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# ICLAPRIM

## 2018 ESCMID/ASM Conference on Drug Development

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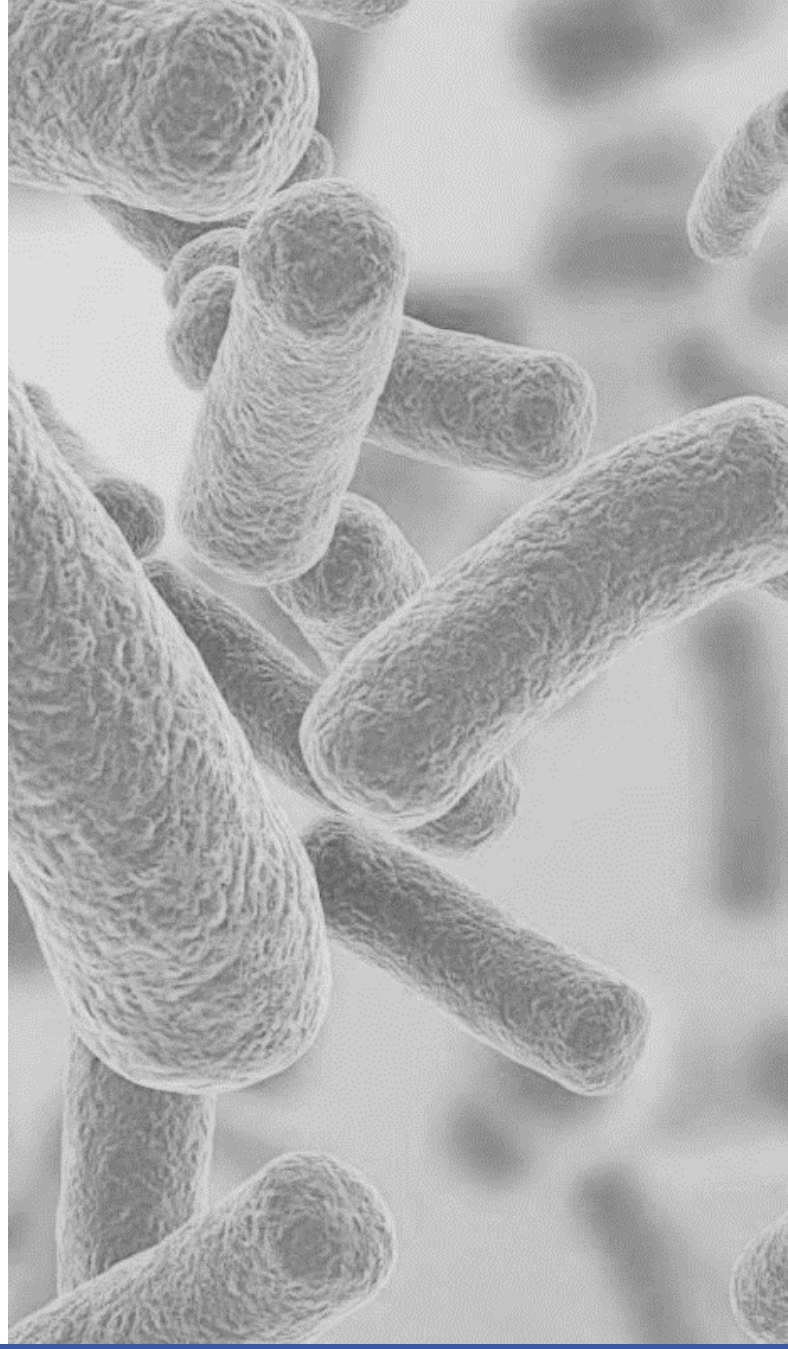

# Conflict of Interest

- I am an employee of Motif Bio.



