COMBACTE-MAGNET EVADE Study Group

Session: P-24. Clinical Trials

Background: *Pseudomonas aeruginosa* (PA) pneumonia is associated with morbidity and mortality in mechanically ventilated, intensive care unit (MV ICU) patients despite best clinical care. We assessed efficacy, PK, and safety of MEDI3902 in MV ICU subjects in the placebo-controlled, randomized Phase 2 EVADE study (NCT02696902; EudraCT 2015-001706-34).

Methods: Subjects with PCR-confirmed PA colonization of the lower respiratory tract were randomized to either a single IV infusion of 1,500 mg MEDI3902 (n = 85) or placebo (n = 83). Primary Efficacy endpoint was Endpoint Adjudication Committee-determined relative risk reduction (RRR) of PA pneumonia incidence in MEDI3902 vs. placebo recipients within 21 days post dose (2-sided $\alpha = 0.2$). Serum MEDI3902 PK levels were measured through 49 days post dose. Treatment-emergent adverse events (TEAEs) and serious AEs (SAEs) were assessed through 49 days post dose.

Results: Baseline characteristics were similar between groups. MEDI3902 did not meet the primary endpoint of PA pneumonia vs. placebo (22.4% vs. 18.1%; RRR -23.7%, P = 0.491). Mean serum MEDI3902 level was 9.46 μg/mL (target 1.7μg/mL) at 21 days post dose, with a t½ 5.6 days. Proportion of subjects with TEAEs was similar between groups: ≥1 TEAE (98.8% MEDI3902; 97.6% placebo); ≥1 serious; and/or ≥grade 3 severity SAE (70.6% MEDI3902; 66.3% placebo). Deaths were numerically higher, although not statistically significant (24 (28.2%) MEDI3902 vs 19 (22.9%) Placebo; RRR -23.3%, P 0.429). Post-hoc analyses suggested RRR 47% among ~70% of the study population who had baseline Procalcitonin levels < 0.55 μg/L (12.5% MEDI3902 vs 23.7% placebo; 80%CI 6.1%-69.9%; P 0.135). Similarly, RRR 83% was observed among 50% of study subjects with baseline absolute neutrophil count (ANC) of < 8170 /μL (2.8% MEDI3902 vs 17.0% placebo; 80%CI 39.5%-95.5%; P 0.038). Subjects with Procalcitonin < 0.55 μg/L and ANC < 8170/ μL also had higher serum PK exposure.

Conclusion: A single IV dose of MEDI3902 provided PK exposure above the target level but did not achieve primary efficacy endpoint of reduction in PA pneumonia. Efficacy trends were observed in subjects with lower levels of baseline inflammatory biomarkers. MEDI3902 may have a path forward in certain patient populations such as ICU patients with lower baseline inflammation.

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636. Immunogenicity, Safety and Tolerability of a Booster Dose of Clostridium difficile Vaccine and 4 Year Antibody Persistence

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Background: Clostroidides difficile (C difficile) is a common cause of antibiotic-associated diarrhea. To date, there is no vaccine to prevent C. difficile infection (CDI). This extension of a phase 2 study explores the immunogenicity, safety, and tolerability of a 4th dose, and antibody persistence of a three-dose regimen of a toxoid-based C difficile vaccine in 300 healthy adults 65 to 85 years of age in the United States.

Methods: The first stage of this study was conducted from 16 July 2015 to 7 March 2017, in which subjects were enrolled and randomized to receive one of two antigen dose levels (100μg or 200μg total toxoid A and B) or placebo, administered in one of two three-dose regimens: Days 1, 8 & 30 or Months 0, 1 & 6. Immunogenicity testing was conducted on samples obtained at each of nine study visits through 12 months post dose 3. In this extension stage, subjects who had received vaccine in the first stage were re-randomized at 12 months post dose 3 to receive either a booster dose or placebo in a 1:1 ratio. Subjects were followed for immunogenicity three (3) years post booster (four years post dose #3)

Results: Peak antibody response to vaccination was observed between day 8 and 30 following booster administration. Both regimens demonstrated robust anamnestic responses with peak levels above the three-dose peak (stage 1). Toxin A geometric mean concentrations (GMCs) remained above pre-booster GMCs, 3 years post booster for both dose levels and regimens. Antibody persistence for both groups demonstrated stable antibody levels four years after the primary vaccination series among subjects who did not receive a booster dose. No Grade 4 reactogenicity was reported during the study. Pain was the most common local reaction. Adverse event rates per subject were similar between both regimens and placebo. There were no Serious Adverse Events (SAEs) considered related to the investigational product at any dose or regimen. The safety profile was consistent with what was seen in the first stage of the study.

