LESSONS LEARNED FROM THE CRESEMBA™ DEVELOPMENT PROGRAM

August 4, 2020 – FDA Workshop

Development Considerations of Antifungal Drugs to Address Unmet Medical Need

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ORPHAN DRUG ACT (1983)

Definition: Any disease or condition which affects <200,000 persons in the US

- Estimated 7,000 rare diseases

Financial incentives

7 year market exclusivity

50% tax credit for clinical testing

Waiver of FDA user fees

Orphan grants program

Non-financial incentives

Does not provide a separate regulatory standard

Common Challenges for OD and AF Drug Development

Small number of eligible patients

Limited information on disease severity and rate of progression

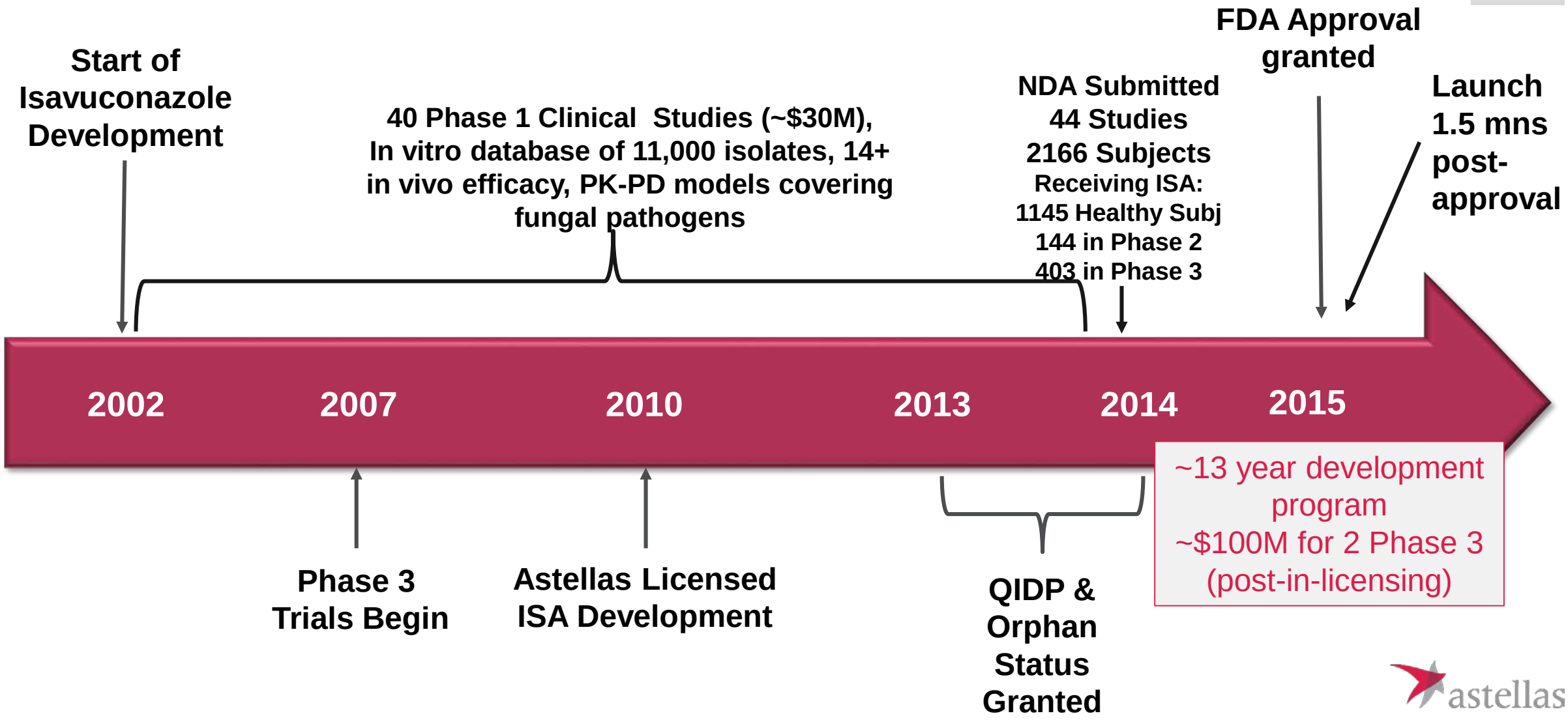
Lack of validated endpoints

Standard of care may not be approved by regulatory authorities

May not be ethical to use a placebo control

CRESEMBA® DEVELOPMENT PROGRAM

CRESEMBA* DEVELOPMENT PROGRAM LEADING TO APPROVAL



*Cresemba or isavuconazonium sulfate is the produg, of the triazole antifungal active moiety isavuconazole

CRESEMBA (ISAVUCONAZONIUM SULFATE)