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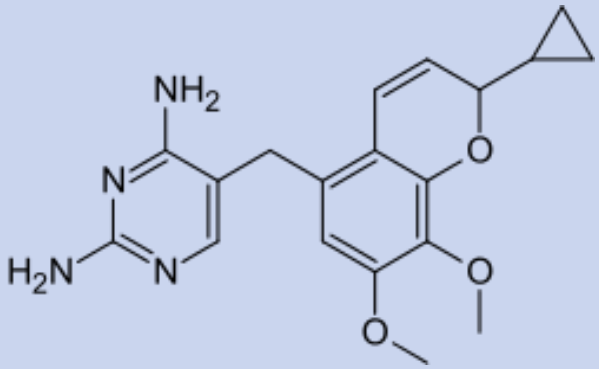
# Iclaprim: Product Overview

- Dihydrofolate reductase (DHFR) inhibitor
- Designed by Hoffman LaRoche to be more potent than TMP and to overcome TMP-resistant bacteria
- Rapidly bactericidal against nonsusceptible MRSA isolates/strains to vancomycin, linezolid and daptomycin
- Concentrates at sites of infection: skin and lung
- 3 target indications: ABSSSI, HABP/VABP, *S. aureus* lung infections in cystic fibrosis



Iclaprim

- Robust, well-established efficacy and safety data in over 1,400 humans
- Optimized iclaprim dose based on pharmacodynamic parameters associated with efficacy and safety
- Not nephrotoxic, no renal dosing or therapeutic drug monitoring
- QIDP and Fast Track Designation



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# Iclaprim: Mechanism of Action

## Cell Wall Synthesis

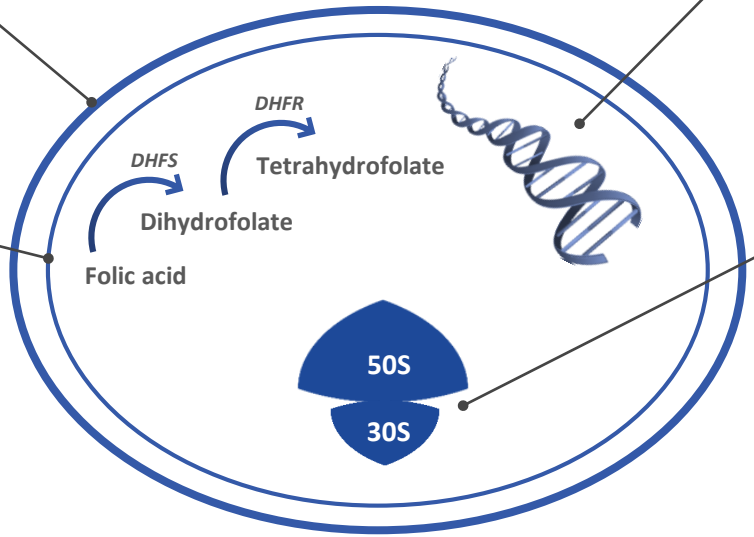
**Beta Lactams**
Carbapenems
Ceftazidime
Ceftaroline
Ceftobiprole
Dalbavancin
Oritavancin
Telavancin
Vancomycin

## Cell Membrane Integrity

Colistin
Daptomycin

## DHFRi*

**Iclaprim**
Trimethoprim




## Nucleic Acid Synthesis

**DNA Gyrase**
Ciprofloxacin
Delafloxacin
Gatifloxacin
Levofloxacin
Moxifloxacin
**RNA Polymerase**
Rifampin

## Protein Synthesis

**50S subunit**
Clindamycin
Lefamulin
Linezolid
Solithromycin
Tedizolid

**30S subunit**
Amikacin
Doxycycline
Eravacycline
Gentamicin
Kanamycin
Minocycline
Neomycin
Omadacycline
Streptomycin
Tobramycin

**Iclaprim is 8-32 times more potent than TMP and overcomes TMP-resistant bacteria due to F98Y**
**No need for combination therapy with a sulfonamide**

*Dihydrofolate reductase inhibitor



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# Iclaprim: *In Vitro* Activity – Global Surveillance

| $MIC_{50}$ / $MIC_{90}$ | | | | |
|---|---|---|---|---|
| **2015-2016 Isolates** | **Iclaprim** | **Vancomycin** | **Linezolid** | **Daptomycin** |
| **MRSA (n=314)** | **0.03 / 0.12** | **1 / 1** | **1 / 2** | **0.25 / 0.5** |
| MSSA (n=304) | 0.06 / 0.06 | 1 / 1 | 1 / 2 | 0.25 / 0.5 |
| *S. pyogenes* (n=159) | 0.015 / 0.03 | - | 1 / 1 | - |
| *S. agalactiae* (n=100) | 0.12 / 0.5 | - | 1 / 1 | - |

Data on file.



