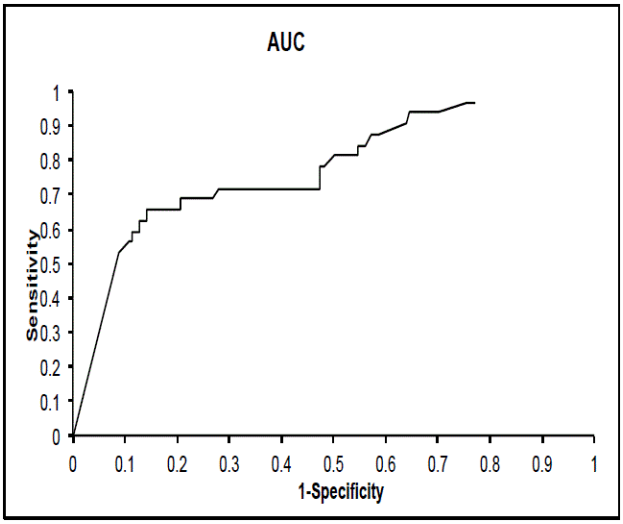
Figure. Accuracy, Sensitivity, and Specificity of Influenza Breath Test. Receiver operating characteristic (ROC) of the breath test (sensitivity versus 1-specificity). The accuracy of the breath test was 78%. With a cutoff point at the "shoulder" of the ROC curve, the test had 74% sensitivity and 70% specificity.



Conclusion. Our findings bolster available benchtop and clinical data suggesting that breath testing may be a useful diagnostic modality for influenza infection. The next step will be to study the predictive algorithm developed in this protocol in a blinded validation cohort. If the predictive algorithm performs well in a validation study, adaptation for its use in a portable, tabletop GC would be warranted to allow for a rapid, accurate, universal point-of-care influenza diagnostic test.

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1230. Clinical and Microbiologic Outcomes by Causative Pathogen in Hospital-Acquired or Ventilator-Associated Bacterial Pneumonia (HABP/VABP) Treated with Imipenem/Cilastatin (IMI)/Relebactam (REL) Versus Piperacillin/Tazobactam (PIP/TAZ)

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Session: P-56. New Drug Development

Background. IMI/REL is a combination of IMI and the novel class A and class C β-lactamase inhibitor REL. Here we present per-pathogen outcomes from a recent phase 3 clinical trial (RESTORE-IMI 2), in which IMI/REL was shown to be non-inferior to piperacillin/tazobactam (PIP/TAZ) for empiric therapy of HABP/VABP, in both primary and key secondary endpoints.

Methods. Randomized, controlled, double-blind, multinational, phase 3, non-inferiority trial in adults with HABP/VABP. Lower respiratory tract specimens were obtained ≤48 hours prior to screening. Participants (pts) were randomized 1:1 to IMI/REL 500 mg/250 mg or PIP/TAZ 4 g/500 mg, given intravenously every 6 h for 7-14 d. Pts also received empiric linezolid until baseline cultures confirmed absence of MRSA. This analysis evaluated outcomes by causative LRT pathogen in modified intent to treat (MITT) pts (randomized pts with ≥1 dose of study drug, excluding pts with only gram-positive cocci present on baseline Gram stain) who had ≥1 baseline LRT pathogen susceptible (according to CLSI criteria) to both study drugs. Outcomes assessed were microbiologic response at end of therapy (EOT), clinical response at early follow-up (EFU; 7-14 d after EOT), and Day 28 all-cause mortality (ACM).

Results. Of 531 MITT pts, 51.4% (130 IMI/REL, 143 PIP/TAZ) had ≥1 baseline LRT pathogen susceptible to both study drugs. The most common causative pathogens in this analysis population were *Klebsiella* spp (30.4% of patients), *Pseudomonas aeruginosa* (22.3%), *Escherichia coli* (22.0%), and *Haemophilus influenzae* (9.2%), consistent with other recent trials in HABP/VABP and with surveillance data. Outcomes by pathogen were generally comparable between IMI/REL and PIP/TAZ (Table). In a separate subgroup analysis of the microbiologic MITT population, in pts with ≥1 ESBL-positive LRT pathogen (45 IMI/REL, 35 PIP/TAZ), microbiologic response at EOT was 82.2% (IMI/REL) vs 68.6%% (PIP/TAZ), clinical response at EFU was 64.4% vs 60.0%, and Day 28 ACM was 20.0% and 22.9%, respectively. In the IMI/REL arm, 8 pts had ≥1 confirmed KPC-positive baseline LRT pathogen; KPC status was not assessed in the PIP/TAZ arm.

Conclusion. IMI/REL is an efficacious treatment option for HABP/VABP, regardless of causative pathogen.