Isavuconazonium sulfate is a water soluble prodrug

The active moiety is isavuconazole a broad-spectrum, triazole antifungal developed for the treatment of invasive fungal disease (IFD) in adults

Isavuconazole has potent activity against *Aspergillus* spp., and Mucorales in vitro, and in animal models[1,2]

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[1]Lepak *et al* 2013 *Antimicrob Agents Chemother* 57:6284–9
[2]Luo *et al* 2014 *Antimicrob Agents Chemother* 58:2450–3

INVASIVE FUNGAL INFECTIONS: KEY POINTS

Typically occur in severely immunocompromised patients

- High comorbidities

Rare infections

- ~12,000 / year aspergillosis in US[1,2]
- ~500 / year mucormycosis in US[3]

Difficult to diagnose and treat

- High morbidity and mortality
- Limited therapeutic options

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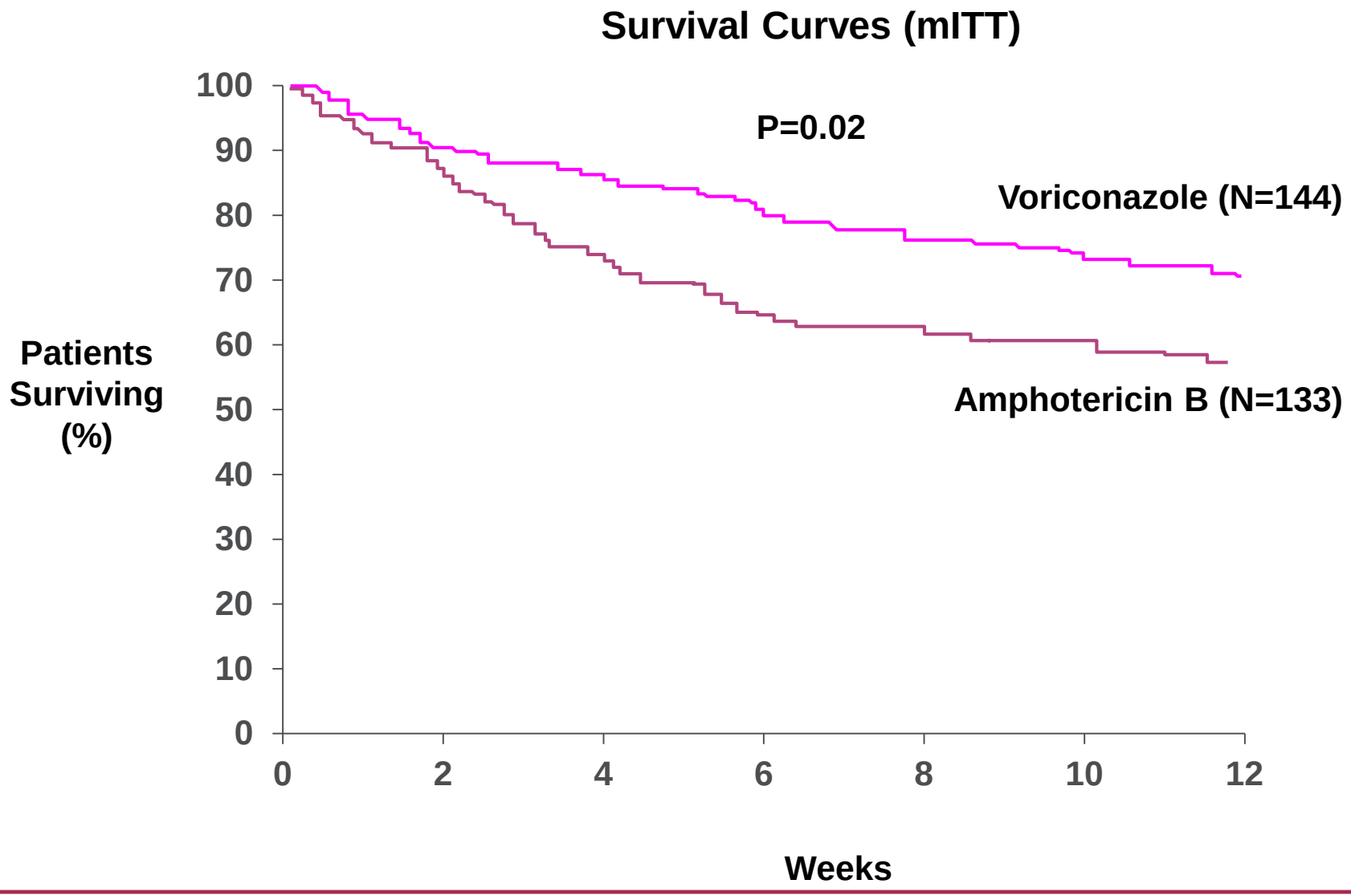
[1]Tong KB, Int J Infect Dis. 2009;13:24-36; [2]Warnock DW. Jpn J Med Mycol. 2007;48(1):1-12; [3]Rees JR, Clin Infect Dis. 1998;27:1138-47

