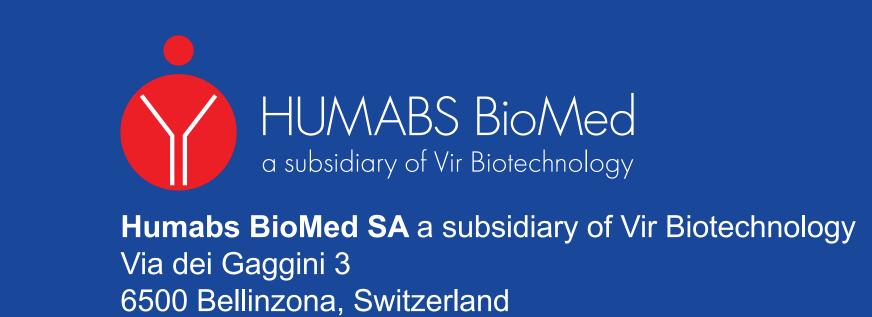
VIR-2482: a Potent and Broadly Neutralizing Antibody for the Prophylaxis of Influenza A Illness

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Introduction

- Influenza A viruses (IAVs) are responsible for seasonal epidemics and zoonotic infections, thus representing a constant threat to human health
- The glycoprotein hemagglutinin (HA) is the main target of influenza-neutralizing antibody response to infection or vaccination¹
- However, seasonal influenza vaccines induce only narrow, strain-specific immune responses that do not provide coverage against new pandemic or emerging viruses
- Moreover, their effectiveness varies dramatically according to the match with the circulating virus strains
- Broadly neutralizing monoclonal antibodies (mAbs) targeting the conserved stem region of HA may provide consistent effectiveness throughout multiple influenza seasons and broaden the coverage to include animal-circulating strains with pandemic potential

Objective

■ To assess new preclinical data on VIR-2482, which is a fully human, influenza A—neutralizing, stem-directed, mAb engineered in the Fc with half-life—extending mutations