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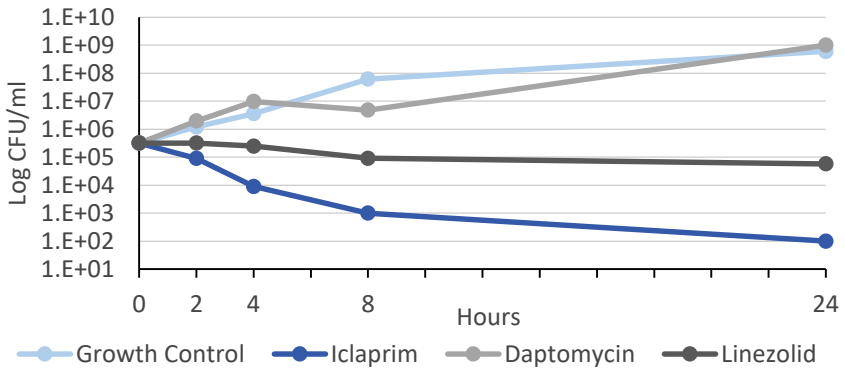
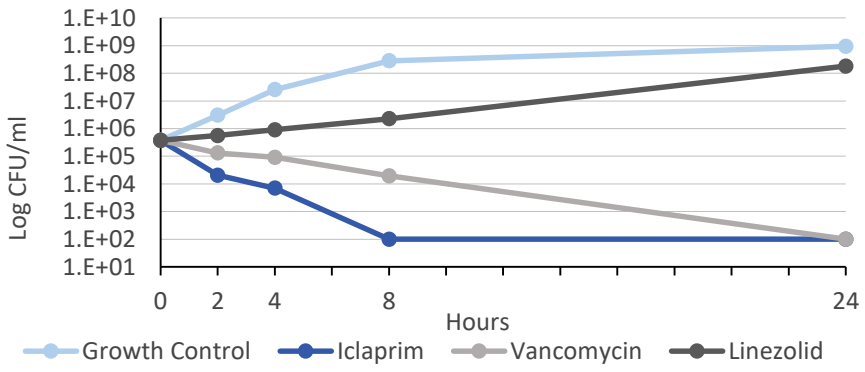
# Iclaprim: *In Vitro* Activity – Time Kill Curves

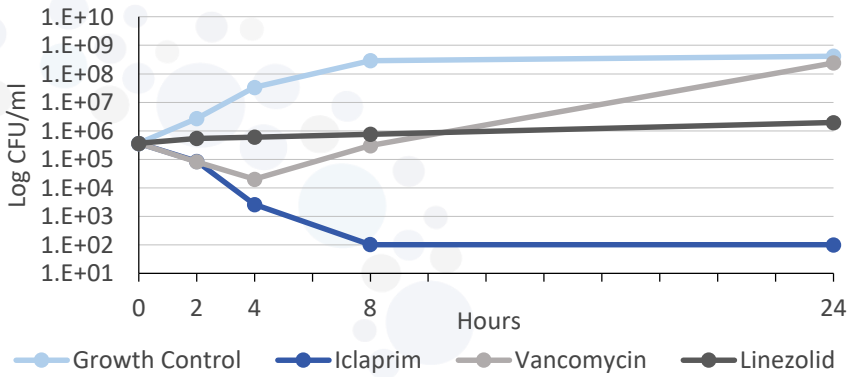
## MRSA, Daptomycin Resistant Strain (MIC ≥4 µg/mL), Clinical Isolate




## MRSA, Linezolid Nonsusceptible Strain (MIC ≥8 µg/mL), ATCC 986537, NRS271




## MRSA, Vancomycin Resistant Strain (MIC ≥32 µg/mL), ATCC 1409053, vanA positive




**Rapidly bactericidal against nonsusceptible MRSA isolates/ strains to vancomycin, linezolid and daptomycin**

Huang et al. Can J of Infect Dis Med Microbiol. 2017.