VORICONAZOLE: STANDARD OF CARE IN INVASIVE ASPERGILLOSIS



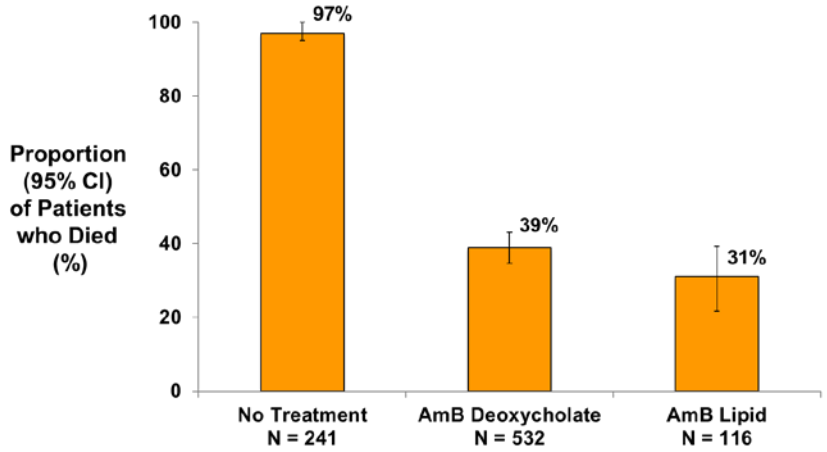
Herbrecht et al., N Engl J Med. 2002 Aug 8;347(6):408-15. doi: 10.1056/NEJMoa020191

INVASIVE MUCORMYCOSIS: TREATMENT APPROACH

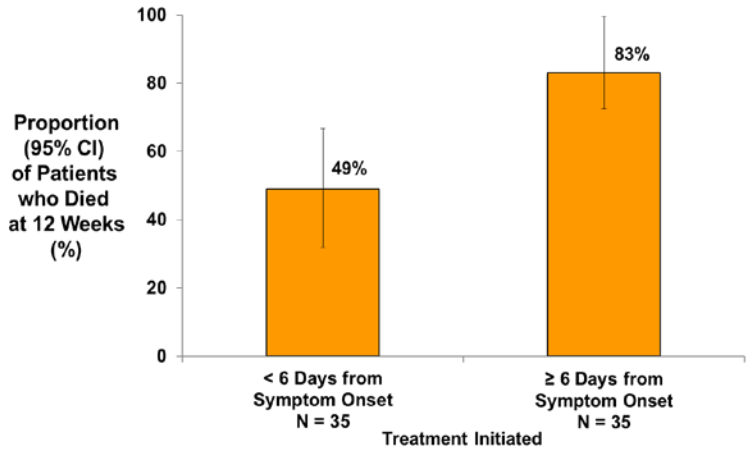
Multimodal approach including[1]

- Treatment of underlying condition
- Immediate antifungal therapy
  - Amphotericin B – Lipid formulation
  - Posaconazole as salvage therapy
- Surgical debridement
  - Often leads to blindness, facial disfiguration, or amputations

Mortality Associated with Invasive Mucormycosis[2]



Impact of Delayed Initiation of Mucorales Active Antifungal Therapy[3]



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[1]Cornely et al, Clin Microbiol Infect. 2014;20(Suppl 3):1-4; [2]Roden et al., Clin Infect Dis. 2005;41:634-53; [3]Chamilos et al. Haematologica. 2006;91:986-9.

MUCORMYCOSIS: CAN AN ACTIVE CONTROLLED STUDY BE CONDUCTED?

Extremely rare condition

- No randomized controlled trials

Amphotericin B deoxycholate

- Only approved therapy
- Only available IV
- Toxicity limits use particularly in renally impaired patients
- Lipid formulations are the standard of care, but are not approved for mucormycosis

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CRESEMBA® PHASE 3 PROGRAM

Study 0104 - SECURE

- Primary support for treatment of Invasive Aspergillosis
- Randomized, double-blind, non-inferiority study vs. voriconazole
- Treatment up to 84 days
- 516 patients enrolled in the primary analysis population (ITT)

Study 0103 - VITAL

- Primary support for treatment of Invasive Mucormycosis
- Open label study in adults; no concurrent control
- Included a range of rare moulds (including Mucorales), yeasts, and dimorphic fungal infections
- Treatment duration up to 180 days
- Primary therapy, refractory, intolerant
- 146 patients received Cresemba

INVASIVE MUCORMYCOSIS: MATCHED CASE-CONTROL METHODS

- **Cresemba for primary therapy from the VITAL Study**
- **Amphotericin* for primary therapy from Fungiscope**
- **Matching criteria**
  - Severe disease
  - Hematologic malignancy
  - Therapeutic debridement
- **Matching conducted independently and blinded to outcomes**
  - Up to 3 controls for each VITAL IM case
- **Day 42 mortality rates analyzed**

