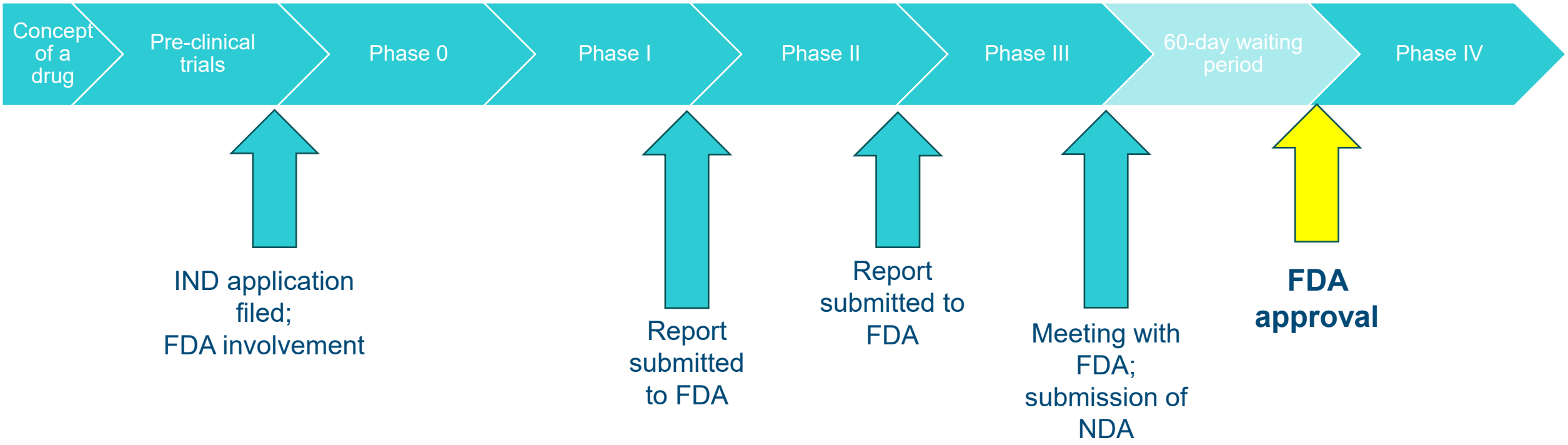
Antibacterial products in clinical development for priority pathogens (who.int)

Overview of medication approval process



- Overall success rate of ~16% to bring an antibacterial from drug IND to FDA approval

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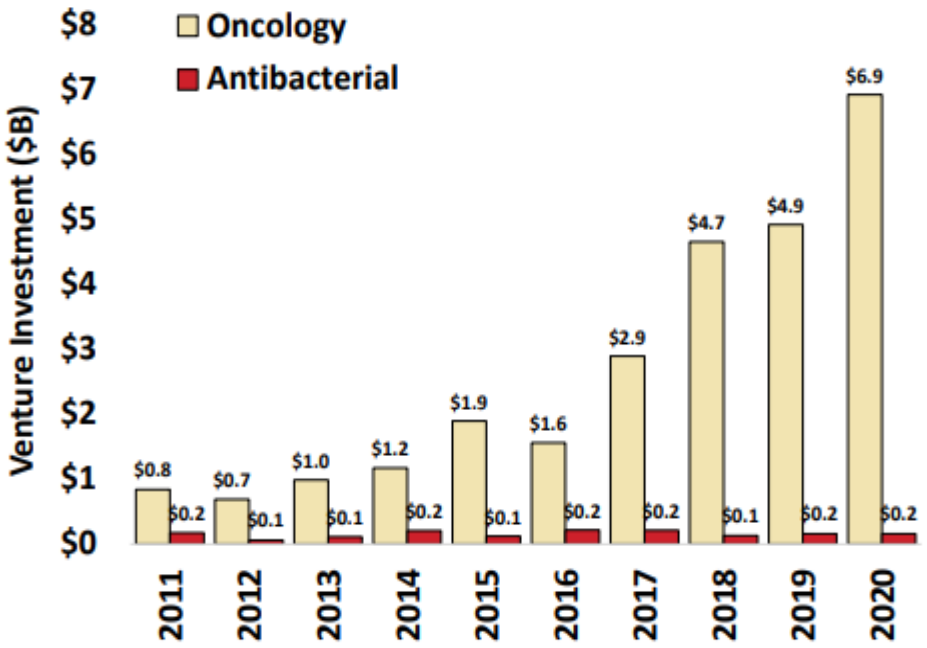
Thomas, D., et al. (2021) BIO Industry Analysis, Informa Pharma Intelligence, QLS Life Sciences. Clinical Development Success Rates and Contributing Factors 2011–2020. (Available at www.bio.org/iareports

Why are we not getting new antibiotics?