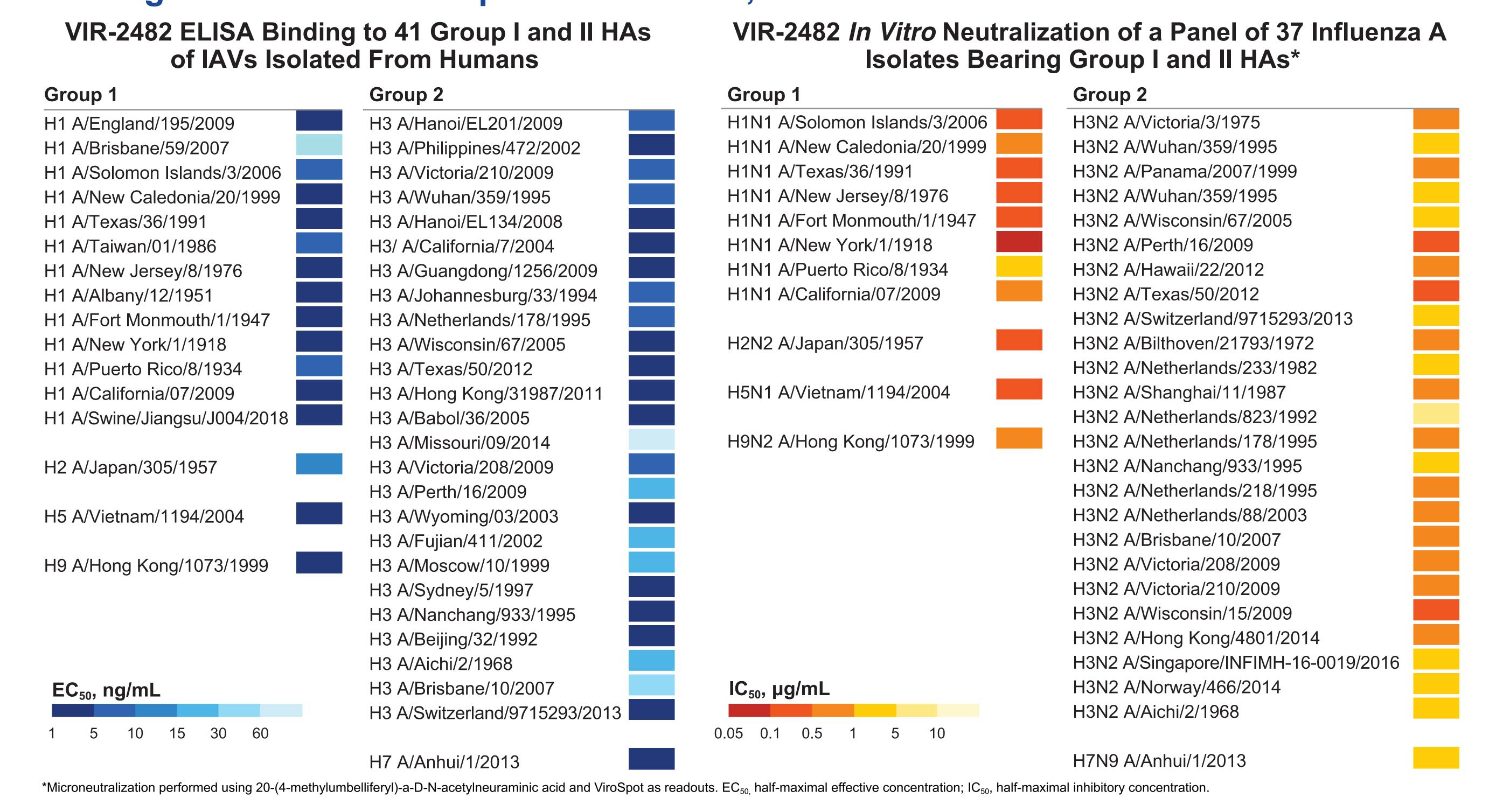
Methods

- Binding of VIR-2482 to a panel of group I and II IAV HAs, and neutralization of H1N1 and H3N2 viruses were measured by enzyme-linked immunosorbent assay (ELISA) and microneutralization, respectively
- ▼Epitope conservation was assessed by analyzing 49,462 sequences retrieved from the GISAID Initiative (originally known as a Global Initiative on Sharing All Influenza Data) of H1N1 and H3N2 strains isolated between 2009 and 2019
- Activation of Fcγ receptors (FcγRs) IIIa and IIa by VIR-2482 was evaluated via activation of engineered Jurkat cells (Promega Corporation, Madison, WI) following incubation of the mAb with A549-H1 target cells stably transfected to express HA from A/California/07/2009 (H1N1)
- ■Antibody-dependent cell-mediated cytotoxicity (ADCC) was measured as in vitro killing of A549-H1 cells by human natural killer (NK) cells, whereas complement-dependent cytotoxicity (CDC) was evaluated incubating VIR-2482 with H1N1-infected cells in the presence of guinea pig complement
- Prophylactic efficacy studies were performed in BALB/c mice administered VIR-2482 24 h before intranasal infection with a lethal dose of H1N1 Puerto Rico/8/1934 (PR8) and H3N2 A/Hong Kong/8/1968 (HK/68)