Conclusion: A booster dose of *Clostroidides difficile* vaccine candidate is highly immunogenic, well tolerated and demonstrates an acceptable safety profile in both dose groups for the Day and the Month regimens. Antibody persistence remains stable from 12 months to 4-year post dose 3.

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637. Outcomes by Body Mass Index (BMI) in the STRIVE Phase 2 Trial of Once-Weekly Rezafungin for Treatment of Candidemia and Invasive Candidiasis Compared with Caspofungin

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Background: There is increasing evidence of antifungal underdosing in the treatment of invasive disease, particularly in special populations such as the obese. Body size is often an important variable affecting drug exposure, and pharmacokinetic (PK) models of antifungal dosing have suggested size-based dose adjustments to achieve target drug exposure.

Rezafungin (RZF) is a novel echinocandin in Phase 3 development for treatment of candidemia and invasive candidiasis (IC) and for prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* in blood and marrow transplant recipients. Distinctive PK properties of RZF (e.g., long half-life, extensive tissue distribution, and front-loaded drug exposure) lend themselves to RZF once-weekly (QWk) dosing and antifungal efficacy. In this sub-analysis of the Phase 2 STRIVE trial of RZF in the treatment of candidemia and/or IC, outcomes based on patient BMI were evaluated.

Methods: The STRIVE trial (NCT02734862) compared the safety and efficacy of RZF QWk compared with once-daily caspofungin (Fig. 1). For this subanalysis, data were stratified by BMI categories of < 30 kg/m^2 and ≥ 30 kg/m^2. Efficacy (overall response [resolution of clinical signs of infection + mycological eradication], mycological response, and investigator assessment of clinical response) and safety (treatment-emergent adverse events [TEAEs]) endpoints by treatment group were evaluated, as well as PK data (area under the curve [AUC]) from RZF-treated patients.

Figure 1.

Figure 1. Treatment Groups of the Phase 2 STRIVE Trial

Treatment Group	Dose Regimen
RZF Group 1	IV rezafungin 400 mg QWk
RZF Group 2	IV rezafungin 400 mg on Week 1, followed by 200 mg QWk
CAS	IV caspofungin 70 mg on Day 1, followed by 50 mg QD (with optional step-down to oral fluconazole)

CAS=caspofungin; RZF=rezafungin; QD=once daily; QWk=once weekly.

Results: Mean BMI values were similar across treatment arms (26.9 kg/m^2 in RZF Group 1 and 26.8 kg/m^2 in RZF Group 2 and CAS arms). Efficacy outcomes at Day 14 were similar between BMI categories (Table 1). Rates of TEAEs were generally similar between BMI categories as well (Table 2), with no concerning safety trends. Following one dose of RZF 400 mg (Week 1), the ranges of AUCs by BMI category overlapped and there was a minor mean difference of ~20% (lower for those with BMI ≥ 30 kg/m^2) (Fig. 2).

Table 1

Table 1. Efficacy Outcomes by BMI Category (<30 kg/m^2 vs ≥30 kg/m^2) from the STRIVE Trial of Rezafungin Treatment of Candidemia and Invasive Candidiasis (mITT Population)

	BMI <30 kg/m^2			BMI ≥30 kg/m^2		
Outcomes at Day 14	RZF Grp 1 N=57	RZF Grp 2 N=34	CAS N=48	RZF Grp 1 N=18	RZF Grp 2 N=11	CAS N=13
Overall Response, n (%)	34 (59.6)	26 (76.5)	32 (66.7)	11 (61.1)	8 (72.7)	9 (69.2)
Mycological Response, n (%)	37 (64.9)	26 (76.5)	33 (68.8)	12 (66.7)	8 (72.7)	9 (69.2)
Investigator Assessment of Clinical Cure, n (%)	40 (70.2)	28 (82.4)	33 (68.8)	12 (66.7)	8 (72.7)	10 (76.9)

BMI=body mass index; CAS=caspofungin 70 mg on Day 1 followed by 50 mg once daily for ≥14 days; RZF Grp 1=rezafungin 400 mg once weekly; RZF Grp 2=rezafungin 400 mg on Week 1 followed by 200 mg once weekly.