Table. Primary and secondary efficacy outcomes in patients who were in the MITT population and had at least 1 baseline LRT pathogen susceptible to both study drugs

Baseline LRT Pathogen	Microbiologic Response at EOT		Clinical Response at EFU		Day 28 All-Cause Mortality	
	IMI/REL n/N (%)	PIP/TAZ n/N (%)	IMI/REL n/N (%)	PIP/TAZ n/N (%)	IMI/REL n/N (%)	PIP/TAZ n/N (%)
Enterobacterales overall	78/97 (80.4%)	72/100 (72.0%)	62/97 (63.9%)	62/100 (62.0%)	13/97 (13.4%)	22/100 (22.0%)
Klebsiella spp.[a]	32/42 (76.2%)	30/41 (73.2%)	25/42 (59.5%)	28/41 (68.3%)	6/42 (14.3%)	8/41 (19.5%)
E. coli	25/27 (92.6%)	23/33 (69.7%)	16/27 (59.3%)	19/33 (57.6%)	5/27 (18.5%)	8/33 (24.2%)
S. marcescens	8/10 (80.0%)	1/4 (25.0%)	7/10 (70.0%)	3/4 (75.0%)	2/10 (20.0%)	1/4 (25.0%)
E. cloacae	6/7 (85.7%)	13/16 (81.3%)	6/7 (85.7%)	12/16 (75.0%)	1/7 (14.3%)	3/16 (18.8%)
P. aeruginosa	17/26 (65.4%)	22/35 (62.9%)	12/26 (46.2%)	20/35 (57.1%)	7/26 (26.9%)	5/35 (14.3%)
A. calcoaceticus-baumannii complex	4/5 (80.0%)	4/10 (40.0%)	4/5 (80.0%)	6/10 (60.0%)	0/5 (0.0%)	1/10 (10.0%)
H. influenzae	12/13 (92.3%)	9/12 (75.0%)	9/13 (69.2%)	8/12 (66.7%)	2/13 (15.4%)	3/12 (25.0%)

[a]*Klebsiella* spp. includes *Klebsiella aerogenes*, *Klebsiella oxytoca*, and *Klebsiella pneumoniae*.

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1231. VIR-2482: A potent and broadly neutralizing antibody for the prophylaxis of influenza A illness

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Session: P-56. New Drug Development

Background. Influenza A viruses are responsible for seasonal epidemics and represent a constant pandemic threat. Influenza vaccines induce predominantly antibodies against the head region of hemagglutinin (HA) and are strain specific. Vaccine effectiveness is often suboptimal due to mismatch with drifting viruses and an inadequate immune response. Broadly neutralizing monoclonal antibodies (mAbs) targeting the conserved stem-region of HA may provide protection through multiple seasons and cover strains with pandemic potential. We report pre-clinical data on VIR-2482, a fully human anti-HA stem mAb with half-life extending Fc mutations.

Methods. Binding of VIR-2482 to a panel of influenza HAs and neutralization of H1N1 and H3N2 viruses were measured by ELISA and microneutralization. Epitope conservation was evaluated using 49,462 HA sequences retrieved from GiSAID. Engagement of human FcγRs by VIR-2482 was assessed by biolayer interferometry. Antibody-dependendent cell-mediated cytoxicity (ADCC) was measured via in vitro killing of A549 cells expressing H1-HA glycoprotein by human NK cells. Complement-dependent cytotoxicity (CDC) was evaluated by incubating VIR-2482 with H1N1 infected cells in the presence of guinea pig complement. Protection studies were performed in Balb/c mice given VIR-2482 24h before intranasal infection with a lethal dose of H1N1 PR8 and H3N2 HK/68.

Results. VIR-2482 binds to the HA proteins representing all 18 influenza A HA subtypes and neutralizes a broad panel of H1N1 and H3N2 viruses spanning almost 100 years of evolution. Bioinformatic analysis revealed >98.8% conservation for the majority of key contact residues examined from sequences retrieved for H1N1 and H3N2 between 2009-2019. The half-life extending mutations in the Fc portion do not affect the ability of the antibody to engage FcγRIIIa, FcγRIIa, and C1q as evidenced by their lack of impact on ADCC and CDC in vitro. Prophylactic administration of VIR-2482 protects Balb/c mice from infection with lethal challenge doses of H1N1 and H3N2 viruses.

Conclusion. The attributes of potency, broad recognition of a highly conserved epitope, retention of high-level effector functions in addition to half-life extension support the development of VIR-2482 as a universal prophylactic for influenza A illness.

Disclosures. Matteo Samuele Pizzuto, PhD, VIR Biotechnology (Employee) Fabrizia Zatta, n/a, Vir Biotechnology (Employee) Andrea Minola, MS, Vir Biotechnology (Employee) Alessia Peter, n/a, Vir Biotechnology (Employee) Katja Culap, n/a, Vir Biotechnology (Employee) Leah Soriaga, PhD, Vir Biotechnology (Employee) Anna De Marco, n/a, Vir Biotechnology (Employee) Barbara Guarino, PhD, Vir Biotechnology (Employee) Nadia Passini, n/a, Vir Biotechnology (Employee) David K. Hong, MD, Vir Biotechnology (Employee) Fabio Benigni, PhD, Vir Biotechnology (Employee) Christy Hebner, PhD, Vir Biotechnology (Employee) Aurelio Bonavia, PhD, Vir Biotechnology (Employee) Davide Corti, PhD, Vir Biotechnology (Employee)