- A cycle of investment/innovation/revenue from biotechnology and pharmacologic industries
- Investment in antibiotic innovation is inadequate to support the cycle
  - One assessment showed the cost of taking a new drug from concept to market is > $1.3B
- This all leads to less companies innovating new products

2011-2020 VENTURE INVESTMENT INTO U.S. COMPANIES WITH LEAD NOVEL DRUG PROGRAMS IN ONCOLOGY VS. ANTIBACTERIALS



DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of health economics*, *47*, 20-33.

FDA's attempt to fix the pipeline

FDA QIDP designation

17 antimicrobial therapies approved from 2012-2022 via the QIDP pathway

Dalbavancin, oritavancin

Ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, cefiderocol

Pretomanid

Isavuconazonium sulfate

Ibrexafungerp

NEW TO MARKET

New to market

Aztreonam-avibactam (Emblaveo)

- MDR Gram-negative infections

Gepotidacin (Blujepa)

- Uncomplicated UTIs in females

Lenacapavir (Yeztugo)

- HIV PrEP

Fosfomycin IV (Contepo)

- Complicated UTIs

Group question

If you could have a drug to treat any infectious disease state, what infection would you like to target?

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Let’s look at what’s coming

Gonorrhea

Group question

How many of you have wished there was a reliable oral option for the treatment of gonorrhea?

Zoliflodacin

MOA: Spiropyrimidinetrione

Activity against MDR *Neisseria gonorrheae, Chlamydia trachomatis, Chlamydophila pneumonia, Mycoplasma genitalium*, and ureaplasma spp.

Developed with public-private partnership (GARDP & Innoviva)

QIDP designation for FDA priority review

FDA accepted NDA application on June 10, 2025

Zoliflodacin: Evidence

Phase 3 multi-Center, open label, non-inferiority RCT

Zoliflodacin PO 3g vs. CRO 500mg IM + azithromycin PO 1000mg

Treatment of uncomplicated gonorrhoea

Primary outcome: Urogenital microbiological cure rate

- 90.9% (zoliflodacin) versus 96.2% (SOC)*
- Included patients w/ MDR gonorrhea strains

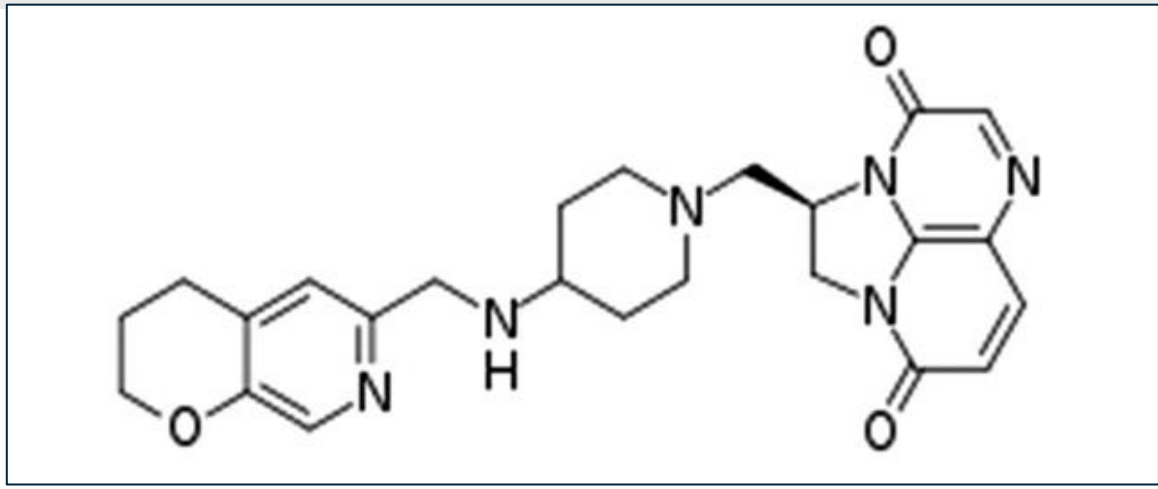
No serious ADEs or deaths*

*Per Clinicaltrials.gov; study not yet published in peer-reviewed journal

Gepotidacin

- **MOA**
  - First in-class **triazaacenaphthylene antibiotic**
  - Inhibits bacterial DNA replication via type II topoisomerase enzymes