Table 2

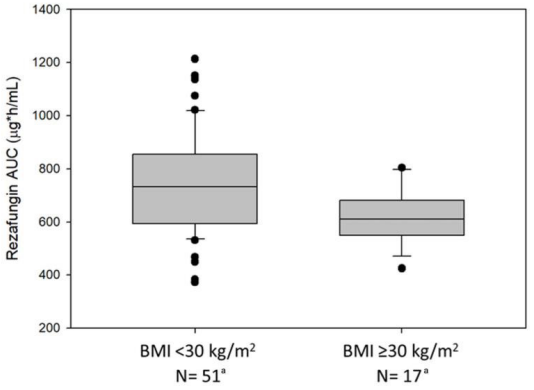
Table 2. Summary of TEAEs by BMI Category (<30 mg/kg² vs ≥30 mg/kg²) from the STRIVE Trial of Rezafungin Treatment of Candidemia and Invasive Candidiasis (Safety Population)

	BMI <30 kg/m²			BMI ≥30 kg/m²		
TEAE	RZF Grp 1 N=59	RZF Grp 2 N=37	CAS N=51	RZF Grp 1 N=21	RZF Grp 2 N=15	CAS N=17
At least 1 TEAE	51 (86.4)	33 (89.2)	42 (82.4)	19 (90.5)	15 (100)	13 (76.5)
Study drug–related TEAE	4 (6.8)	5 (13.5)	6 (11.8)	3 (14.3)	1 (6.7)	3 (17.6)
TEAE leading to study drug discontinuation	4 (6.8)	1 (2.7)	4 (7.8)	2 (9.5)	0	0

BMI=body mass index; CAS=caspofungin 70 mg on Day 1 followed by 50 mg once daily for ≥14 days; RZF Grp 1=rezafungin 400 mg once weekly; RZF Grp 2=rezafungin 400 mg on Week 1 followed by 200 mg once weekly; TEAE=treatment-emergent adverse event.

Figure 2.

Figure 2. Rezafungin AUC (µg•h/mL) Following One 400-mg Dose at Week 1 by BMI Category (<30 kg/m² vs ≥30 kg/m²)



[a]AUC data shown for patients with PK data available for this analysis.

Conclusion: The safety, efficacy, and PK of RZF in the Phase 2 STRIVE trial was consistent across BMI categories. These results suggest that dose adjustments in obese patients are not necessary. These findings contribute to the evaluation of RZF in a range of patient populations and its ongoing development.

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638. Safety, Efficacy, and Durability of Long-Acting CAB and RPV as Maintenance Therapy for HIV-1 Infection: LATTE-2 Week 256 Results

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Background: Long-acting (LA) injectable suspensions of cabotegravir (CAB) & rilpivirine (RPV) are in phase III development. LATTE-2 W160 results demonstrated high rates of virologic response & overall tolerability. This W256 analysis evaluated long-term efficacy, safety, & tolerability of every 8-week (Q8W) & 4-week (Q4W) intramuscular (IM) dosing.

Methods: LATTE-2 is a phase IIb, multicenter, parallel arm, open-label study in antiretroviral therapy–naive adults with HIV. After a 20-week Induction Period on oral CAB+abacavir/lamivudine, participants (pts) with plasma HIV-1 RNA< 50c/mL were randomized 2:2:1 to IM CAB LA+RPV LA Q8W, Q4W, or continue oral (PO) regimen in the Maintenance Period (MP). After W96, pts on IM regimens continued their current MP regimen. Pts randomized to PO in MP chose a Q8W or Q4W IM regimen in the Extension Period (EP). W256 analysis of MP & EP included virologic success with HIV-1 RNA< 50 c/mL (Food & Drug Administration Snapshot analysis), protocol-defined virologic failure (PDVF), & safety (intention-to-treat–Maintenance Exposed population).

Results: At W256, 88% (101/115; Q8W) & 74% (85/115; Q4W) of randomized IM pts had HIV-1 RNA< 50 c/mL, as did 93% (41/44) of PO to IM pts. No pt developed PDVF after W48. In the randomized IM arm (MP & EP), excluding injection-site reactions (ISRs), nasopharyngitis (45%), diarrhea (28%), & headache (24%) were the most common adverse events (AEs), with 34% (39/115; Q8W) & 33% (38/115; Q4W) of pts reporting AEs ≥grade 3, of which 12% (14/115; Q8W) & 11% (13/115; Q4W) were drug related. 3% (3/115; Q8W) & 17% (20/115; Q4W) of pts had AEs leading to withdrawal. 22% (25/115; Q8W) & 23% (27/115; Q4W) reported serious AEs (3 were drug related). In the PO to IM arm (EP only), most common AEs excluding ISRs were nasopharyngitis (25%), influenza (23%), & back pain (18%). 23% (10/44) reported AEs ≥grade 3 & 5% (2/44) had AEs leading to withdrawal. Majority of ISRs were mild/moderate pain & discomfort. < 1% of ISRs were severe, with 5 pts discontinuing due to ISRs.

