(Employee, Shareholder) Uros Midic, PhD, Inflammatix Inc. (Employee, Shareholder) Roland Luethy, PhD, Inflammatix Inc. (Employee, Shareholder) David C. Rawling, PhD, Inflammatix Inc. (Employee, Shareholder) Timothy Sweeney, MD, Inflammatix, Inc. (Employee)

631. Preliminary safety and pharmacokinetic profile of VIR-2482: a monoclonal antibody for the prevention of influenza A illness

Jennifer Sager, PharmD[1]; David K. Hong, MD[1]; Aurelio Bonavia, PhD[1]; Lynn Connolly, MD, PhD[1]; Deborah Cebrik, PhD[1]; Marie Christine Fanget, MS[1]; Erik Mogalian, PharmD, PhD[1]; Paul Griffin, BSc(Hons), MBBS, FRACP, FRCPA[2]; [1]Vir Biotechnology, San Francisco, California; [2]Q-Pharm, Brisbane, Queensland, Australia

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Background: VIR-2482 is a fully human immunoglobulin G1(IgG) monoclonal antibody (mAb) directed against a highly-conserved epitope in the influenza A hemagglutinin stem region and is in clinical development for the prevention of influenza A illness. The Fc region of VIR-2482 has been modified to provide an extended half-life.

Methods: This is a randomized, placebo-controlled, Phase 1/2 study of VIR-2482 administered intramuscularly (IM) to healthy adult volunteers aged 18-64 years old who have not received a current influenza vaccine. The Phase 1 portion of the study will evaluate the safety, tolerability, pharmacokinetic (PK), and immunogenicity profile of VIR-2482 following single (Part A) or multiple doses (Part B). The Phase 2 study will evaluate the efficacy of VIR-2482 in the prevention of influenza A illness as well as safety, tolerability, and PK. Part A is ongoing and consists of four single dose cohorts (N=25/cohort) randomized (4:1) to a single dose of VIR-2482 or placebo at 60, 300, 1200, or 1800 mg. Safety, tolerability, PK and immunogenicity will be evaluated for at least 52 weeks post-dose.

Results: In Part A, all 100 subjects received a single dose of VIR-2482 (N=80) or placebo (N=20). Preliminary blinded safety data for all cohorts and PK data for the 300 and 1200 mg cohorts are reported here. Dosing was well tolerated; 6% (6/100) of subjects experienced mild injection site reactions, which generally resolved within 48 hrs. Through 12 weeks post-dosing, the majority (124/126; 98.4%) of adverse events (AEs) were mild to moderate in nature, no serious AEs were reported, and no subjects discontinued due to an AE. Based on available data, exposure (C_{max} and AUC) between 300 and 1200 mg of VIR-2482 increased in a dose proportional manner. The PK profile of VIR-2482 is consistent with a half-life extended IgG.

Conclusion: Based on available data, VIR-2482 has been well tolerated following single IM doses of up to 1800 mg in healthy subjects. The preliminary PK profile of VIR-2482 enables once per season dosing. Overall, these data support initiation of a Phase 2 study to evaluate efficacy of VIR-2482 for the prevention of influenza A illness.

Disclosures: Jennifer Sager, PharmD, Vir Biotechnology (Employee) David K. Hong, MD, Vir Biotechnology (Employee) Aurelio Bonavia, PhD, Vir Biotechnology (Employee) Lynn Connolly, MD, PhD, Vir Biotechnology (Employee) Deborah Cebrik, PhD, Vir Biotechnology (Independent Contractor) Marie Christine Fanget, MS, Vir Biotechnology (Employee) Erik Mogalian, PharmD, PhD, Vir Biotechnology (Employee)

632. A Randomized, Placebo-Controlled, Double-Blind, Clinical Trial Evaluating Two Dose Regimens of Rifaximin (550mg daily or twice-daily) for Chemoprophylaxis Against Travelers' Diarrhea Among Deployed U.S. and U.K. Military Personnel (PREVENT TD)