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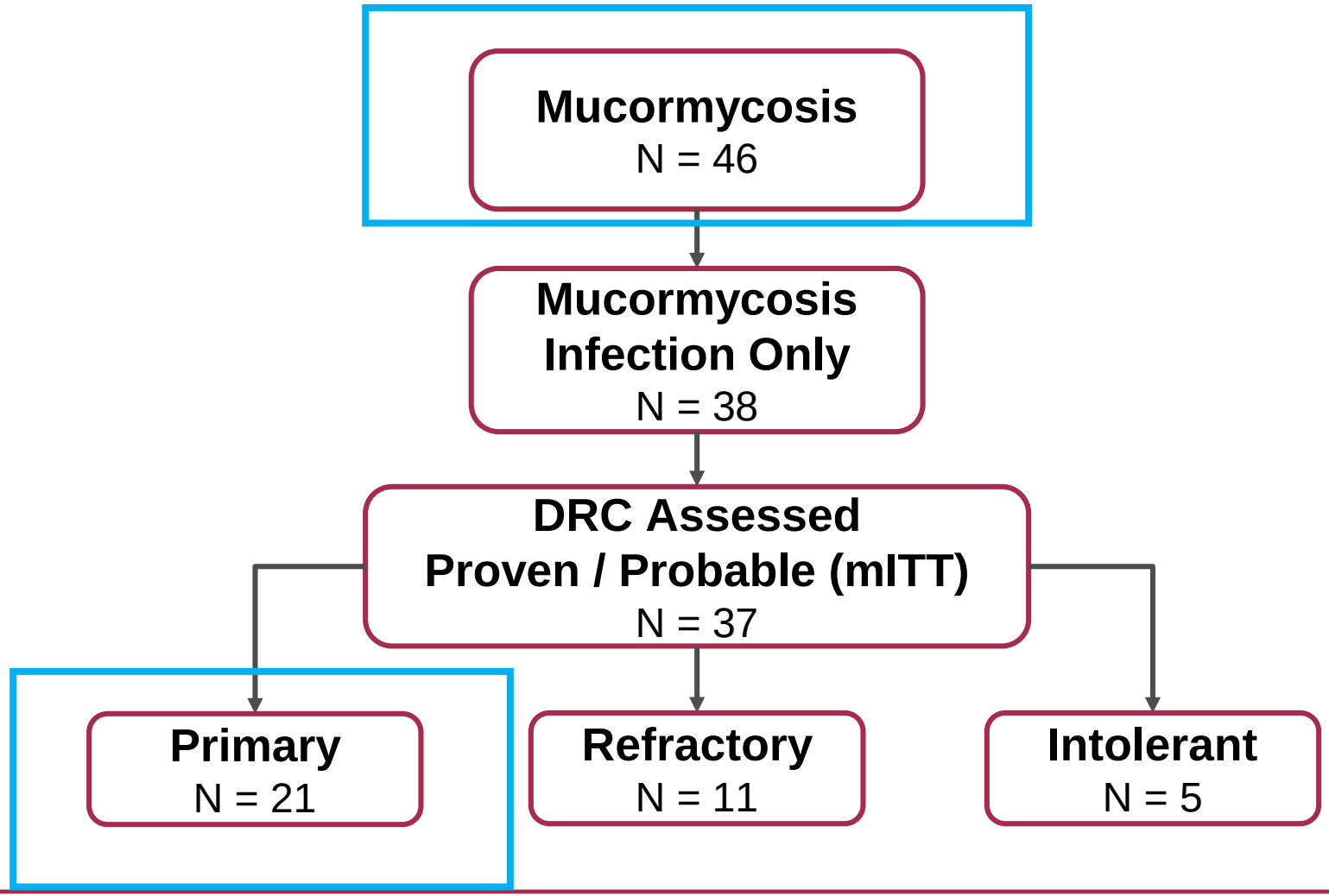
*Amphotericin B deoxycholate or lipid formulations

Marty et al., Lancet Infect Dis. 2016 Jul;16(7):828-837. doi: 10.1016/S1473-3099(16)00071-2.

