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Preliminary Safety and Pharmacokinetic Profile of VIR-2482: a Monoclonal Antibody for the Prevention of Influenza A Illness

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Introduction

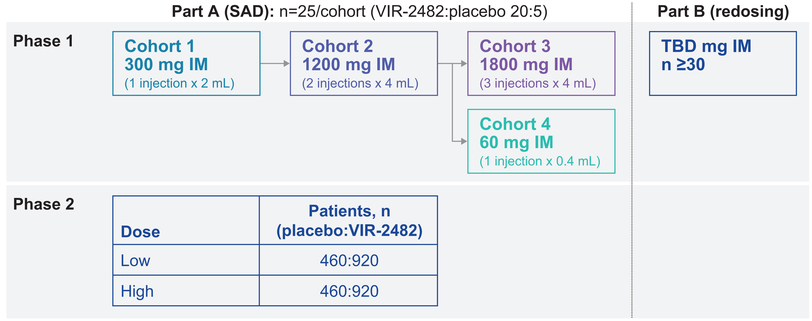
- VIR-2482 is a fully human immunoglobulin G1 (IgG) monoclonal antibody directed against a highly conserved epitope in the influenza A hemagglutinin stem region and is in clinical development for the prevention of influenza A illness
  - The Fc region of VIR-2482 has been modified to provide an extended half-life ($t_{1/2}$) and has potential to increase lung tissue bioavailability[1]
- *In vitro*, VIR-2482 demonstrated coverage of all major strains from the last 100 y and was more potent than a representative panel of other influenza A stem antibodies
- VIR-2482 provides passive immunity and does not require the person to generate their own antibodies
- Preliminary safety, tolerability, and pharmacokinetic (PK) data from the first-in-human, randomized, placebo-controlled, Phase 1/2 study in healthy subjects are reported herein

Objectives

- To evaluate the safety, tolerability, PK, and efficacy profile of VIR-2482 for the prevention of influenza A illness in healthy adults

Methods

Phase 1/2 Study Design



- Randomized, blinded, placebo-controlled study of VIR-2482 following IM administration to healthy adults who have not received the seasonal influenza vaccine
- Part A is ongoing, and the design and preliminary results are presented
- 4 cohorts (n=25/cohort) were randomized (4:1) to receive VIR-2482 or placebo
- Sentinel subjects were used throughout Part A
- Progression within and between cohorts was guided by review of blinded safety data

SAD, single ascending dose; TBD, to be determined.

- Serum PK samples were collected at specified visits for 52 wk
- VIR-2482 serum concentrations were determined using an electrochemiluminescent method validated on the Meso Scale Discovery (Rockville, MD) platform
- PK parameters were estimated using standard noncompartmental methods in WinNonlin® 8.2 (Certara L.P., Princeton, NJ) and summarized using descriptive statistics
- Adverse event (AE) monitoring, clinical laboratory examinations, physical examinations, and electrocardiographic evaluations were performed throughout the study
- Injection-site tolerability assessments were performed ~30 min, 2, 12, 24, and 48 h, and 1 wk postdose
- The study is ongoing and remains blinded

Results

Part A Enrollment and Demographics

	VIR-2482 or Placebo			
	60 mg n=25	300 mg n=25	1200 mg n=25	1800 mg n=25
Mean age, y (range)	38 (19–63)	29 (18–56)	28 (18–57)	29 (18–52)
Sex, n (%)				
Men	17 (68)	13 (52)	11 (44)	15 (60)
Women	8 (32)	12 (48)	14 (56)	10 (40)
Race or ethnic group, n (%)				
Asian	2 (8)	1 (4)	3 (12)	4 (16)
Black	0	1 (4)	0	0
White	21 (84)	21 (84)	17 (68)	16 (64)
Other	2 (8)	2 (8)	5 (20)	5 (20)
Hispanic or Latino	2 (8)	4 (16)	5 (20)	0
Median BMI, kg/m^2 (range)	26.3 (18.0–31.8)	24.8 (19.8–31.8)	23.8 (19.0–29.2)	25.7 (19.9–30.4)

BMI, body mass index.

Safety*

Injection-Site Reactions

	VIR-2482 or Placebo			
n/n (%)	60 mg n=25	300 mg n=25	1200 mg n=25	1800 mg n=25
Grade 1	1/25 (4) Bruising (only observed on Day 8)	2/25 (8) Bruising, redness, swelling (30 min), pain (up to 12 h), or pain/ tenderness (2 h)	2/25 (8) Pain (2 h) or bruising (3 d)	1/25 (4) Bruising (12 h)
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0