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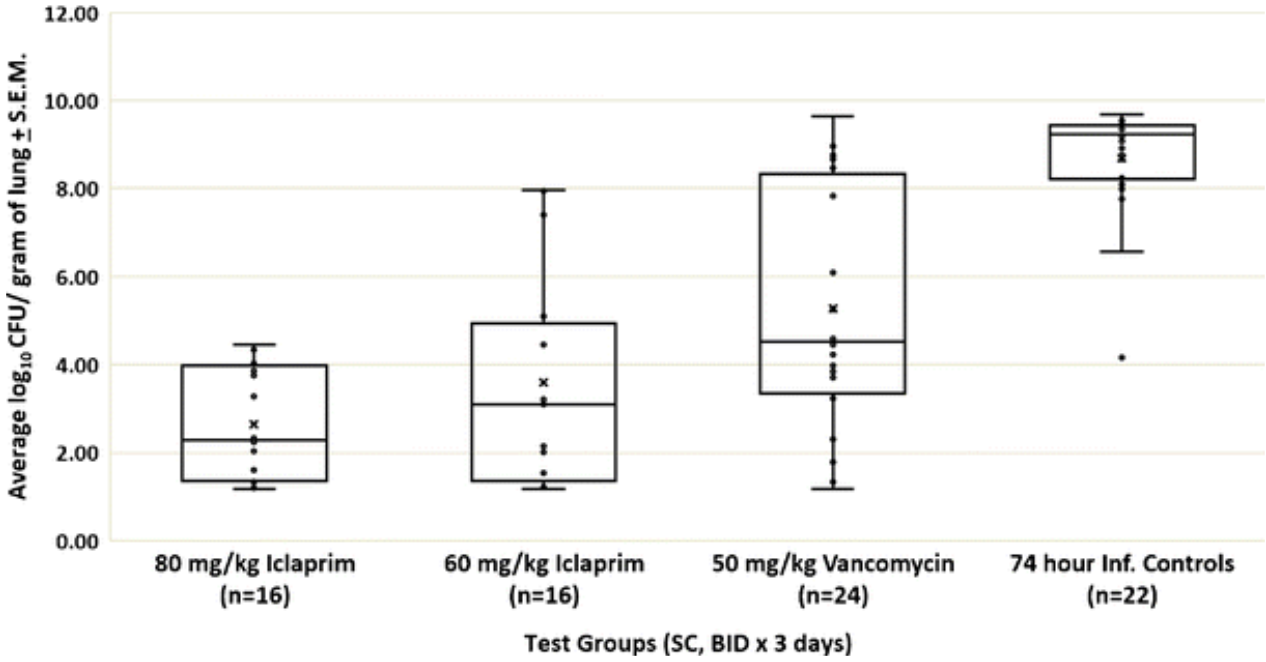
# Iclaprim: Potential to Address Critical Need in Cystic Fibrosis Patients with *Staphylococcus aureus* Lung Infections

- Neutropenic rat lung infection model/alginate microspheres
- Statistically significantly higher reduction of CFU compared to vancomycin
- Granted Orphan Drug Designation by U.S. FDA OOPD
- Formulation development ongoing in pediatric patients
  - Intravenous
  - Inhaled




**Both iclaprim doses showed 100% survival vs. vancomycin groups (91.7% survival and control 48.3% survival)**

Huang et al. Eur J Clin Microbiol Infect Dis. 2017.



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# Iclaprim: High Concentration in Lung

## Antibiotic Concentrations in Epithelial Lining Fluid (ELF) and Alveolar Macrophages (AM) Compared with Serum Levels

| Antibiotic | Dose | Epithelial lining fluid (mg/L) | Alveolar macrophages (mg/L) | Serum (mg/L) | ELF/serum concentration | AM/serum concentration |
|---|---|---|---|---|---|---|
| Iclaprim | 1.6mg/kg IV, single dose | 40.9 | 67.7 | 1.8 | 22.7 | 37.6 |
| Linezolid | 600 mg q12h PO, 5 doses | 622.8 | 27.2 | 190.0 | 3.3 | 0.14 |
| Vancomycin | 1g q12h IV, 9 doses | 92.0 | 926.0 | 367.0 | 0.25 | 2.5 |

High and sustained **iclaprim** concentrations in epithelial lining fluid and alveolar macrophages were **more than 20 and 30 times** the serum concentration, respectively, throughout an entire 7 hour sampling period

Kiem and Schentag. Infect Chemother. 2014.