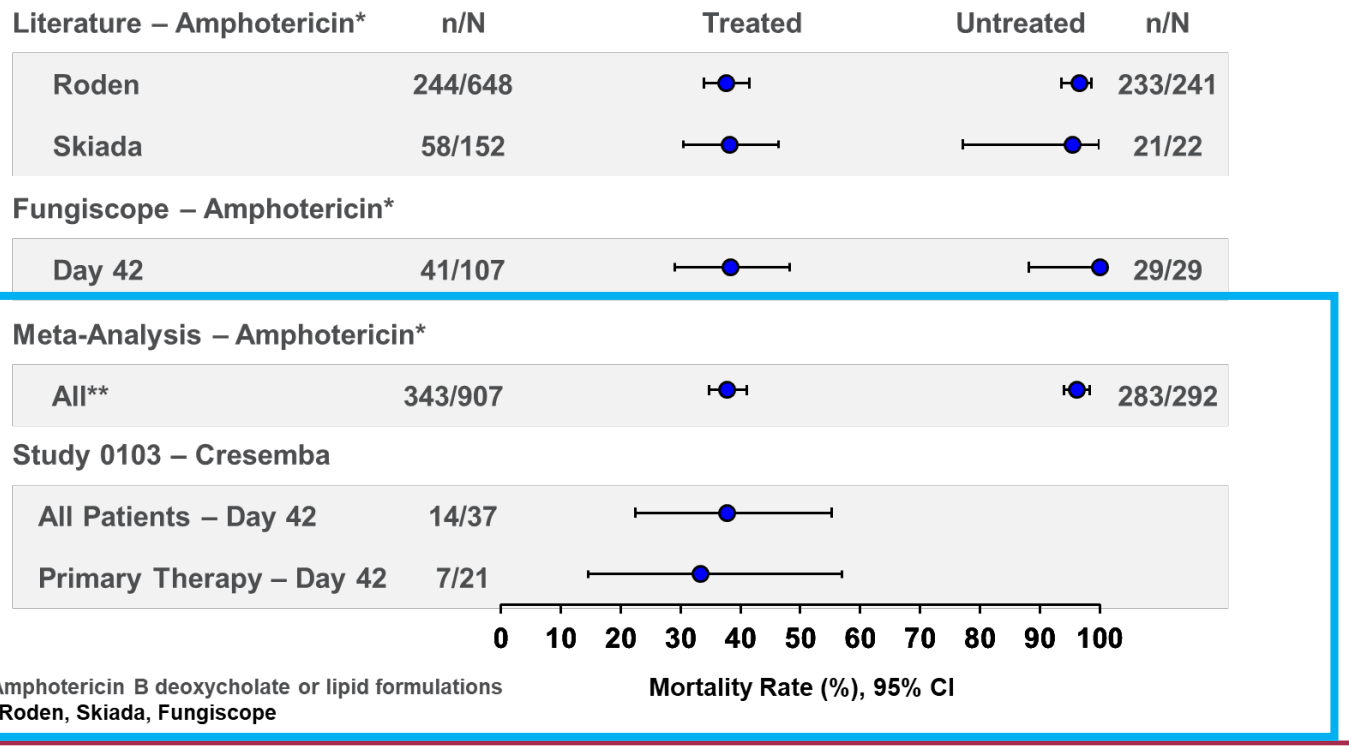
STUDY 0103/VITAL: MUCORMYCOSIS ANALYSIS POPULATIONS



Marty et al., Lancet Infect Dis. 2016 Jul;16(7):828-837. doi: 10.1016/S1473-3099(16)00071-2**.**

STUDY 0103/VITAL: ALL-CAUSE MORTALITY MUCORMYCOSIS

Outcome mITT Mucorales	Primary N = 21 %	Refractory N = 11 %	Intolerant N = 5 %	Total N = 37 %
Day 42	33.3	45.5	40.0	37.8
Day 84	42.9	45.5	40.0	43.2



Marty et al., Lancet Infect Dis. 2016 Jul;16(7):828-837. doi: 10.1016/S1473-3099(16)00071-2.

21 CFR 314.126: ADEQUATE AND WELL CONTROLLED STUDIES

(v) *Historical control.* The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

CANDIDEMIA / INVASIVE CANDIDIASIS

LESSONS LEARNED

ACTIVE: CRESEMBA VS CASPOFUNGIN IN INVASIVE CANDIDIASIS

Primary objective	**Compare the efficacy of treatment with Cresemba vs caspofungin in patients with candidaemia or other invasive *Candida* infections**
Study design	Multi-national, double-blind, randomised, non-inferiority study of intravenous (IV) Cresemba versus IV caspofungin; switch to oral treatment allowed from Day 11
Study population	450 adult patients with candidaemia or other invasive *Candida* infections to ensure at least 85% power to demonstrate non-inferiority of isavuconazole to caspofungin at a non-inferiority margin of 15%
Primary endpoint	Overall response* at end of IV treatment (EOIVT) as determined by an independent, blinded Data-Review Committee (DRC) in the mITT population
Key secondary efficacy endpoints	DRC-assessed overall response at Follow-Up 1 (i.e., 2 weeks after end of treatment [EOT]) All-cause mortality by Day 14 and Day 56

*Successful overall response required successful clinical and mycological response plus no use of alternative systemic antifungal therapy (SAT) within 48 hours after the last dose of study drug
mITT, modified intent-to-treat population