Table 1

Table 1.

Week 256 Snapshot Study Outcomes[a], n (%)	Randomized Q8W IM[d] (N=115)	Randomized Q4W IM[e] (N=115)	PO to Q8W IM[bf] (N=34)	PO to Q4W IM[bg] (N=10)
HIV-1 RNA <50 c/mL	**101 (88)**	**85 (74)**	**32 (94)**	**9 (90)**
HIV-1 RNA ≥50 c/mL	**4 (3)**	**0**	**1 (3)**	**0**
Discontinued for lack of efficacy	1 (<1)	0	1 (3)	0
Discontinued for other reason while not below threshold	3 (3)[c]	0	-	-
No Virologic Data at Week 256 Window	**10 (9)**	**30 (26)**	**1 (3)**	**1 (10)**
Discontinued due to AE or Death	2 (2)	18 (16)	1 (3)	1 (10)
Discontinued for Other Reasons	8 (7)	11 (10)	-	-
Missing data during window but on study	0	1 (<1)	-	-

a. W256 represents 276 weeks on study (20-Week Induction with oral CAB 30 mg + ABC/3TC followed by 256-Week Maintenance);
b. Patients completing 96-week Maintenance with oral CAB 30 mg + ABC/3TC could continue in Extension by switching to IM dosing regimen of their choice (Q8W or Q4W).
c. Includes withdrawn consent (n=1, intolerance to injections)
d. Randomized Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks (Q8W)
e. Randomized Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks (Q4W)
f. PO to Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks during Extension
g. PO to Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks during Extension

Table 2

Table 2.

Week 256 Adverse Events Overview[a], n (%)	Randomized Q8W IM[d] (N=115)	Randomized Q4W IM[e] (N=115)	PO to Q8W IM[bf] (N=34)	PO to Q4W IM[bg] (N=10)
Any AE	**115 (100)**	**115 (100)**	**34 (100)**	**10 (100)**
Any Grade 3/4 AE	39 (34)	38 (33)	7 (21)	3 (30)
Any Grade 3/4 AE Excluding ISR	31 (27)	35 (30)	4 (12)	2 (20)
Any AE Leading to Withdrawal	**3 (3)**	**20 (17)**	**1 (3)**	**1 (10)**
Any Drug-Related AE	**111 (97)**	**115 (100)**	**32 (94)**	**8 (80)**
Any Grade 3/4 Drug-Related AE	14 (12)	13 (11)	4 (12)	2 (20)
Any Grade 3/4 Drug-Related AE Excluding ISRs	4 (3)	7 (6)	0	0
Any SAE	**25 (22)**	**27 (23)**	**6 (18)**	**1 (10)**
Any Drug-Related SAE	1 (<1)	2 (2)	0	0
Any Fatal AE	**0**	**3 (3)**	**0**	**0**
Most Common non-ISR AEs[c]				
Nasopharyngitis	50 (43)	53 (46)	6 (18)	5 (50)
Diarrhoea	35 (30)	30 (26)	-	-
Headache	29 (25)	26 (23)	-	-
Influenza	-	-	7 (21)	3 (30)
Back Pain	-	-	5 (15)	3 (30)

a. W256 represents 276 weeks on study (20-Week Induction with oral CAB 30 mg + ABC/3TC followed by 256-Week Maintenance);
b. Patients completing 96-week Maintenance with oral CAB 30 mg + ABC/3TC could continue in Extension by switching to IM dosing regimen of their choice (Q8W or Q4W).
c. Only top 3 most common non-ISR AEs shown
d. Randomized Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks (Q8W)
e. Randomized Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks (Q4W)
f. PO to Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks during Extension
g. PO to Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks during Extension

Conclusion: CAB+RPV LA injectable therapy, administered Q8W or Q4W, demonstrated high rates of virologic response & tolerability through 5 years. W256 results add to previous results & demonstrate long-term durability of CAB+RPV LA for people living with HIV.

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