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# Iclaprim: Clinical Efficacy for Treatment of HABP/VABP

- Phase 2 study in 70 patients with nosocomial pneumonia suspected or confirmed caused by Gram-positive bacteria, treated with iclaprim or vancomycin for 7–14 days
- Primary efficacy endpoint was the proportion of patients achieving a clinical cure 7–14 days post-treatment

| | **Iclaprim** 0.8 mg/kg q12h (n = 23) | **Iclaprim** 1.2 mg/kg q8h (n = 24) | **Vancomycin** 1 g q12h (n = 23) |
|---|---|---|---|
| Clinical cure | 73.9%[1] | 62.5%[2] | 52.2% |
| Day 28 mortality | 8.7%[3] | 12.5%[4] | 21.7% |

Difference in clinical cure rates (97.5% CI) vs vancomycin: [1]21.7% (-9.3 to 52.8), p = 0.13; [2]10.3% (-21.9 to 42.5), p = 0.47; [3]-13.0% (-33.5 to 7.4); [4]-9.2% (-30.7 to 12.2)

Huang et al. Clin Ther. 2017.



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# Optimized Iclaprim Dosing Regimen to Fixed Dose

| | Iclaprim Dosing Regimens | | | |
|---|---|---|---|---|
| **Parameter, median (95% CI)** | **0.8 mg/kg/0.5 hr** | **64 mg/2hr** | **72 mg/2hr** | **80 mg/2hr** |
| **$C_{maxss}$, ng/mL** | 702 (572-953) | 524 (411-679) | 590 (462-764) | 655 (514-849) |
| **$AUC_{0-24ss}$** | 3865 (2992-5394) | 3970 (3092-5540) | 4466 (3479-6233) | 4962 (3865-6926) |
| **AUC/MIC, hr** | 32 (24-45) | 33 (26-46) | 37 (29-52) | 41 (32-58) |
| **T > MIC, %** | 39 (28-55) | 45 (35-61) | 48 (38-65) | 51.7 (41-70) |

**Optimized iclaprim dose for efficacy (AUC/MIC and T > MIC) and safety (Cmax) based on median pharmacokinetic parameters projected by population PK-based simulations**

Lodise et al. AAC 2018.



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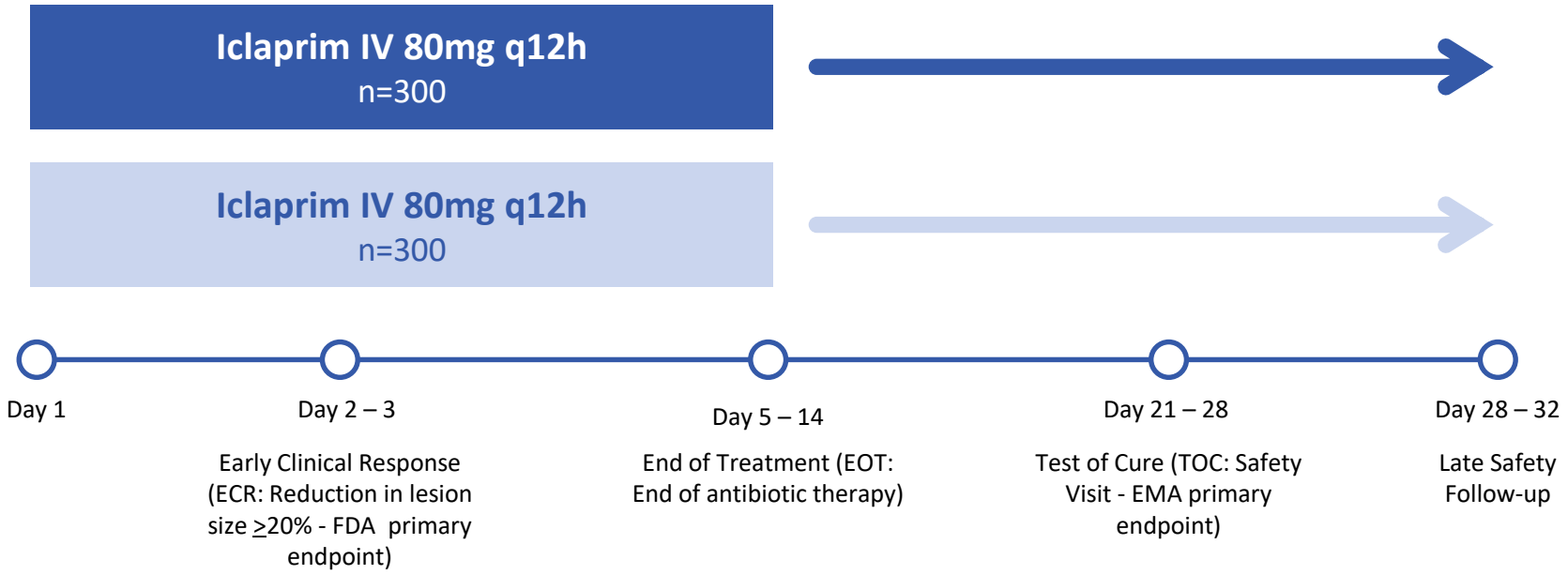
# REVIVE-1/2 Phase 3 ABSSSI Trial Study Design




