Disclosures. **C. Ford**, Seres Therapeutics, Inc: Employee and Shareholder, Salary. **M. Henn**, Seres Therapeutics, Inc: Employee and Shareholder, Salary. **J. Bryant**, Seres Therapeutics, Inc: Employee and Shareholder, Salary. **L. Diao**, Seres Therapeutics, Inc: Employee and Shareholder, Salary. **J. Wortman**, Seres Therapeutics, Inc: Employee and Shareholder, Salary. **A. Tomlinson**, Seres Therapeutics, Inc: Employee and Shareholder, Salary. **K. Litcofsky**, Seres Therapeutics, Inc: Employee and Shareholder, Salary. **P. Bernardo**, Seres Therapeutics, Inc: Employee and Shareholder, Salary. **B. McGovern**, Seres Therapeutics, Inc: Employee and Shareholder, Salary. **J. G. Aunins**, Seres Therapeutics, Inc: Employee and Shareholder, Salary. **D. N. Cook**, Seres Therapeutics, Inc: Employee and Shareholder, Salary. **M. Trucksis**, Seres Therapeutics, Inc: Employee and Shareholder, Salary.

1642. Safety and Efficacy of Bacteriophage Therapy: Analysis of Clinical Case Series Data

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Session: 168. Novel Therapies for Superbugs
Friday, October 5, 2018: 2:00 PM

Background. Bacteriophage therapy (BT) is a re-emerging strategy to treat antibiotic-resistant infections. Here, we describe our initial experience with intravenous (IV) and inhaled BT to treat life-threatening *Staphylococcus aureus* and *Pseudomonas aeruginosa* infections not responding to antibiotic therapy. Emergency Investigational New Drug application approvals (United States) or Special Access Scheme Category A notifications (Australia) and informed consent from the patients were obtained.

Methods. Patients were treated with AB-SA01 (3-phage product targeting *S. aureus*) and AB-PA01 (4-phage product targeting *P. aeruginosa*) produced in a Good Manufacturing Practice-certified facility. Pre- and posttreatment bacterial isolates were tested for phage susceptibility during BT. In all cases, concomitant antibiotics were continued. Safety was assessed clinically and using laboratory parameters with up to 90 days of follow-up. Samples to assess bacterial loads, bacteriophage kinetics in blood, and immune responses to phage were collected.

Results. As of April 2018, 8 patients were treated with BT; 5 with AB-SA01 (bacteremia, $n = 4$; endocarditis, $n = 1$) and 3 with AB-PA01 (lung infection, $n = 3$). Median duration of BT was 14 days and treated patients received over 90 IV doses of AB-SA01 (3×10^9 PFU/dose) and over 490 IV and nebulized doses of AB-PA01 (4×10^9 PFU/dose). BT was well tolerated, with no treatment-related adverse events. Clinical treatment success was documented in 75% of patients. Isolates collected during therapy showed ongoing susceptibility to the BT products with changes in sensitivity to the individual phage components observed in some cases. Bacteriophage kinetics revealed bloodstream clearance within a few hours after IV infusion, with an inferred initial bacteria:bacteriophage ratio of ~200 for the bacteremia patients.

Conclusion. BT was well tolerated as an adjunct to antibiotics, with several examples presented of microbiological eradication and improvement of objective clinical criteria. BT appears to be a safe adjunct to antibiotic therapy in life-threatening *S. aureus* and *P. aeruginosa* infections and is a promising candidate for controlled clinical trials.

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1643. Pharmacodynamics (PD) of Daptomycin (DAP) in Combination Therapy for Enterococcal Bloodstream Infection (BSI)

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Session: 168. Novel Therapies for Superbugs
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Background. DAP is frequently employed in combination with a second antibiotic for enterococcal BSI. We previously observed that a free drug area under the curve to MIC ratio (*f*AUC/MIC) >27.43 was predictive of survival when DAP was administered as monotherapy. The extent to which combination therapy affects DAP PD remains unexplored.

Methods. This study pooled data from 7 published trials assessing outcomes in DAP treated enterococcal BSI. *f*AUC/MIC was calculated using a published population pharmacokinetic model based on creatinine clearance, 90% protein binding, and baseline DAP MIC for each patient that received ≥72 hours of DAP as part of a combination antibiotic regimen. The *f*AUC/MIC threshold predictive of 30-day survival was determined by classification and regression tree analysis and confirmed by multivariable logistic regression. To control for comorbidities, the threshold was examined in the low-acuity patients only (APACHE-II score <21, Charlson co-morbidity index <5, or Pitt bacteremia score <4). Monte Carlo simulation was performed to determine the probability of target attainment (PTA) over a range of MICs.