- FDA accepted for priority review on Aug 11
  - PDUFA date Dec 11



Gepotidacin

EAGLE-1 – treatment of urogenital gonorrhea

- Primary endpoint of microbiological response at the test of cure visit 3-7d after treatment
- Met non-inferiority endpoint compared to IM ceftriaxone + azithromycin PO

Other indications?

- NTM and TB
- Ureaplasma & mycoplasma infections
- Pneumonia

Antifungals

Group question

What fungal pathogen is the most challenging to treat with currently available antifungal options?

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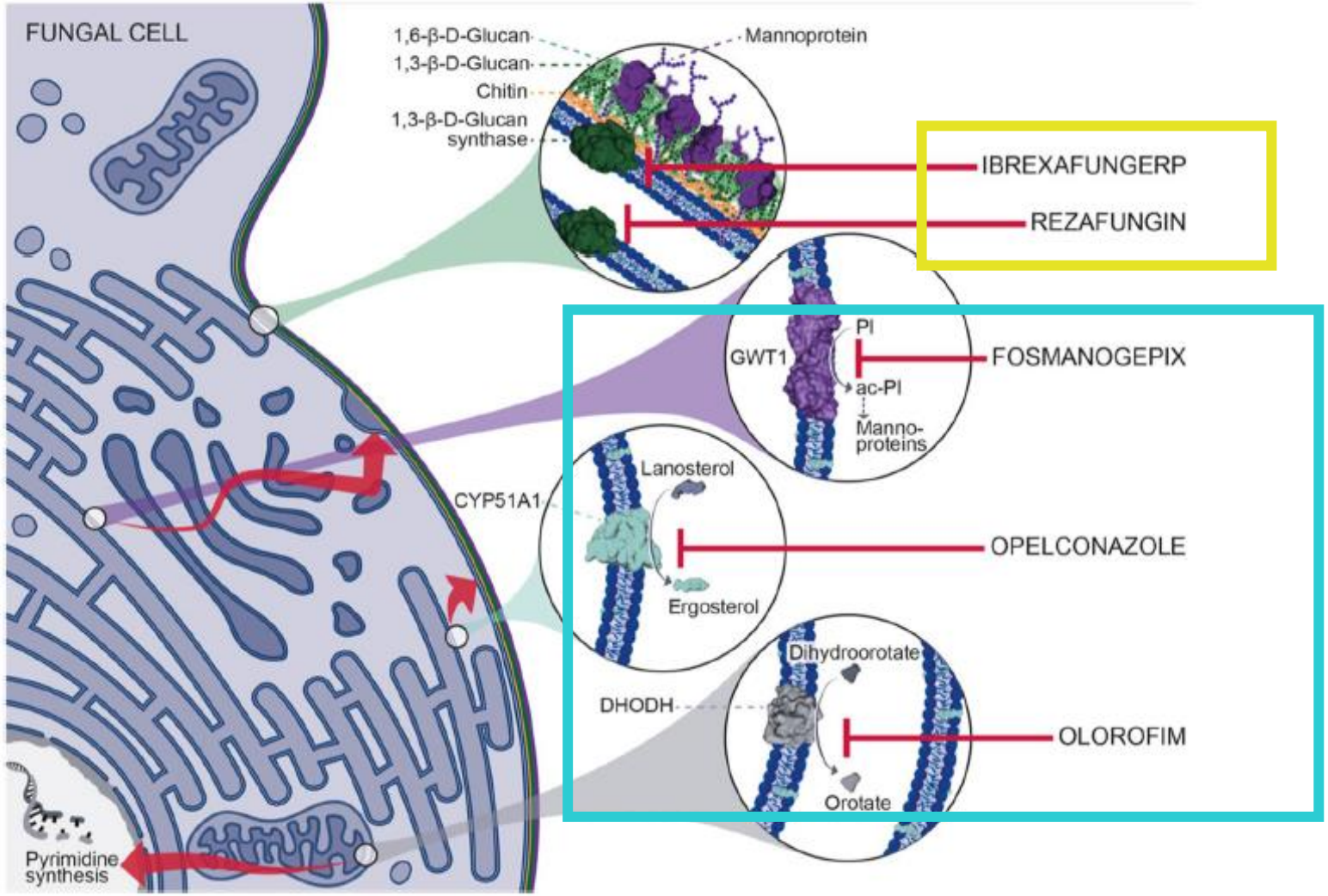
Antifungal Pipeline