## Key inclusion criteria:

- ≥18 years old
- Bacterial skin infection with lesion size ≥75cm2
- Major cutaneous abscess, cellulitis/erysipelas, and/or wound infections caused by external trauma
- Fever/lymphadenopathy/increased WBC/ >10% bands/increased CRP

## Key exclusion criteria:

- Severely impaired arterial blood supply
- >1 dose of short-acting systemic antibiotic within 7 days, unless treatment failure/resistance
- Child-Pugh class C cirrhosis
- Cardiovascular conditions/meds known to prolong QT interval

Huang et al. CID 2018; Holland et al. AAC 2018.



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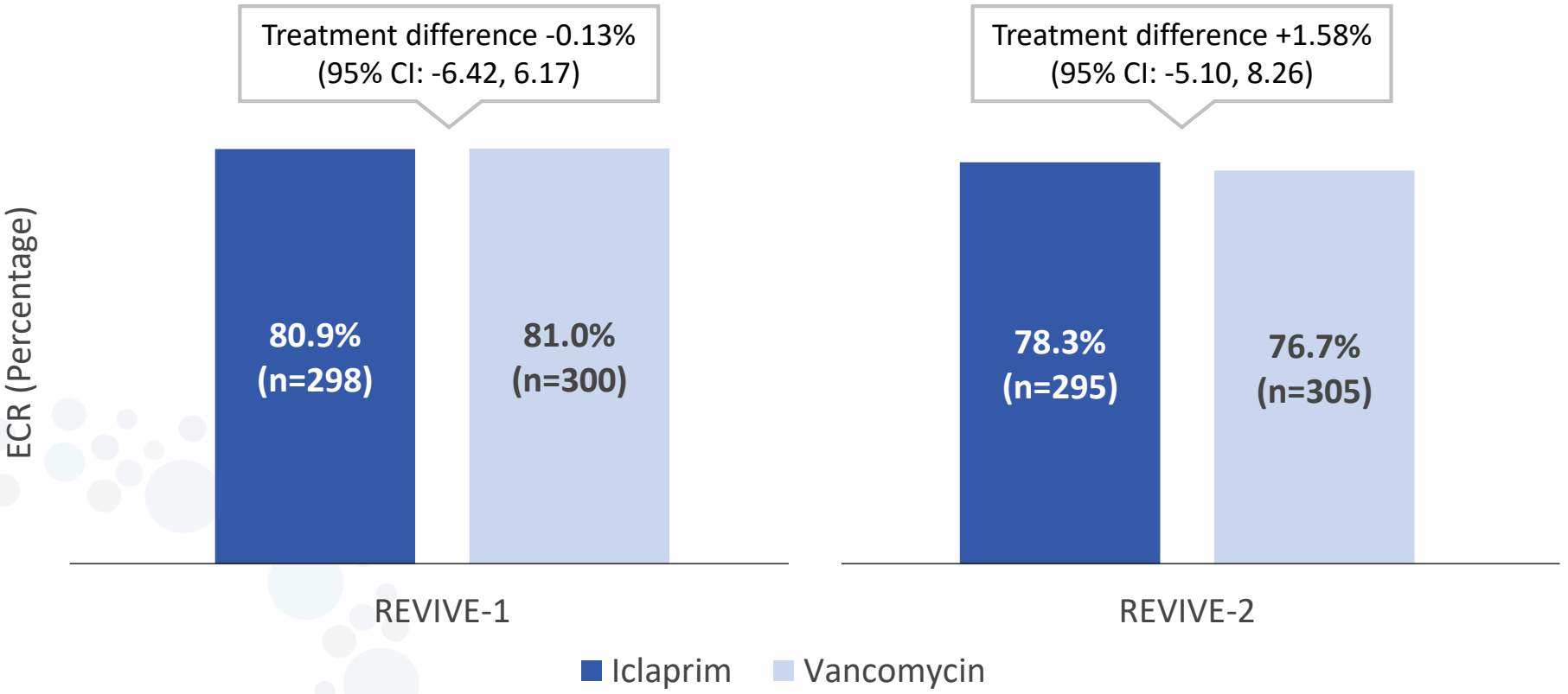
# Iclaprim in ABSSSI
## *Both Phase 3 Trials (REVIVE-1 /-2) Met Primary Endpoint*