Results. In total, 240 adults were included and 137 (57.1%) were alive at 30 days. A majority of patients (62.8%) were immunosuppressed. Combination therapy with DAP plus a β-lactam was observed in 187 (77.9%) patients and with a β-lactam and 1 other active agent in 34 (14.2%) patients. Low-acuity patients ($n = 135$) were more likely to survive when *f*AUC/MIC >12.3 was achieved (63.2% versus 20.0%, $P = 0.015$). This difference remained significant when controlling for BSI source and immunosuppression ($P = 0.017$). The PTA for a 6 mg/kg/day dose was 95.2% at MIC=2 mg/L and 43.0% at MIC=4 mg/L; PTA for a 12 mg/kg/day dose was 95.2% at 4 mg/L.

Conclusion. Compared with our previous observations for DAP monotherapy against enterococcal BSI, a lower DAP PD exposure was required when administered with at least one additional antibiotic. For combination therapy with DAP, a *f*AUC/MIC >12.3 was associated with 30-day survival. As part of an active combination therapy regimen, DAP 6 mg/kg/day was appropriate for treatment of BSI caused by enterococci with MICs ≤2 mg/L, while 12 mg/kg/day was optimal for isolates with MICs of 4 mg/L.

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1644. A Potent Broadly Neutralizing Antibody Isolated From Human Memory B-cells Binding to Conserved Site IV on the RSV F Protein

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Session: 169. Respiratory and Gastroenteritis Viruses
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Background. Respiratory syncytial virus (RSV) infection is a major public health burden for infants and the elderly worldwide. Currently, there are

no approved vaccines and only one moderately effective marketed antibody (Synagis®) for the prevention of RSV infection in high-risk infants. Sampling the human antibody repertoire has led to the realization that the RSV fusion (F) protein in its prefusion conformation is the preferred target for potent neutralizing antibodies and thus makes the protein an attractive candidate for vaccine developers.

Methods. We report the isolation of a potent and broad RSV neutralizing monoclonal antibody (mAb), which was discovered through molecular cloning of cultured RSV postfusion F protein-baited single-sorted human memory B cells. The epitope for the mAb was mapped to RSV F protein using various methods; including X-ray crystallography, alanine scan, and RSV escape mutant generation

Results. The mAb binds to both RSV pre- and postfusion F proteins at site IV and can neutralize RSV A and B laboratory strains with subnanomolar potency, superior to that of Palivizumab. Antigenic site IV is conserved between pre- and postfusion F proteins in both RSV A and B subgroups, and sequence alignment showed that the mAb-binding site was conserved in >1,000 RSV A and B clinical isolates. *In vivo* cotton rat studies demonstrated protection of both the upper and lower respiratory tract of antibody-infused animals challenged with either RSV A or RSV B.

Conclusion. Overall, the fully human mAb we have isolated has great potential to be developed for passive immune-prophylaxis in infants. A prevalent view of the RSV scientific community is that RSV neutralizing mAbs in human sera primarily target the prefusion F protein and predominantly bind antigenic site Ø. In contrast, our finding demonstrates that very broad and potent RSV neutralizing mAb can also recognize sites common to pre- and postfusion F proteins. Furthermore, the RSV F antigenic site IV presents a neutralizing epitope which is highly conserved. Therefore, it is worthwhile to consider site IV, in addition to site Ø, in the design of RSV subunit vaccines.

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1645. Exploring Clinical and Antiviral Efficacy of Baloxavir Marboxil in a Phase 3, Randomized, Double-Blind, Placebo- and Active-Controlled Study of Otherwise Healthy Adults/Adolescents in Seasonal Influenza: Impact on Regional Participants, Treatment Time and Influenza Type B Virus Infection (CAPSTONE-1 Study)

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Session: 169. Respiratory and Gastroenteritis Viruses
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Background. Baloxavir marboxil (BXM), a selective cap-dependent endonuclease inhibitor, has demonstrated efficacy + safety for influenza in otherwise healthy patients. We present subgroup analyses for (i) United States vs. Japan (J), (ii) time (t) of treatment (early: ≥0 to ≤24 hours, vs. late: >24 to ≤48 hours), and (iii) influenza type B infections from the global Ph 3 trial (16/17 season).

Methods. A multicenter, randomized, double-blind, placebo (PLC)- and oseltamivir (OV)-controlled study recruited patients in Japan (n = 846) and United States (n = 590). Inclusion criteria: age 12–64 years, fever + flu symptoms, and ≤48 hours from symptom onset. Patients (20–64 years) randomized (2:2:1) to a single oral dose of BXM, PLC, or 75 mg OV BID for 5 days; patients 12–19 years were randomized (2:1) to receive BXM or PLC. BXM dose: 40/80 mg for BW </≥80 kg. Primary endpoint: time to alleviation of symptoms (TTAS) in ITTI population (pop). Viral titers measured from pre-/postdose nasal swabs.