Ramiro L. Gutierrez, MD, MPH[1]; Daniel Burns, MD, DTM&H[2]; Tahaniyat Lalani, MBBS[3]; Denise Bennett-Carter, MS[4]; Jamie Fraser, MPH[5]; Mark Riddle, MD, DrPH[6]; Patrick Connor, MD[7]; Chad Porter, PhD, MPH[8]; Thomas Troth, MD[7]; Richard Ruck, MD[9]; Jerry Barton, MD[9]; Drake H. Tilley, MD, MPHT&M[10]; Anjali Kunz, MD[11]; Mary Fairchok, MD[11]; Heather Yun, MD[12]; Bryan Alvarez, MD[13]; Robert Higgins, MS[13]; Indrani Mitra, MS[14]; Laveta Stewart, PhD, MSc, MPH[15]; Azizur Rahman, MA[4]; JoAnna Rimmer, MD[7]; Emma Hutley, PhD[7]; Brett Swierczewski, PhD[16]; Bethany Tabberer, BS[7]; David Tribble, MD, DrPH[17]; [1]Naval Medical Research Center, Silver Spring, Maryland, Gaithersburg, Maryland; [2]UK Ministry of Defence, Birmingham, England, United Kingdom; [3]Infectious Disease Clinical Research Program, Bethesda, MD, The Henry M. Jackson Foundation, Bethesda, MD, and Naval Medical Center Portsmouth, VA, Portsmouth, Virginia; [4]Infectious Diseases Clinical Research Program, Uniformed Services University of the Health Sciences, Bethesda, Maryland; [5]Infectious Disease Clinical Research Program - USU, Rockville, Maryland; [6]University of Nevada, Reno School of Medicine, Reno, Nevada; [7]Royal Centre for Defense Medicine, Birmingham, England, United Kingdom; [8]Naval Medical Research Center, Silver Spring, Maryland; [9]US Army, Honolulu, Hawaii; [10]Naval Medical Center San Diego, San Diego, CA; [11]Madigan Army Medical Center, Tacoma, WA; [12]Brooke Army Medical Center; Department of Medicine, Uniformed Services University of the Health Sciences, San Antonio, Texas; [13]Naval Hospital Camp Lejeune, Jacksonville, North Carolina; [14]Henry M. Jackson Foundation for the Advancement of Military Medicine; Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, MD; [15]USU Infectious Disease Clinical Research Program, Henry M. Jackson Foundation, Rockville, MD; [16]Walter Reed Army Institute of Research, Silver Spring, Maryland; [17]Uniformed Services University, Bethesda, MD

PREVENT-TD Study Team

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Background: Travelers' diarrhea (TD) is a leading threat to military readiness. Most trials of rifaximin chemoprophylaxis involve civilians or short-duration travel, whereas military travelers are exposed for longer periods at austere locations and are often physically taxed. We sought to assess efficacy of two regimens among military personnel deployed overseas.

Methods: This was a multi-site, double-blind, placebo-controlled trial of deployed military, randomized to placebo, rifaximin 550 mg daily, or rifaximin 550 mg twice-daily, for up to 42 days (1:1:1; 6 randomizations/block). Diaries were reviewed with subjects on return. Primary endpoint was time to first unformed stool (TFUS) in a TD episode. Other endpoints were assessed by intention to treat (ITT) and subgroups included incidence of any loose stool, meeting criteria for TD, safety, efficacy, adherence and impact to activity endpoints.

Results: 343 subjects were included in the ITT population. All UK travelers deployed to a single-site in Kenya; US travelers mostly deployed to various Asia-Pacific locations. Of 73 (21.2%) subjects reporting diarrhea, 42 (57.5%) met TD criteria. Among rifaximin-treated subjects, 15.9% (n=17) reported diarrhea in the twice-daily arm, 20.7% (n=25) in the daily arm, vs. 27.0% (n=31) of placebo recipients; p=.04 and 0.26 respectively. TD was reported by 10.3% (n=11) and 10.7% (n=13) in the daily and twice-daily arms, vs. 15.7% (n=18) among placebo recipients; p=0.24 vs. 0.26 respectively. Among UK personnel, a twice-daily regimen vs. placebo resulted in significantly fewer TD episodes (1.6% vs. 11.9%; p=0.03). Adverse events were similar between groups.