**Early Clinical Response (ECR)*
Intent-to-treat (ITT) population**




* ECR: defined by FDA as ≥20% reduction in lesion size at 48-72h (Early Time Point) compared to baseline
Huang et al. CID 2018; Holland et al. AAC 2018.



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# Iclaprim Clinical Safety in ABSSSI
## *REVIVE-1 and REVIVE-2*

| | REVIVE-1 | | REVIVE-2 | |
|---|---|---|---|---|
| | Iclaprim N=293 | Vancomycin N=297 | Iclaprim N=299 | Vancomycin N=302 |
| Study drug- related TEAEs* | 57 (19.5%) | 53 (17.8%) | 42 (14.0%) | 39 (12.9%) |
| Study drug-related SAEs | 2 (0.7%) | 0 | 1 (0.3%) | 2 (0.7%) |

- Most common AEs in iclaprim arm - nausea (7.8%), headache (6.3%), infusion site extravasation (4.6%), and cellulitis (4.6%)
  - 75-80% of adverse events in REVIVE-1 and -2 categorized as mild to moderate
- No patients in iclaprim group with clinically significant creatinine increases versus 7 reported cases in the vancomycin group
- No significant differences between arms in elevated liver enzymes or QTc prolongation

*TEAEs=treatment-emergent adverse events
Huang et al. CID 2018; Holland et al. AAC 2018.



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# Iclaprim: Rationale, Challenges and Key Decisions

- Antibiotic development is challenging
- ABSSSI chosen as the primary approval indication because of prior SSSI data, cost and time efficiencies
- Prior SSSI trials informed clearance of iclaprim was independent of weight and PD parameters were not optimized for efficacy (AUC/MIC and T > MIC) nor safety (Cmax)
- The REVIVE studies used an optimized and fixed 80 mg dose infused over 2 hours administered q12h for 5-14 days for the treatment of ABSSSI
  - REVIVE studies were funded by institutional and private investors
  - Frequent communications and agreement with both FDA and EMA rapporteurs facilitated accelerating the iclaprim drug development program

**Potential changes in retrospect**

- Increased enrollment in EU and LA
- Limited enrollment of IVDAs
- Block randomization