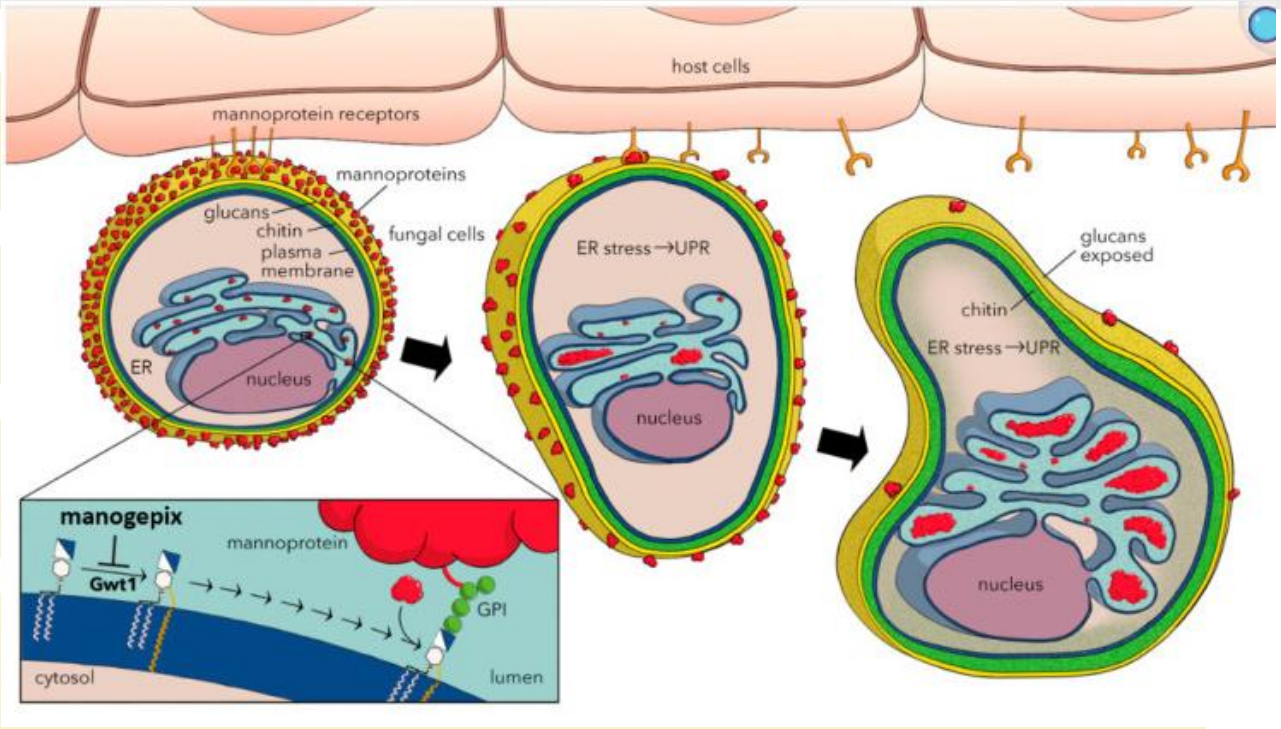
Fosmanogepix

Class: N-phosphono-oxymethyl drug (novel)

MOA: Gwt1 enzyme inhibitor

Current status: Phase III

IV and PO



Spectrum: *Candida, Aspergillus, Fusarium, Scedosporium, Cryptococcus, Cladosporium*, among other difficult-to-treat invasive fungal infections

Developed by Amplyx Pharmaceuticals (now acquired by Pfizer)