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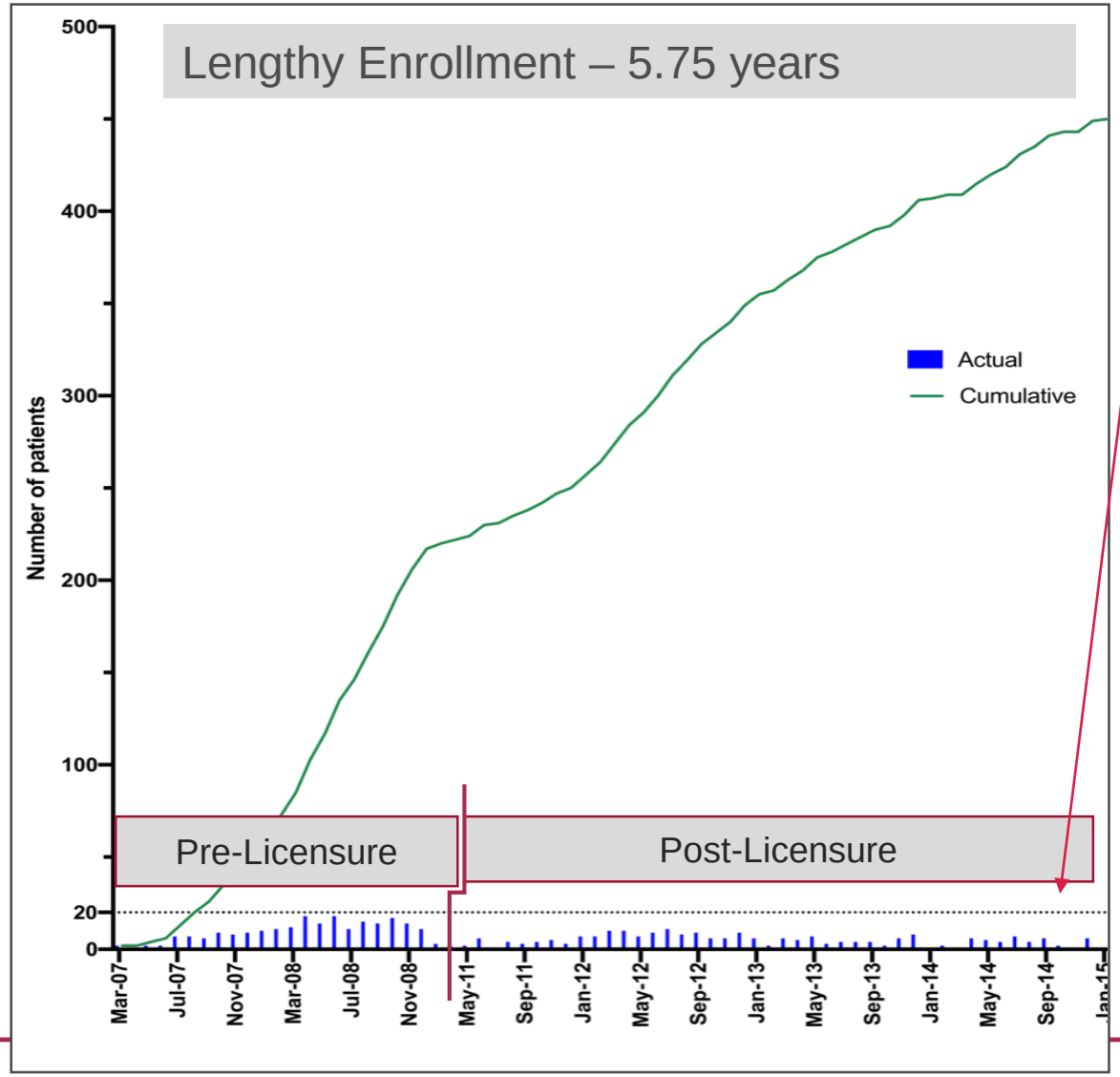
Kullberg et. al. Clinical Infect Dis. 2019 May 30;68(12):1981-1989. doi: 10.1093/cid/ciy827