Table 1: Demographics, endpoints, and adverse events (Comparisons are across placebo vs. each dosing regimen. Intent-to-treat [ITT] population defined as subjects enrolled into the study, randomized, travelled and had follow-up. p-values calculated from chi-square or Fisher's exact test [categorical variables] and Wilcoxon-Mann-Whitney test [continuous variables]. Analyses performed on SAS v9.4. BID: twice-daily)

	Rifaximin 550mg BID	Rifaximin 550mg daily	Placebo	Total	p-value twice-daily	p-value daily
Total ITT population n (%)	107 (31.2)	121 (35.3)	115 (33.5)	343	NA	NA
Gender n (%)					0.786	0.291
Male	97 (90.6)	113 (93.4)	103 (89.6)	313 (91.2)		
Travel Duration (days)						
Median (IQR)	45 (39-50)	45 (38-50)	45 (40-50)	45 (38-50)	0.955	0.592
Subject Group n (%)					0.926	0.749
US	44 (41.1)	53 (43.8)	48 (41.7)	145 (42.3)		
UK	63 (58.9)	68 (56.2)	67 (58.3)	198 (57.7)		
Region n (%)					0.659	0.901
South America	1 (0.9)	1 (0.8)	1 (0.9)	3 (0.9)		
Sub-Saharan Africa	71 (66.4)	73 (60.8)	75 (65.2)	219 (64.0)		
South-East Asia	22 (20.6)	32 (26.7)	28 (24.4)	82 (24.0)		
East-North Asia	8 (7.5)	11 (9.2)	10 (8.7)	29 (8.5)		
Central America	2 (1.9)	0 (0)	0 (0)	2 (0.6)		
South-Central Asia	3 (2.8)	3 (2.5)	1 (0.9)	7 (2.0)		
Subjects Reporting any diarrhea (Loose stools)	17 (15.9)	25 (20.7)	31 (27.0)	73 (21.2)	0.045	0.256
Subjects Meeting TD Criteria	11 (10.3)	13 (10.7)	18 (15.7)	42 (12.2)	0.235	0.264
Subjects Reporting any Diarrhea (Loose stools – by UK Subject Group)	4 (6.4)	11 (16.2)	15 (22.4)	30 (15.2)	0.0097	0.360
Subjects Meeting TD Criteria (by UK Subject Group)	1 (1.6)	5 (7.4)	8 (11.9)	14 (7.1)	0.034	0.366
Subjects Reporting any Diarrhea (Loose stools – by US Subject Group)	14 (29.6)	14 (26.4)	16 (33.3)	43 (29.7)	0.696	0.441
Subjects Meeting TD Criteria (by US Subject Group)	10 (22.7)	8 (15.1)	10 (20.8)	28 (19.3)	0.826	0.452
TFUS						
Days: Median (IQR)	11.8 (5.3-50.6)	21.3 (12.9-30.3)	14.3 (5.9-34.9)		0.75	0.76
Adverse events					0.559	0.139
None	77 (72.0)	90 (74.4)	77 (67.0)	244 (71.1)		
Mild/Moderate	30 (28.0)	27 (74.4)	37 (32.2)	94 (27.4)		
Severe	0 (0)	4 (3.3)	1 (0.9)	5 (1.5)		

Conclusion: This is the first trial comparing two high-dose regimens of rifaximin prophylaxis in deployed personnel. Unlike prior reports, neither regimen was associated with an overall significant decrease in TD, potentially due to low overall TD incidence. However, the twice-daily regimen was associated with a numerically lower incidence of diarrheal stool, and in the UK subject group, there was a significant decrease of both TD and diarrheal stool. The impact of variability in regional TD risk, pathogen distribution and adherence in austere deployment environments on efficacy will be reviewed.