Results. BXM reduced the median TTAS by 30.6 hours versus PLC (87.3 versus 117.9 hours, P = 0.1373) in the US pop and t to cessation of viral shedding: 24 versus 72 hours for PLC (P < .0001). Median TTAS in the United States versus J pop was longer, due to imbalances between groups. In both early/late treatments from symptom onset, BXM reduced TTAS versus PLC (Table 1). Regardless of the t to treatment from symptom onset, BXM reduced virus titer significantly from BL versus PLC and OV (Table 2). No significant reduction in TTAS was seen, while BXM reduced virus titer versus PLC and OV in type B virus infection.

Conclusion. Outcomes for United States were aligned with the Ph 3 Results. Early treatment with BXM leads to a significantly faster TTAS vs. PLC. BXM caused significant viral titer reduction regardless of treatment time versus OV. BXM reduced virus titer vs. PLC and OV in type B virus infection.

Table 1: Median TTAS (hours) to TTAS

t to Treatment From Symptom Onset	BXM	PLC	Strat. Gen. Wilcoxon Test[a]
Early	49.3 (N = 238)	82.1 (N = 120)	P < 0.0001
Late	66.2 (N = 217)	79.4 (N = 110)	P = 0.0080

[a]Stratification factors: region and composite symptom scores at baseline.

Table 2: Mean Change (Log_{10} [$TCID_{50}$/mL]) From BL of Viral Titer at 1 Day After Start of Treatment (Age ≥20)

t to treatment from symptom onset	BXM	OV	Strat. Gen. Wilcoxon Test[a]
Early	-4.46 (n = 180)	-2.57 (n = 187)	P < 0.0001
Late	-4.32 (n = 160)	-2.48 (n = 161)	P < 0.0001

[a]Same with Table 1.

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1646. Combined Resistance Analyses From Phase 2b Studies of Presatovir Treatment in RSV-Infected Adults

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Session: 169. Respiratory and Gastroenteritis Viruses
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Background. Presatovir is an oral respiratory syncytial virus (RSV) fusion inhibitor in development for the treatment of RSV infection. Results from a healthy volunteer challenge study show that presatovir significantly reduced RSV viral load and clinical signs and symptoms. Here we present combined resistance analyses from 4 phase 2b studies in naturally RSV-infected adults.

Methods. RSV RNA was isolated from nasal swabs collected at baseline and postbaseline in studies GS-US-218-0108, GS-US-218–1502, GS-US-218–1227, and GS-US-218–1797. Full-length RSV fusion (F) gene was PCR amplified and population sequencing was performed.

Results. Of 233 presatovir-treated adults in the efficacy analyses, post-baseline resistance-associated substitutions were detected in 18 (7.7%) subjects. Frequencies of resistance development varied by study (Table 1). Resistance substitutions known to confer high-level (>200 fold) reduced susceptibility to presatovir detected in >1 subject were: T400I (n = 6), S398L (n = 3), L141F (n = 2), and F140I (n = 2) in F. Subjects with resistant virus had less viral load reduction than presatovir-treated subjects without resistant virus. Resistance development did not impact clinical outcomes. In study GS-US-218-0108, subjects with lymphopenia (<200 cells/μL) at baseline were significantly more likely to develop resistance substitutions.

Table 1: Resistance Development Frequencies in Phase 2b Studies

Study	Subject Population	Presatovir Dose	Presatovir-Treated Subjects in Efficacy Analysis, n	Subjects with Resistance-Associated Substitutions, n (%)
GS-US-218-0108	Hematopoietic cell transplant (HCT) recipients with upper respiratory tract infection	Days 1, 5, 9, 13, and 17: 200 mg	89	10 (11.2%)
GS-US-218-1502	HCT recipients with lower respiratory tract infection	Days 1, 5, 9, 13, and 17: 200 mg	29	6 (20.7%)
GS-US-218-1227	Hospitalized adults	Day 1: 200 mg	80	1 (1.3%)
GS-US-218-1797	Lung transplant recipients	Day 1: 200 mg Days 2–14: 100 mg	35	1 (2.9%)

Conclusion. Presatovir treatment resulted in varying rates of resistance development across 4 phase 2b studies. Resistance development impacted virologic response without affecting clinical outcomes. Differences among study populations and dosing regimens may have influenced rates of resistance development.