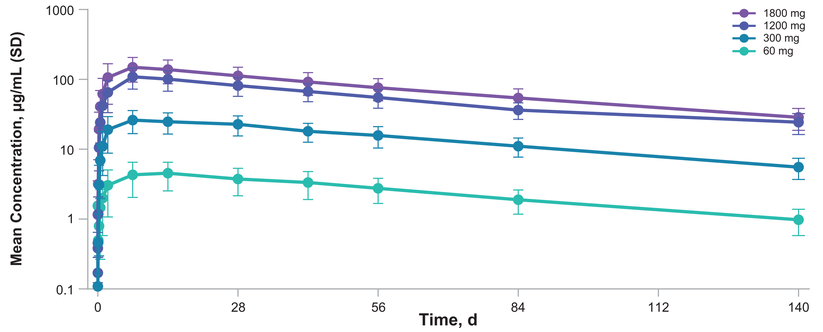
Treatment-Emergent Adverse Events

	VIR-2482 or Placebo			
Subjects With ≥1 AE, n (%)	60 mg n=25	300 mg n=25	1200 mg n=25	1800 mg n=25
Grade 1	15 (60)	12 (48)	12 (48)	17 (68)
Grade 2	3 (12)	4 (16)	5 (20)	1 (4)
Grade 3	0	0	1 (4)†	0
Grade 4	0	0	0	0
Related AE	7 (28)	8 (32)	5 (20)	6 (24)
Serious AE	0	0	0	0
AE leading to study discontinuation	0	0	0	0

*Preliminary safety data up to Week 20; †Adjudicated as not related to study drug (vasovagal AE).

- All 100 subjects have received a single IM dose of VIR-2482 (n=80) or placebo (n=20)
- All safety data remain double blinded
- Based on review of preliminary blinded safety data for each cohort through at least Week 20:
  - There were minimal injection-site reactions at all doses tested (maximum: 1800 mg, 3 x 4-mL injections); 6 subjects experienced mild injection-site reactions, which generally resolved within 48 h
  - Overall, VIR-2482 demonstrated a favorable safety profile
  - No serious AEs were noted and no Grade 3 AEs were related to study drug
  - No clinically significant laboratory abnormalities were noted

Preliminary VIR-2482 Serum Pharmacokinetics



	VIR-2482 Dose			
Parameter*	60 mg n=20	300 mg n=20	1200 mg n=20	1800 mg n=20
C_{max}, µg/mL	4.52 (45.4)	26.6 (35.2)	110 (32.9)	152 (38.4)
C_{max}/D, µg/mL/mg	0.075 (45.4)	0.088 (35.2)	0.091 (32.9)	0.084 (38.4)
T_{max}, d	14 (7, 17.5)	7.0 (7.0, 14.0)	7.0 (7.0,7.0)	7.0 (7.0, 14.0)
T_{last}, d	140	140	140	140
AUC_{last}, d·µg/mL	343 (41.5)	2010 (32.3)	7180 (32.7)	9930 (38.7)
AUC % extrapolated	19.0 (24.5)	18.8 (19.3)	21.4 (22.2)	19.3 (17.8)
AUC_{∞}, d·µg/mL	455 (34.1)	2470 (32.3)	9750 (30.0)	12700 (34.8)
AUC_{∞}/D, d·µg/mL/mg	7.59 (34.1)	8.24 (32.3)	8.12 (30.1)	7.05 (34.8
CL/F, mL/d	157 (58.0)	137 (39.1)	134(29.5)	164 (47.0)
V/F, L	12.8 (63.1)	11.1 (36.1)	11.7 (30.4)	14.1 (55.4)
$t_{1/2}$, d	58.1 (49.6, 62.5)	58.7 (53.3, 61.4)	60.1 (56.7, 67.9)	57.8 (54.6, 63.4)

*All parameters are listed as mean (% coefficient of variation) except for time to maximal concentration (C_{max}; T_{max}) and $t_{1/2}$, which are displayed as median (quartiles 1, 3). AUC, area under curve; AUC_{∞}, AUC from time 0 to ∞; AUC_{last}, AUC to last measurable concentration; CL/F, apparent oral clearance; D, divided by dose; SD, standard deviation; T_{last}, time of last measurable concentration; V/F, apparent volume of distribution.

- PK profile of VIR-2482 was consistent with that of a $t_{1/2}$-extended IgG, with concentrations measurable for ≥20 wk
- Approximately dose-proportional increases in C_{max} and AUC from Day 0 to 140
- Preliminary $t_{1/2}$ estimate: ~58 d

Conclusions

- Following a single IM dose in healthy subjects, VIR-2482 has been well tolerated at doses up to 1800 mg and maintained systemic exposure for ≥20 wk
- The preliminary PK profile of VIR-2482 enables once-per-season dosing
- Overall, these first-in-human data support initiation of a Phase 2 study to evaluate the efficacy of VIR-2482 for the prevention of influenza A illness

Reference: 1. Ko S-Y, et al. Nature 2014;514:642-5. **Acknowledgments:** This study was funded by Vir Biotechnology, Inc.