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633. Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) Efficacy in Participants with Pre-Existing Primary Integrase Inhibitor Resistance Through 48 Weeks of Phase 3 Clinical Trials

Michelle L. D'Antoni, PhD[1]; Kristen Andreatta, MSc[2]; Rima K. Acosta, BS[3]; Silvia Chang, Masters[4]; Ross Martin, PhD[4]; Kirsten L. White, PhD[3]; [1]Gilead Sciences Inc, Foster City, California; [2]Gilead Sciences, Inc, Foster City, California; [3]Gilead Sciences, Inc., Foster City, California; [4]Gilead Sciences, Foster City, California

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Background: Pre-existing drug resistance can affect the efficacy of antiretroviral therapy. Studies in treatment-naïve and virologically suppressed participants have demonstrated safety and efficacy of B/F/TAF, including in patients with M184V/I mutations. In this pooled analysis, we investigated virologic outcomes after 48 weeks of B/F/TAF treatment in individuals with pre-existing integrase strand transfer inhibitor resistance (INSTI-R).

Methods: Although INSTI-R was prohibited per study entry criteria, pre-existing INSTI-R (T66A/I/K, E92G/Q, F121Y, Y143C/H/R, S147G, Q148H/K/R, N155H/S, R263K) was evaluated in participants from studies 1489, 1490, 1844, 1878, 4030. INSTI-R was assessed by historical genotypes and/or retrospective deepType HIV assay (Seq-IT, Germany), GenoSure IN, GenoSure Archive (Monogram Biosciences). Virologic outcomes were defined by last on-treatment observation carried forward (LOCF) method.

Results: Pre-existing primary INSTI-R substitutions were detected in 20/1907 participants (1.0%) after enrolment. Of the 20, 75% were male, 30% white, and 85% had HIV-1 subtype B, baseline median CD4 counts of 594 (IQR 517, 700), and median age of 52 (43, 59) years. One participant was treatment-naïve with a baseline viral load of 30,000 copies/ml and had Q148H (+ G140S on plasma RNA genotype) and was sensitive to bictegravir (< 2.5-fold change). The other 19 participants were virologically suppressed and had E92G (n=3), Y143C (n=2), Y143H (n=4), S147G (n=2), N155S (n=1), Q148H (n=3), Q148K (n=1), Q148R (n=1), or R263K (n=2) INSTI-R mutations by DNA genotype. The treatment-naïve individual was suppressed by Week 4 and maintained viral loads of < 50 copies/mL through Week 48. All suppressed participants had HIV RNA < 50 copies/mL throughout Week 48. All study participants had virologic success by LOCF (< 50 copies/mL) at Week 48.

Conclusion: Participants with primary INSTI-R substitutions had or maintained virologic suppression through 48 weeks of B/F/TAF treatment. Consistent with the potent in vitro activity of bictegravir against many INSTI-R mutations, these virologic outcomes suggest that B/F/TAF may have potential as a treatment option for some patients with pre-existing INSTI-R, if confirmed by further studies.

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634. Chlorhexidine Oral Rinses to Alter the Oral and Sputum Microbiota in COPD (CLIMB): a Randomized, Double-blinded, Placebo-controlled, Parallel-group Pilot Study

Alexa Pragman, MD, PhD[1]; Ann Fieberg, MS[2]; Cavan Reilly, PhD[2]; Chris Wendt, MD[1]; [1]Minneapolis VA Medical Center, Minneapolis, Minnesota; [2]University of Minnesota, Minneapolis, Minnesota

Session: P-24. Clinical Trials

Background: Chronic obstructive pulmonary disease (COPD) is a progressive, inflammatory lung disease with few available disease-modifying therapies. Acute exacerbations of COPD (AECOPD) increase morbidity and mortality, and their occurrence coincides with sputum and oral microbiota dysbiosis. The oral microbiota also serves as the source of the lower airway microbiota. Chlorhexidine oral rinses are known to alter the oral microbiota. We hypothesized that subjects randomized to 8 weeks of chlorhexidine oral rinses (vs. placebo) will demonstrate decreased microbiota biomass compared to baseline and those on placebo.

