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633. Preliminary Results from a Phase 1 Single Ascending-Dose Study Assessing Safety, Serum Viral Neutralizing Antibody Titers (sVNA), and Pharmacokinetic (PK) Profile of ADG20: an Extended Half-Life Monoclonal Antibody Being Developed for the Treatment and Prevention of Coronavirus Disease (COVID-19)

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Background. ADG20 is a fully human IgG1 monoclonal antibody engineered to have high potency and broad neutralization against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other SARS-like CoVs with pandemic potential by binding to a highly conserved epitope in the receptor-binding domain (RBD) of the spike protein. The Fc region of ADG20 has been modified to provide an extended half-life. ADG20 is in clinical development for the treatment and prevention of COVID-19.

Methods. This is an ongoing Phase 1, randomized, placebo (PBO)-controlled, single ascending-dose study of ADG20 administered intramuscularly (IM) or intravenously (IV) to healthy adults aged 18–50 years with no evidence of prior or current SARS-CoV-2 infection. Participants were randomized 8:2 in 3 cohorts (N=10/cohort: n=8 ADG20, n=2 PBO): ADG20 300 mg IM, 500 mg IV, and 600 mg IM. Safety, tolerability, PK, and sVNA titers were assessed up to 3 months post dose. Serum ADG20 concentrations were measured with a validated hybrid ligand binding liquid chromatography–mass spectrometry (MS)/MS assay. sVNA titers against authentic SARS-CoV-2 were determined by a plaque reduction neutralization assay.

Results. Overall, 30 participants received ADG20 (n=24) or PBO (n=6). Blinded safety data for all cohorts and PK/sVNA titer data for the 300 mg IM cohort are reported. Through a minimum of 10 weeks post dose, no study drug-related adverse events (AEs), serious AEs, injection site reactions, or hypersensitivity reactions were reported. The observed preliminary PK profile was dose proportional, consistent with an extended half-life monoclonal antibody, and well predicted by translational physiologically-based PK modeling. The measured 50% sVNA titer (MN50; geometric mean [coefficient of variation, %]) was 1382 (32.7%) 13 days after a single 300 mg IM dose. These values are within the range of peak serum neutralizing antibody titers reported for COVID-19 mRNA vaccines.

Conclusion. A single dose of ADG20, up to 600 mg IM, was well tolerated. Preliminary PK and sVNA titer profiles support the ongoing Phase 2/3 trials of ADG20 at a 300 mg IM dose for the prevention of COVID-19 (EVADE: NCT04859517) and treatment of ambulatory patients with mild to moderate COVID-19 (STAMP: NCT04805671).

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634. Investigational Microbiome Therapeutic SER-109 Reduces Recurrence of *Clostridioides difficile* Infection (CDI) Compared to Placebo, Regardless of Risk Factors for Recurrence

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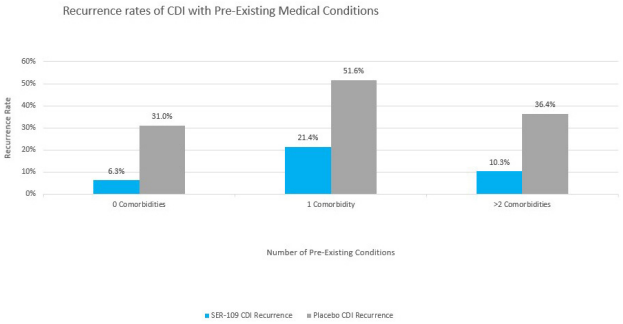
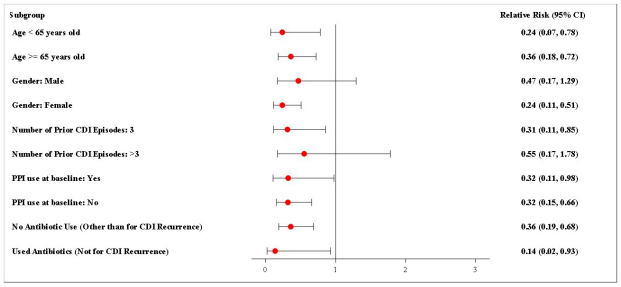
Background. Several demographic and clinical characteristics, including age, sex, medication use and presence of comorbid conditions are considered risk factors for recurrent CDI (rCDI). We examined the efficacy of an investigational purified oral microbiome therapeutic, SER-109, versus placebo in an exploratory analysis of subgroups of patients with risk factors for recurrence who enrolled in ECOSPOR III, a double-blind, placebo controlled trial.