Results

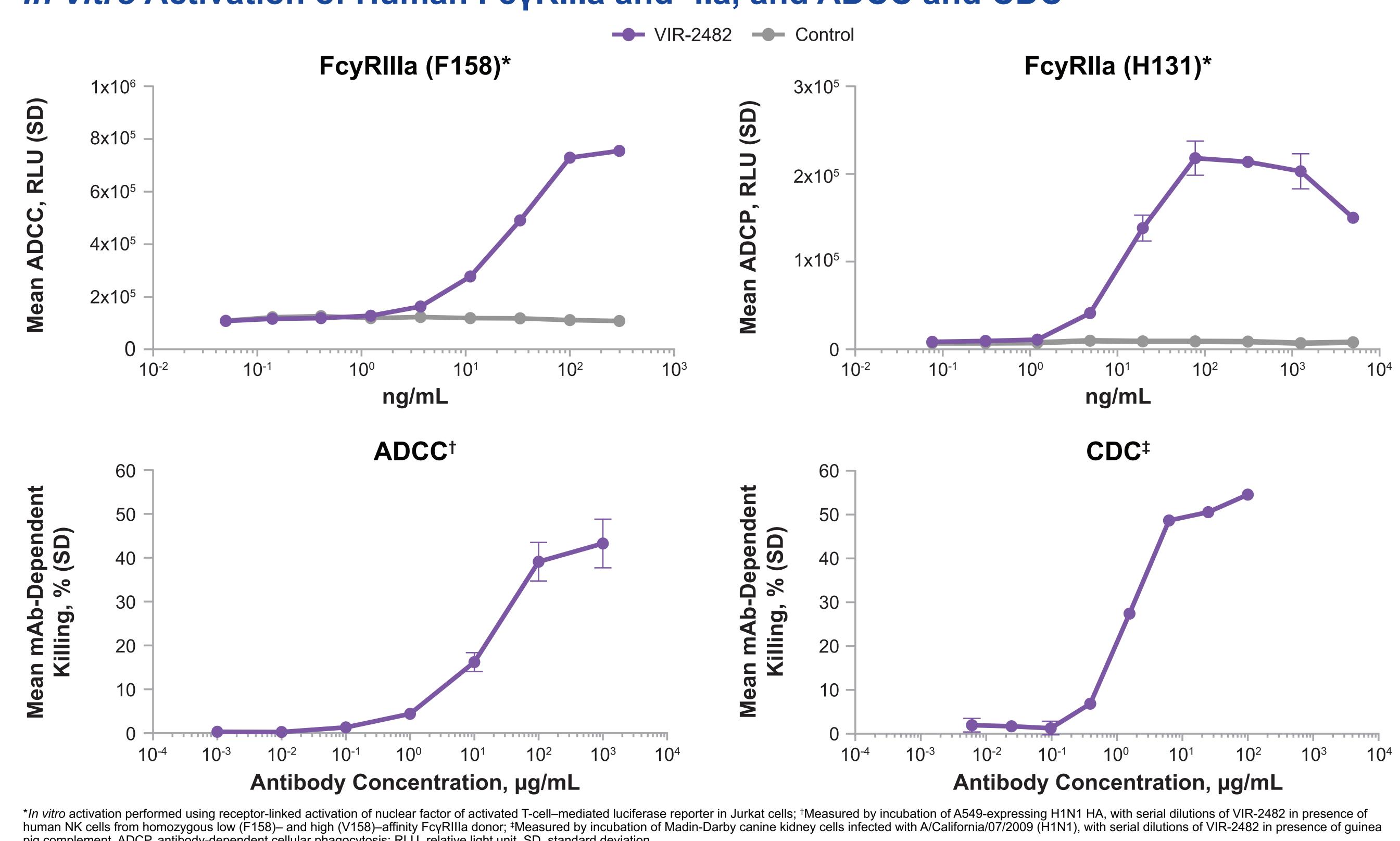
■ Bioinformatic analysis revealed >98% conservation for most of the key contact residues examined from sequences retrieved for H1N1 and H3N2 between 2009 and 2019

Binding of VIR-2482 to Group I and II IAV HAs, and Neutralization of H1N1 and H3N2 Viruses