Methods: We performed a randomized, double-blind, placebo-controlled, 8-week study of the effects of twice-daily chlorhexidine oral rinses on 44 subjects with COPD. Baseline and post-treatment data were obtained evaluating oral and sputum microbiota biomass and composition, systemic inflammation (CRP, fibrinogen, and WBC count), and respiratory symptoms (Breathlessness, Cough, and Sputum Scale [BCSS], St. George's Respiratory Questionnaire [SGRQ], and AECOPD assessment). All analyses were prespecified.

Table 1. Baseline Characteristics by Treatment Group

	Chlorhexidine	Placebo
	Mean ± SD or N (%)	Mean ± SD or N (%)
Number of Participants	**24**	**20**
Gender (% female)	2 (8.3)	1 (5.0)
Age (years)	67.6 ± 7.2	68.3 ± 6.0
Race non-white	1 (4.2)	0 (0.0)
Season**		
Spring	3 (15.0)	6 (30.0)
Summer	7 (35.0)	4 (20.0)
Fall	7 (35.0)	6 (30.0)
Winter	3 (15.0)	4 (20.0)
Years smoked	40.8 (10.4)	43.6 (10.3)
Current smoker	6 (25.0)	7 (35.0)
SGRQ	49.2 (17.2)	41.8 (12.3)
FEV_1 % predicted	39.9 (12.6)	43.8 (11.1)
FVC % predicted	66.2 (14.8)	71.4 (12.9)
COPD exacerbations (past 12 months)	2.3 (1.5)	1.8 (1.0)
COPD hospitalizations (past 12 months)	0.5 (0.7)	0.7 (0.7)

**Assigned to the season that covered >50% of the study period for a given participant.
Abbreviations: SD = Standard deviation; SGRQ = St. George's Respiratory Questionnaire; FEV_1 = Forced expiratory volume in one second; FVC = Forced vital capacity; COPD = Chronic obstructive pulmonary disease.

Results: Forty of 44 participants completed the study. The primary analysis of the mean differences in oral and sputum microbiota biomass between treatment groups was not significant. Chlorhexidine use was associated with a decrease in oral and sputum microbiota alpha diversity compared with placebo (Shannon diversity index change [standard error]: -0.349 [0.091] and -0.622 [0.169] respectively; p_{adj}=0.001 for both). There was no significant change in CRP, fibrinogen, WBC count, or BCSS score between treatment groups over the study period. Chlorhexidine use was associated with a significant improvement in SGRQ score when compared to the placebo (mean change ± standard deviation: chlorhexidine -4.7 ± 8.0 vs. placebo 1.7 ± 8.9, p=0.011; minimal clinically important difference in SGRQ score -4). Few adverse events were reported.

Table 2. Linear regression results of the effect of treatment group on the change in alpha diversity

	Linear Regression			
Outcome	**Predictor**	**Estimate(SE)**	**Unadjusted P-value**	**Adjusted P-value[1]**
Shannon Diversity Index Change (Week 8- Baseline)				
Oral Wash (N=40)	Treatment Group[2]	-0.349 (0.091)	0.0005	0.0010
	Baseline Index	-0.197 (0.073)	0.0100	
Sputum (N=35)	Treatment Group	-0.622 (0.169)	0.0008	0.0010
	Baseline Index	-0.312 (0.111)	0.0083	
Simpson Diversity Index Change (Week 8- Baseline)				
Oral Wash (N=40)	Treatment Group	-0.030 (0.008)	0.0005	0.0010
	Baseline Index	-0.196 (0.114)	0.0938	
Sputum (N=35)	Treatment Group	-0.091 (0.034)	0.0123	0.0123
	Baseline Index	-0.109 (0.179)	0.5472	
Inverse Simpson Diversity Index Change (Week 8- Baseline)				
Oral Wash (N=40)	Treatment Group	-6.391 (1.799)	0.0011	0.0022
	Baseline Index	-0.451 (0.061)	<0.0001	
Sputum (N=35)	Treatment Group	-6.870 (2.311)	0.0056	0.0056
	Baseline Index	-0.313 (0.110)	0.0077	

[1]A Step-down Bonferroni p-value adjustment is made for the two comparisons (oral wash and sputum) within each Diversity Index.
[2]Treatment group is coded as Chlorhexidine = 1, Placebo = 0.