Fosmanogepix Clinical Trials

NCT03604705 (phase II): Single arm treatment for Candidemia

Outcome: Treatment success at end of study drug treatment

Results: 80% (16/20) in mITT met primary endpoint; day 30 survival was 85%

Safety: Well tolerated with no treatment-related SAEs/discontinuations (most common AEs included diarrhea, vomiting, peripheral edema & pleural effusion each in 3 participants)

APEX (phase II): Single arm treatment for *C. auris* candidemia or candidiasis

Outcome: Treatment success at end of study drug treatment

Results: 89% (8/9) met primary endpoint; day 30 survival also 89%

Safety: No treatment related treatment-emergent adverse events or SAEs identified (although all patients had adverse events during the time of treatment)

Fosmanogepix Clinical Trials

- **AEGIS (phase II): Single arm treatment for *Aspergillus* spp. and rare molds**
  - Outcome: Percentage of patients who died after the first dose through day 42
  - Results: All-cause mortality was 25%, treatment success was 40%, and treatment failure was 50%
  - Safety: All participants experienced at least 1 treatment-emergent adverse event and 13/21 (61.9%) experienced a serious adverse event
- **Phase III launched in July 2025**

Opelconazole

- Class: Triazole
- MOA: inhibition of ergosterol synthesis
- Current status: Phase III
- Administered via inhalation (limited systemic exposure)
- Spectrum: *Candida, Cryptococcus, Aspergillus, & Rhizopus* spp.
- Developed by Pulmocide Ltd. (London, UK)

Opelconazole Clinical Trials

OPERA-S (phase II): Opelconazole vs standard of care for *Aspergillus* prophylaxis/pre-emptive therapy in lung transplant

Outcome: Pending

OPERA-T (phase III): Opelconazole vs placebo for refractory invasive aspergillosis

Currently recruiting

Olorofim

- Class: Orotomide (novel)
- MOA: novel dihyroorotate dehydrogenase enzyme inhibitor
- Current status: Phase III; Breakthrough Therapy, Orphan Drug; QIDP designation for FDA priority review
- IV and PO
- Spectrum: *Aspergillus,* Dimorphics, *Scedosporium, Lomentospora, Scopulariopsis* (and other invasive molds with limited treatments)
- Developed by F2G, Inc. (Manchester, UK)

Olorofim Clinical Trials

FORMULA-OLS (phase II): Single arm for invasive fungal infections with limited treatment options

Outcome: day 42 overall response

Results: 28.7% (58/202)