ACTIVE INVASIVE CANDIDIASIS TRIAL ENROLLMENT CHALLENGES



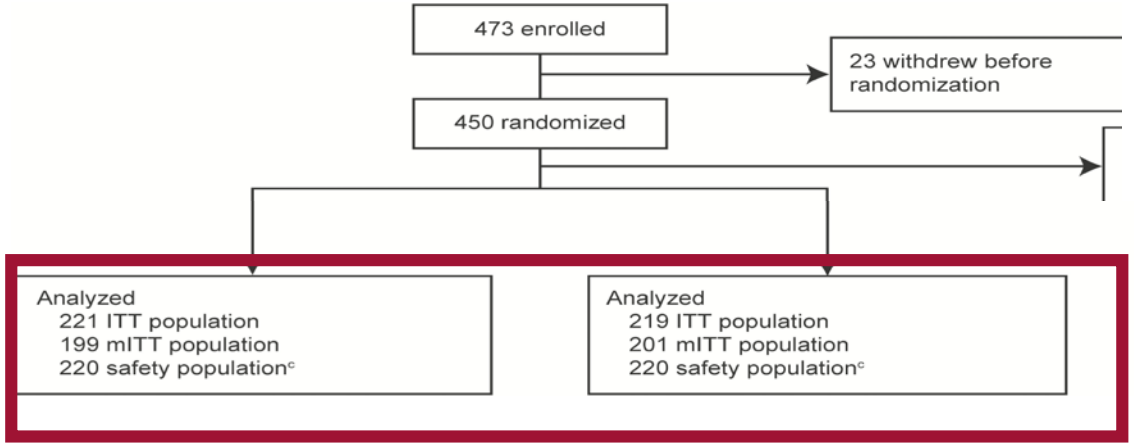
Monthly enrollment never over 20 patients

- 30 countries of which 25 enrolled a patient
- 80% of enrollment in 8 countries
- 158 sites of which 111 enrolled at least 1 subj (70%); 43% enrolled 2 or less

- Focus on smaller set of countries?
  - Each new country adds $$$ to the operational costs – CHOSE CAREFULLY

Not a “more is better” situation!

MITIGATIONS



Modified Figure 1. Patient flow[1]. Abbreviations: ITT, intent-to-treat; mITT, modified ITT

- Closed non-performing sites/countries mid-way through the trial.
- Re-examined the sample size assumptions:
  - actual vs projected (80%) evaluability rate
  - study power

Adjustment

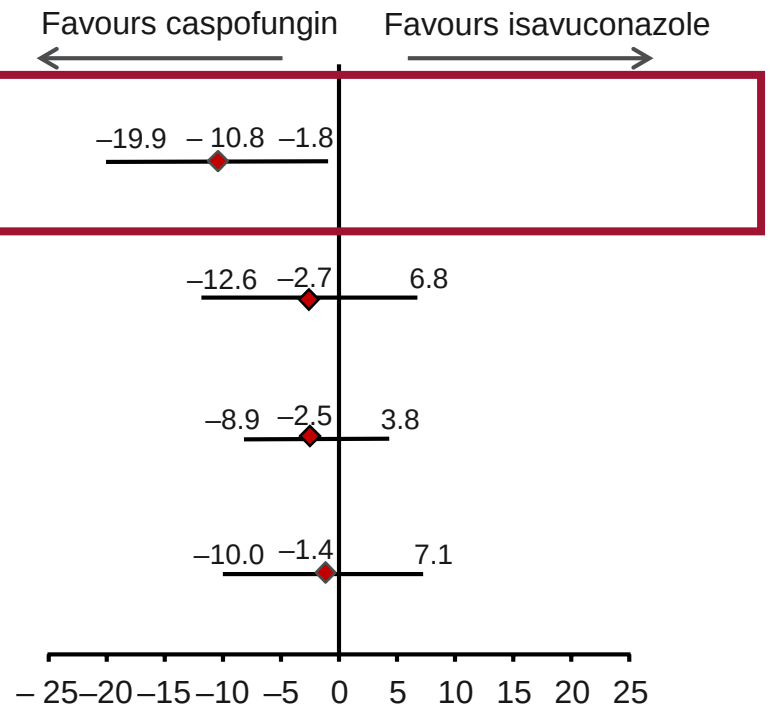
- 526 to be randomized to get 420 in mITT at 90% power → 420 to get 350 in mITT at 85% power

Final evaluability rate was ~90%

[1]Kullberg, et. al. *Clin Infect Dis*, Volume 68, Issue 12, 15 June 2019, Pages 1981–1989, https://doi.org/10.1093/cid/ciy827

TREMENDOUS EFFORT HOWEVER… TRIAL DIDN'T MEET PRIMARY ENDPOINT

Category, n (%)	Isavuconazole (n = 199)	Caspofungin (n = 201)
Successful overall response at EOIV*	120 (60.3)	143 (71.1)
Successful overall response at EOT + 2 weeks	109 (54.8)	115 (57.2)
All-cause mortality Day 14	29 (14.6)	25 (12.4)
All-cause mortality Day 56	61 (30.7)	60 (29.9)



Adjusted difference (%; 95% CI) between isavuconazole versus caspofungin

*Stratified by geographical region and baseline neutropenia status

Taken from Kullberg et. al. ECCMID 2016 oral presentation

LIFE-CYCLE POST-APPROVAL

Post-approval commitments defined by the FDA

1. **Registry - clinical efficacy-related outcome data on patients with IM or infection with non-*fumigatus Aspergillus* species.**
2. **In vitro micro-surveillance - prospective study over a 5-year period**
3. **2-year CARC rat & mouse**

Costs ~$10mil

Not including costs of general product upkeep, including manufacturing, commercial activities, PV activities, MSL team, etc