Table 3. Secondary outcomes by Treatment Group

		Chlorhexidine (N=20)		Placebo (N=20)	P-value*
8-week Change	N	Mean ± SD or N (%)	N	Mean ± SD or N (%)	
BCSS	19	-0.3 (1.9)	18	-0.1 (1.5)	0.810
SGRQ Total Score	20	-4.7 (8.0)	20	1.7 (8.9)	0.011
Activity Domain	20	-0.5 (9.1)	20	3.9 (12.9)	0.140
Impacts Domain	20	-5.4 (12.6)	20	0.7 (10.0)	0.064
Symptoms Domain	20	-10.1 (15.2)	20	0.8 (18.8)	0.083
C-reactive Protein (mg/L)	20	1.8 (7.5)	20	0.4 (6.8)	0.989
Fibrinogen (mg/dL)	19	22.5 (77.8)	20	10.0 (77.0)	0.574
Leukocytes (K/cmm)	20	0.2 (1.8)	19	0.5 (1.8)	0.790

*P-values for the comparisons of Chlorhexidine vs. Placebo are from the Wilcoxon Two-Sample Test.
Abbreviations: SD = Standard deviation; BCSS = Breathlessness, Cough and Sputum Scale; SGRQ = St. George's Respiratory Questionnaire.

Conclusion: Among those with COPD, use of twice-daily chlorhexidine oral rinses resulted in decreased oral and sputum microbiota alpha diversity and clinically significant improvement in COPD symptoms. Chlorhexidine use did not result in decreased oral or sputum microbiota biomass or decreased systemic inflammation.

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635. Efficacy, Pharmacokinetics (PK), and Safety Profile of MEDI3902, an Anti-Pseudomonas aeruginosa Bispecific Human Monoclonal Antibody in Mechanically Ventilated Intensive Care Unit Patients; Results of the Phase 2 EVADE Study Conducted by the Public-Private COMBACTE-MAGNET Consortium in the Innovative Medicines Initiative (IMI) Program.

Jean Chastre, MD[1]; Bruno François, Physician[2]; Marc Bourgeois, MD[3]; Apostolos Komnos, MD, PhD[4]; Ricard Ferrer, MD, PhD[5]; Galia Rahav, MD[6]; Nicolas De Schryver, MD[7]; Alain Lepape, MD[8]; Iftihar Koksal, Prof. MD[9]; Charles-Edouard Luyt, Md, PhD[1]; Miguel Sanchez Garcia, MD, PhD[10]; Antoni Torres, MD, PhD[11]; Thomas L. Holland, MD[12]; Thomas L. Holland, MD[12]; Omar Ali, PhD[13]; Kathryn Shoemaker, MS[13]; Pin Ren, PhD[13]; Alexey Ruzin, PhD[13]; Yu Jiang, PhD[13]; Susan Colbert, BSN[14]; Drieke Vandamme, PhD[2]; Terramika Bellamy, n/a[13]; Colin Reisner, MD[13]; Filip Dubovsky, MD, MPH[13]; Hasan S. Jafri, MD, FAAP[13]; [1]Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, APHP Sorbonne Université, Paris, Ile-de-France, France; [2]CHU Limoges, Limoges, Limousin, France; [3]AZ Sint-Jan Brugge-Oostende AV, Brugge, West-Vlaanderen, Belgium; [4]General Hospital of Larisa, Larissa, Larisa, Greece; [5]Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain; [6]Sheba Medical Center and Tel Aviv University, Ramat Gan, HaMerkaz, Israel; [7]Clinique Saint-Pierre, Ottignies, Brabant Wallon, Belgium; [8]Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Lyon, Rhone-Alpes, France; [9]Faculty of Medicine, Trabzon, Trabzon, Turkey; [10]Hospital Clínico San Carlos, Madrid, Madrid, Spain; [11]Hospital Clinic, University of Barcelona, IDIBAPS, CIBERES, Barcelona, Catalonia, Spain; [12]Duke University, Raleigh, North Carolina [13]AstraZeneca, Gaithersburg, Maryland; [14]Astrazeneca, Gaithersburg, Maryland