Forest Plot of Relative Risks for Recurrence at Week 8 for Selected Baseline Characteristics in the ITT population



Methods. Patients with ≥ 3 CDI episodes were treated with SER-109 or placebo (four capsules daily for three days) following standard treatment of CDI. The primary efficacy objective was to demonstrate superiority of SER-109 versus placebo in reducing rCDI up to 8 weeks after treatment. In this exploratory analysis, we analyzed the rate of CDI recurrence among SER-109 treated subjects compared to placebo in subgroups defined by rCDI baseline risk factors: proton-pump inhibitor use, number of CDI recurrences, prior FMT history, presence of comorbid conditions and exposure to non-CDI antibiotics after dosing. We also analyzed the rate of CDI recurrence among SER-109 treated subjects by age (≥ 65 and ≤ 65) and gender, which were pre-specified.

Results. Of 281 patients screened,182 were enrolled. Overall recurrence rates were lower in SER-109 treated patients compared to placebo (12.4% vs 39.8%, respectively); relative risk (RR), 0.32 [95% CI, 0.18-0.58; P< 0.001 for RR< 1.0:P< 0.001 for RR< 0.833]. Co-morbidities including diabetes, renal disease, malignancy, cardiac disease, COPD/asthma, colitis, or immunocompromised status were observed in most patients in the overall study population; 33.5%, 32.4% and 34.1% had 0, 1, or ≥ 2 comorbidities. SER-109 was consistently observed to show greater benefit than placebo in reducing CDI recurrence in all subgroups regardless of the presence or absence of the rCDI risk factor (Fig 1).

Conclusion. Regardless of risk factor status, SER-109 reduced recurrence of CDI compared to placebo. Most subjects in ECOSPOR III had co-morbidities consistent with the broad inclusion criteria in this Phase 3 trial. Despite a high proportion of patients with co-morbidities in ECOSPOR III, SER-109 significantly reduced the risk of recurrence compared to placebo.

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636. A Phase I Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Live, Attenuated, Quadrivalent Dengue Vaccine (V181)

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Background. Dengue (DENV) is a mosquito-borne virus with four serotypes causing substantial morbidity in tropical and subtropical areas worldwide. A dengue vaccine that can be given to both seronegative and seropositive populations remains an important unmet medical need. V181 is an investigational live, attenuated, quadrivalent dengue vaccine.

Methods. In this phase 1 double-blind, placebo-controlled study, the safety, tolerability, and immunogenicity of V181 in healthy adults were evaluated in two formulations: TV003 and TV005. TV005 has a 10-fold higher DENV2 component as compared to TV003. Two-hundred participants [~ 50% baseline flavivirus-experienced (BFE) and 50% baseline flavivirus-naive (BFN)] were randomized 2:2:1 to receive TV003, TV005, or placebo on Days 1 and 180. Immunogenicity against each of the four DENV serotypes was measured using a Virus Reduction Neutralization Test ($VRNT_{60}$) after each vaccination and out to 1 year after the second dose.

Results. There were no discontinuations due to adverse events (AEs) or vaccine-related serious AEs. The most common AEs Days 1-28 after any TV003 or TV005 vaccination were rash, headache, fatigue, and myalgia. DENV $VRNT_{60}$ seropositivity to 3 or 4 serotypes (i.e. tri-or tetravalent) was demonstrated in 92.6% of BFN TV003 participants, 74.2% of BFN TV005 participants, and 100% of the BFE participants at 6 months postdose 1 (PD1). Vaccine viremia, a measure of vaccine infectivity, was transiently detected from all four DENV types after the first dose of TV003 and TV005. Tri- or tetravalent vaccine-viremia was detected in 63.9 % and 25.6 % of BFN TV003 and TV005 participants, respectively, PD1. Compared to baseline, robust increases in $VRNT_{60}$ GMTs were observed after the first dose of TV003 and TV005 in both flavivirus subgroups for all DENV serotypes and minimal increases were observed PD2. GMTs in the TV003 and TV005 BFE and BFN subgroups remained above the respective baselines and placebo at 1-year PD2.

Conclusion. Both formulations of V181 were generally well tolerated in healthy adults. Overall, viremia and immunogenicity were higher after TV003 as compared to TV005. These data support the continued development of the V181 TV003 formulation as a single-dose vaccine for the prevention of DENV disease.

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637. Treatment Outcomes in Secondary Analysis Populations of Adult Patients the ALLIUM Phase 3 study Comparing Cefepime-Enmetazobactam to Piperacillin-Tazobactam for Complicated Urinary Tract Infections (cUTI) or Acute Pyelonephritis (AP)

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Session: P-28. Clinical Trials

Background. Superior treatment outcomes were observed with the β-lactam/β-lactamase inhibitor combination of cefepime-enmetazobactam (FPE) compared to piperacillin-tazobactam (PTZ) in the primary efficacy population (m-MITT) of the ALLIUM phase 3 study of adult patients with cUTI/AP. We present here the outcomes in the microbiologically evaluable (ME) and ME+Resistant (ME+R) populations.