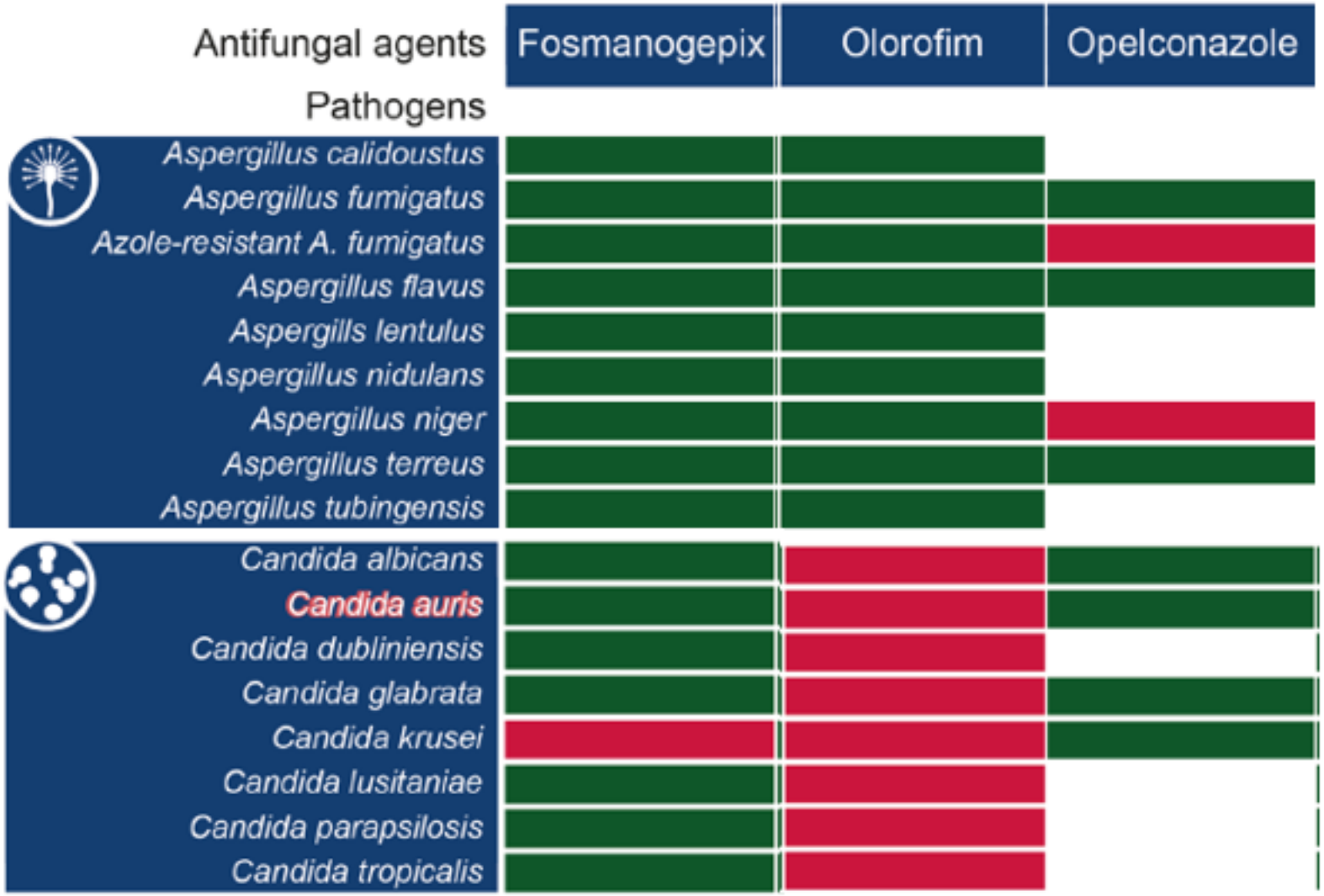
Safety: LFT elevations at least possibly due to olorofim occurred in 10% (n=20) & mild or moderate GI intolerance reported in 10% (n=20)

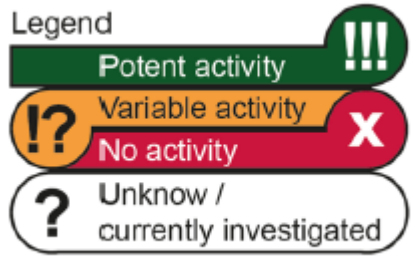
OASIS (phase III): Olorofim vs Ambisome/standard of care for invasive aspergillosis