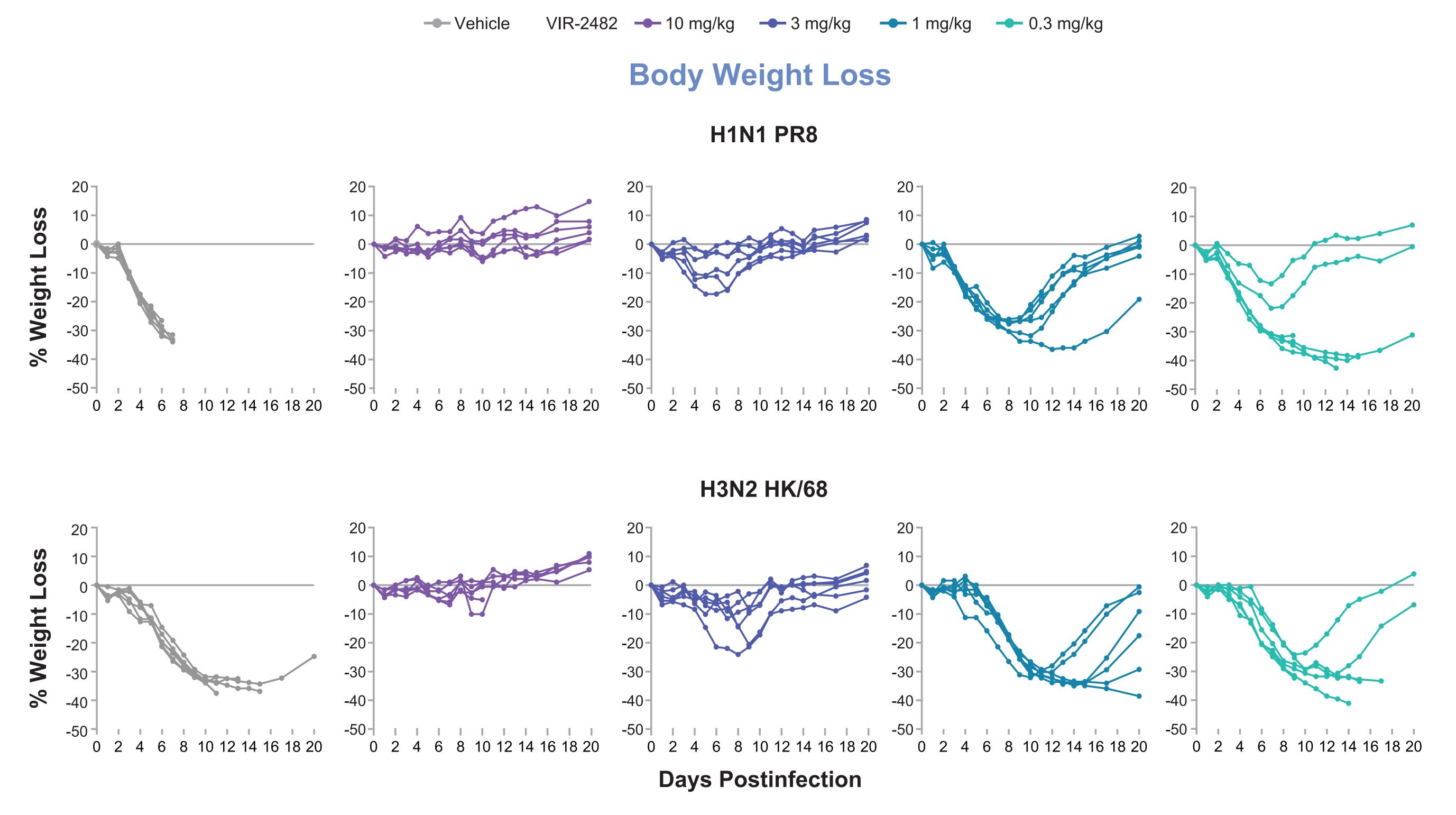
▼VIR-2482 bound Group I and II IAV HA subtypes, and neutralized a broad panel of Group I and II IAV HAs spanning almost 100 y of evolution