Methods. 1034 cUTI/AP patients randomized 1:1 in a double-blind, multicenter trial received either 2 g cefepime/0.5 g enmetazobactam or 4 g piperacillin/0.5 g tazobactam q8h by 2h infusion for 7 to 14 days. Patients in m-MITT had a Gram-negative urinary baseline pathogen (BP) at $>10^5$ CFU/ml with FPE MIC ≤8 μg/ml and PTZ MIC ≤64 μg/ml. ME included patients in m-MITT who received ≥15 consecutive doses of study drug or were classified as clinical failures after receiving ≥9 doses; had a clinical assessment at test-of-cure (TOC) unless clinical failure occurred earlier; did not receive concomitant antibiotics with a non-study agent; and did not have any other protocol violation. ME+R included patients in ME along with those who had BP resistant to either FPE (MIC >8 μg/ml) or PTZ (MIC >64 μg/ml), or a missing MIC value. Overall success was the composite of clinical cure and microbiological eradication (< 10^3 CFU/ml in urine). Two-sided 95% confidence interval (CI) were computed using the stratified Newcombe method.

Results. In the ME population, superiority in overall success of FPE (87.0%; 268/308) compared to PTZ (65.4%; 195/298) was demonstrated as the lower bound of the CI (16.6%) of the treatment difference (TD; 23.3%) was greater than 0 (Table). Higher rates of microbiological eradication with FPE contributed to the superior treatment outcomes. In the ME+R population in which BP susceptibility was not an exclusion criterion, favorable outcomes with FPE in overall success (TD 21.6%; 95% CI [15.3, 27.8]) and microbiological eradication (TD 21.0%; 95% CI [14.8, 27.0]) were also observed.

Population/Outcome at TOC	Cefepime/enmetazobactam n (%)	Piperacillin/tazobactam n (%)	Treatment difference % (95% CI)
m-MITT	N=345	N=333	
Overall success	273 (79.1)	196 (58.9)	21.2 (14.3, 27.9)
Clinical cure	319 (92.5)	296 (88.9)	3.5 (-1.0, 8.0)
Microbiological eradication	286 (82.9)	216 (64.9)	19.0 (12.3, 25.4)
ME	N=308	N=298	
Overall success	268 (87.0)	195 (65.4)	23.3 (16.6, 29.9)
Clinical cure	300 (97.4)	285 (95.6)	2.1 (-1.5, 5.5)
Microbiological eradication	271 (88.0)	202 (67.8)	22.0 (15.4, 28.4)
ME+R	N=347	N=337	
Overall success	300 (86.5)	224 (66.5)	21.6 (15.3, 27.8)
Clinical cure	335 (96.5)	323 (95.8)	1.1 (-2.1, 4.3)
Microbiological eradication	305 (87.9)	231 (68.5)	21.0 (14.8, 27.0)

Conclusion. The confirmation of superior treatment outcomes with FPE in the ME and ME+R populations supports the robustness of the corresponding superiority observed in adult cUTI/AP patients in m-MITT.

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638. The Impact of *in vitro* Synergy Between Colistin and Meropenem on Clinical Outcomes in Invasive Carbapenem-resistant Gram-negative Infections: A Report from the OVERCOME Trial

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Session: P-28. Clinical Trials

Background. Consensus guidelines caution against colistin (COL) monotherapy due to efficacy and resistance development concerns. The COL + meropenem (MEM) combination often displays *in vitro* synergy against carbapenem-resistant (CR) Gram-negative bacilli (GNB). We recently completed a clinical trial comparing outcomes in patients receiving COL vs. COL + MEM. Herein we assess if, amongst patients receiving COL + MEM, outcomes differed as a function of the presence (or absence) of *in vitro* synergy against the index pathogen.

Methods. OVERCOME was an international, multicenter, randomized, double-blind, placebo-controlled study comparing COL + placebo and COL + MEM for the treatment of pneumonia and/or bloodstream infection (BSI) due to CR GNB. Baseline isolates were COL susceptible (MIC ≤ 2 mg/L) and underwent synergy testing to COL + MEM in 24-hour time kill experiments (TKE). Synergy was defined as a >2-log CFU/ml reduction with combination therapy compared to the most active single agent. Outcomes assessed included 28-day mortality, clinical failure, and the development of COL resistance (MIC ≥ 4 mg/L) for both the overall cohort and the subgroup with *A. baumannii*.

Results. Of the 211 patients who received COL + MEM in OVERCOME, 186 had baseline synergy testing performed and were eligible for this analysis. The median age of the cohort was 70 years, 35% were female, 48% were white, and 44% Asian. Sixty-eight percent were in the intensive care unit (ICU) at infection onset. *A. baumannii* was the most common pathogen (78%) and pneumonia was the most common infection (68%). Synergy was demonstrated in most isolates (76%). Baseline characteristics, clinical, and microbiological outcomes were similar amongst patients infected with isolates against which COL + MEM demonstrated synergy and those where no synergy was demonstrated (Table 1). In patients with *A. baumannii* infections, the presence of *in vitro* synergy was associated with a decrease in clinical failure (53% vs. 79%; p = 0.04). No significant impact of synergy on 28-day mortality or development of COL resistance was demonstrated (Table 2).