Outcome: day 42 all-cause mortality

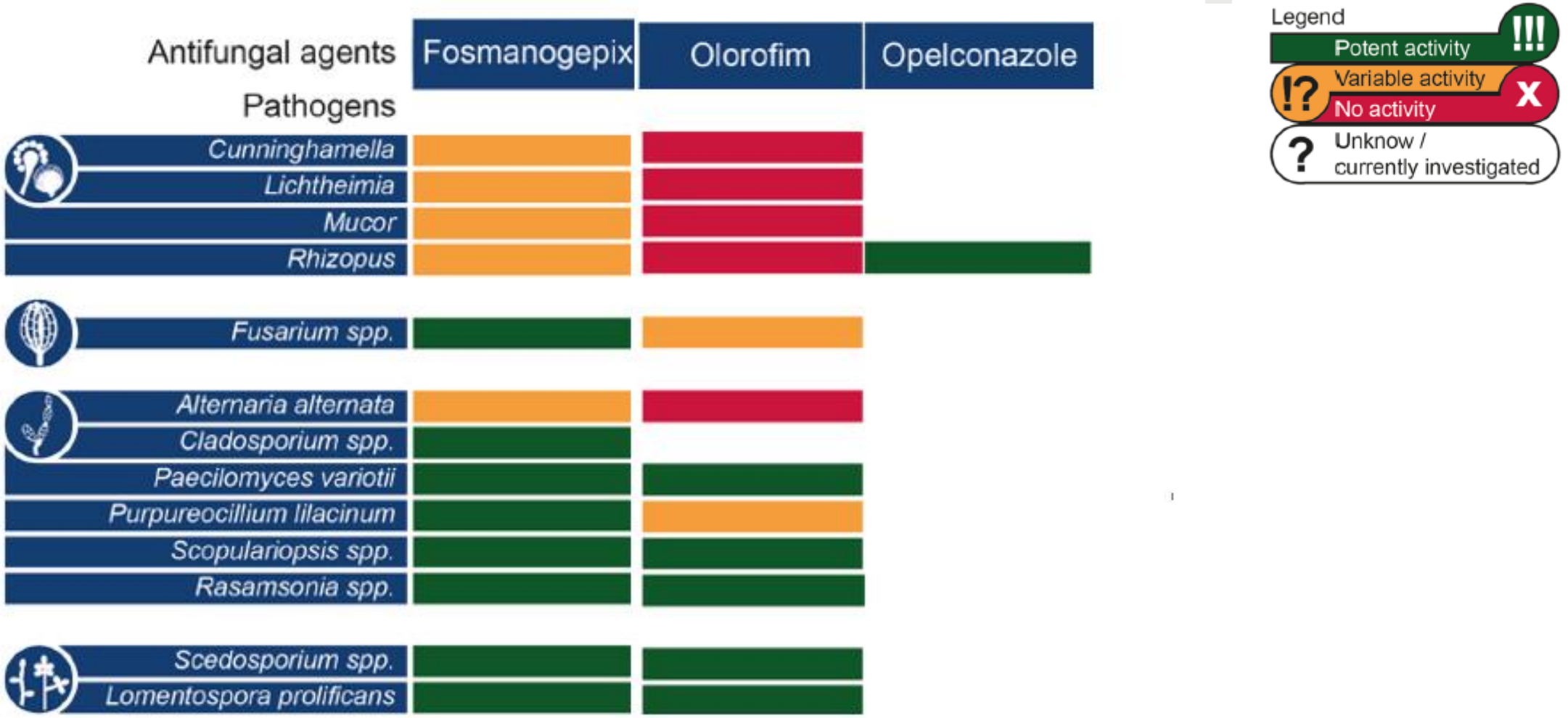
Results: TBD

Antifungal Pipeline Spectrum

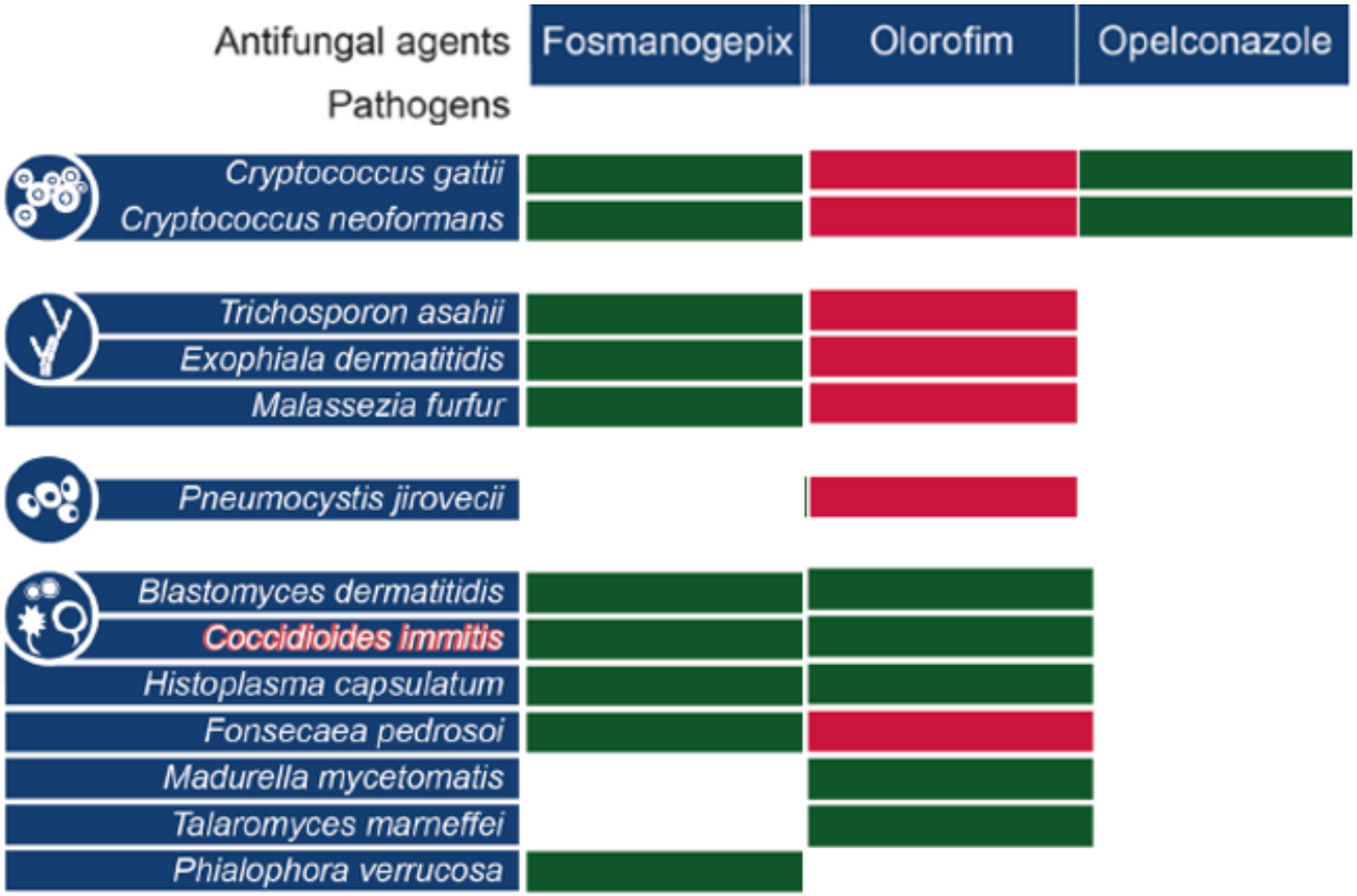


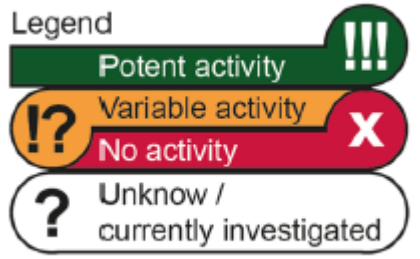


Antifungal Pipeline Spectrum



Antifungal Pipeline Spectrum





Expanded Access to Pipeline Antifungals

Access Programs Available

- Fosmanogepix
- Olorofim

Not Available

- Opelconazole

Summary

Recently Approved

- Aztreonam-avibactam (Emblaveo)
- Gepotidacin (Blujepa)
  - uUTIs
- Lenacapavir (Yeztugo)
- Fosfomycin IV (Contepo)

Late Clinical Pipeline

- Gonorrhea
  - Zoliflodacin
  - Gepotidacin
- Antifungals
  - Fosmanogepix
  - Opelconazole
  - Olorofim

- **Donnie, a 35 yoM, is newly diagnosed with gonorrhea. He has extreme needlephobia and absolutely refuses to receive an injection of ANY. TYPE. What would you do to treat his infection?**

A. Restrain him and give him IM ceftriaxone 500mg x1 dose

B. Try some azithromycin 500mg PO x1 dose

C. Prescribe gepotidacin 3000mg PO BID x 2 doses

Question #1: Answers

- **Donnie, a 35 yoM, is newly diagnosed with gonorrhea. He has extreme needlephobia and absolutely refuses to receive an injection of ANY. TYPE. What would you do to treat his infection?**

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Question #2

- **Which of the novel antifungals has a notable gap in coverage of *Candida* species?**

A. Olorofim

B. Opelconazole

C. Fosmanogepix

Question #2: Answers

- **Which of the novel antifungals has a notable gap in coverage of *Candida* species?**

A. Olorofim

B. Opelconazole

C. Fosmanogepix

- **Which upcoming antifungal agent is administered via inhalation route?**

A. Gepotidacin

B. Opelconazole

C. Ibrexafungerp

Question #3: Answers

- **Which upcoming antifungal agent is administered via inhalation route?**

A. Gepotidacin

B. Opelconazole

C. Ibrexafungerp

References

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Questions?

Image from New Kids On The Block: Charity Work & Causes - Look to the Stars