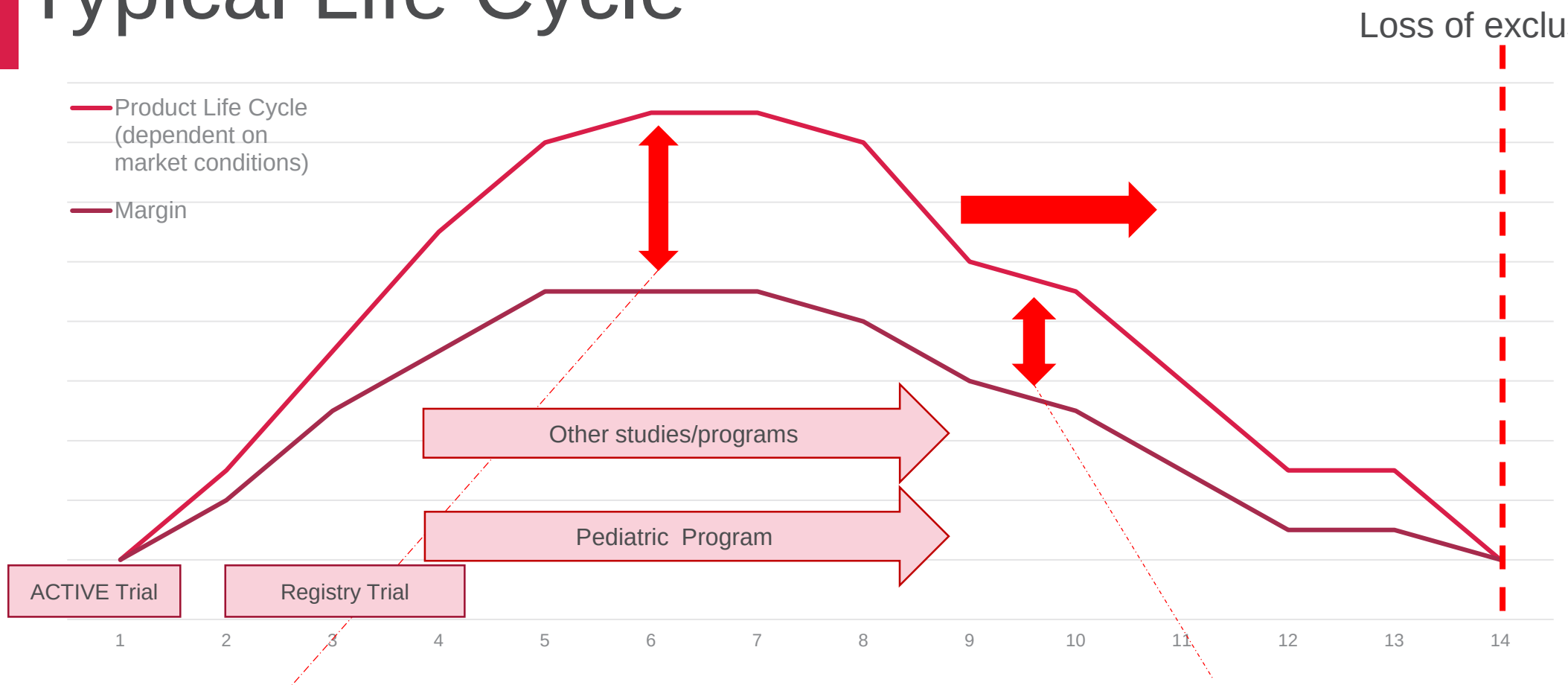
Pediatric Development

- **Waived in US due to Orphan Drug Status**
- **Significant unmet need in pediatrics with IA and IM**

Costs ~$15-20 mil

- **Astellas, in collaboration with our partner, Basilea, are committed to generating data to support the safe and effective use of Cresemba in pediatric patients and is working closely with the FDA to define and complete the pediatric development for Cresemba.**

Typical Life Cycle



Source for funding additional activities

Additional LCM activities must either improve the life cycle value prior to LOE or grow future margin – improve blue curve or increase gap between curves, generating additional revenue potential to, at minimum, cover costs of investment

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TAKE HOME

- **Cresemba development program is not likely to be replicated**
- Each Phase 3 study costs in excess of $125K per patient; global footprint is required and study durations are long
- Alternative options to RCTs are available for orphan diseases per the regulations but generally accompany larger efficacy and safety trials in another invasive fungal disease
- High cost of AF drug development from discovery to the initial marketing authorization, post-approval commitments, pediatric development topped with the cost of product upkeep, such as commercial manufacturing, product education are not a sustainable business scenario today and weigh heavy on the decisions to reinvest post-approval.
  - Emphasizing the need to continue to introduce new push and pull incentives to continue investment in new AF compounds to address the significant unmet needs of patients.

THANK YOU