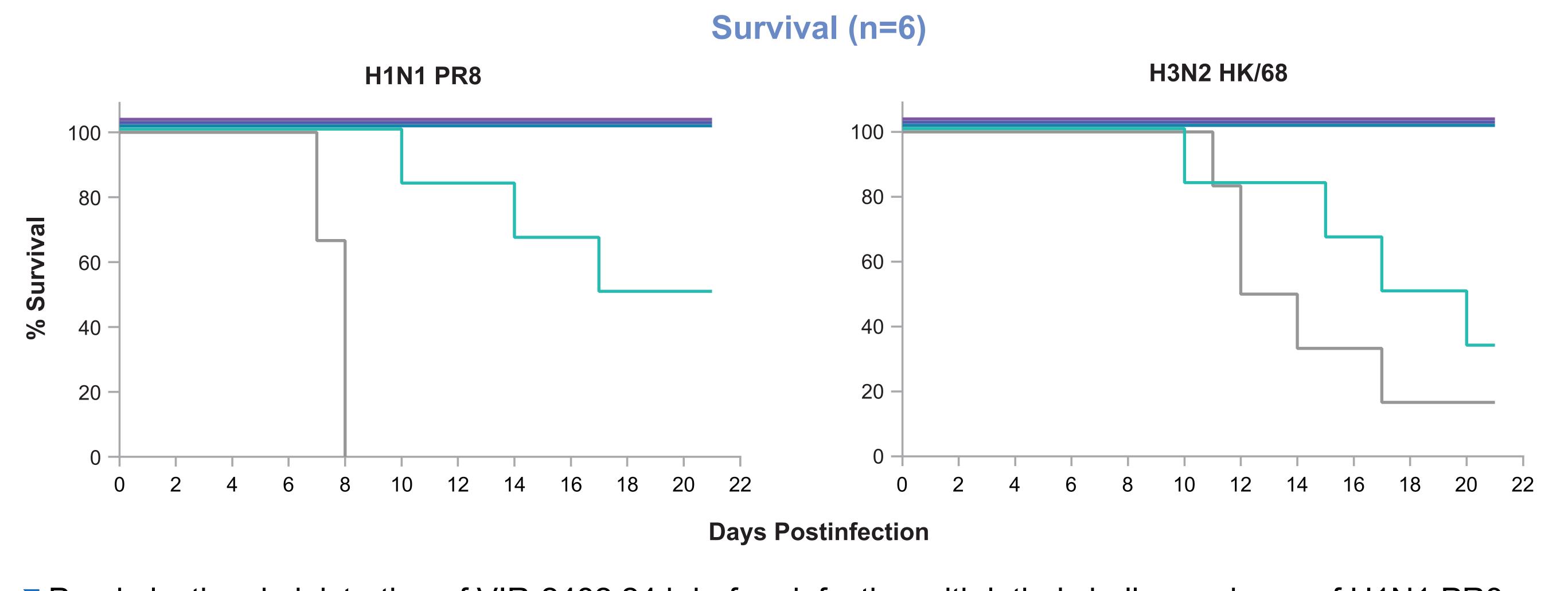
In Vitro Activation of Human FcyRIIIa and -IIa, and ADCC and CDC



■ The half-life—extending mutations introduced in the Fc portion did not affect the ability of VIR-2482 to activate FcγRs, as evidenced also by their lack of impact on ADCC and CDC in vitro

Body Weight Loss and Survival of BALB/c Mice Prophylactically Administered VIR-2482 Before Lethal Challenge Doses of H1N1 and H3N2





■ Prophylactic administration of VIR-2482 24 h before infection with lethal challenge doses of H1N1 PR8 and H3N2 HK/68 viruses significantly reduced morbidity and prevented mortality in BALB/c mice

Conclusions

The attributes of potency, broad recognition of a highly conserved epitope, and 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

Reference: 1. Krammer F, Palese P. Nat Rev Drug Discov 2015;14:167-82. Acknowledgment: This study was funded by Vir Biotechnology, Inc.