**Need for commercial and regulation changes favoring drug development**



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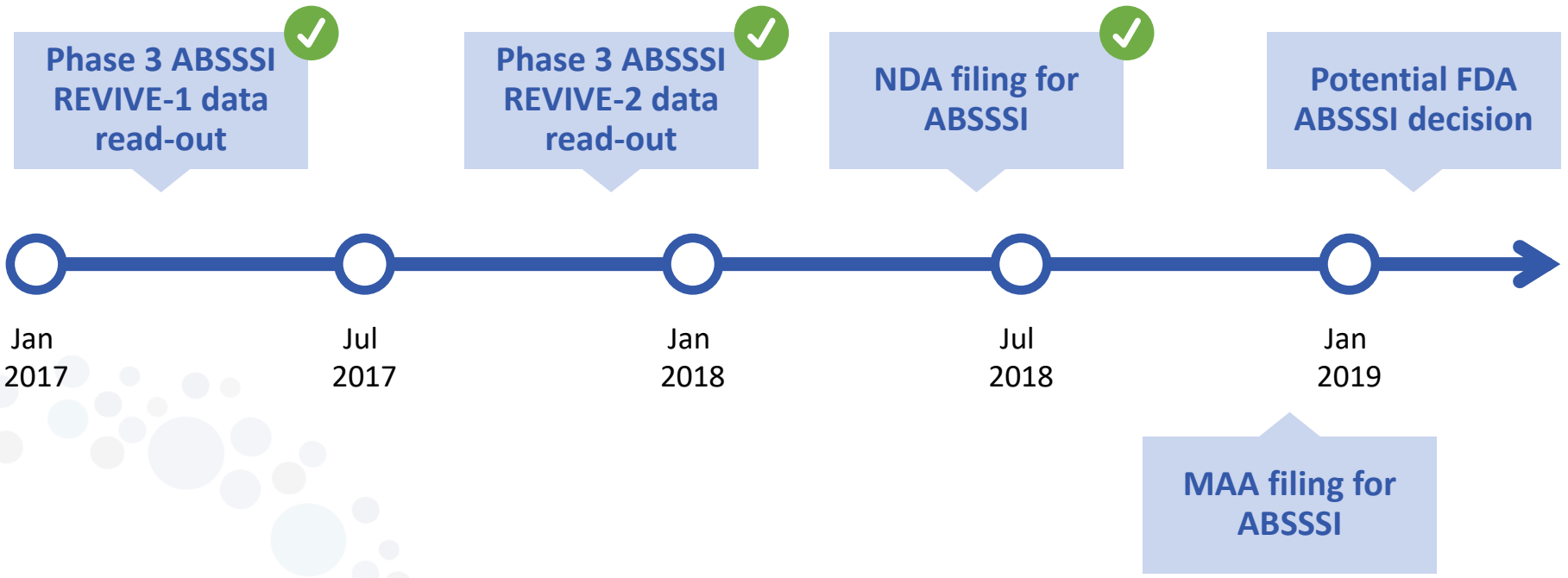
# Iclaprim: Development Timeline



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# Iclaprim: Summary and Conclusions

**The development of antibiotics is challenging**

**A DhFRi and rapidly bactericidal against nonsusceptible MRSA isolates/strains to trimethoprim, vancomycin, linezolid, and daptomycin**

**Concentrates at sites of infection: skin and lung**

**Optimized iclaprim fixed dose based on pharmaco-dynamic parameters associated with efficacy and safety for indications of ABSSSI and HABP/VABP**

**In two Phase 3 ABSSSI studies, iclaprim was**

- Non-inferior to vancomycin with a -10% margin (met primary endpoint)
- No nephrotoxicity, no renal dosing requirement and no therapeutic drug monitoring

**Regulatory submissions**

- NDA filed for ABSSSI in 2Q2018 & MAA filing for ABSSSI planned in 4Q2018



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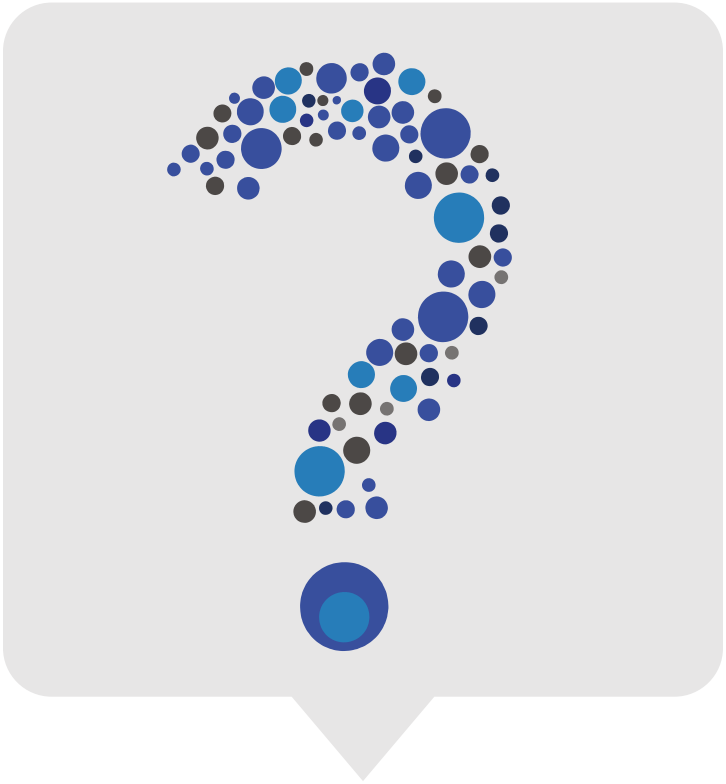
Thank you for your attention

# Questions



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