Rationale and Design of FLINTLOCK: A Phase 2a Randomized, Placebo-Controlled Trial of the Monoclonal Antibody VYD2311 in Adults with Long COVID or Post-Vaccination Syndrome and Persistent SARS-CoV-2 Spike Antigen

Michael J. Peluso[1], David Putrino[2], Michael Mina[3], SPEAR Study Group

[1]University of California, San Francisco, CA, USA; [2]Mount Sinai Health System, New York, NY, USA; [3]Invivyd, Inc., New Haven, CT, USA

Background

- Long COVID (LC) may be driven by SARS-CoV-2 persistence and, in a subset of people, continued presence of spike antigen[1-3]
- Spike antigen has been detected in individuals reporting post-vaccination syndrome (PVS) after COVID-19 vaccination[4]
- Whether reducing antigen persistence confers clinical benefit has not been tested at scale
- Potent, neutralizing anti-spike monoclonal antibodies (mAbs) permit a direct testing of this concept, with case reports of symptom improvement supporting further evaluation[5]
- A prior randomized trial of mAbs suggested treatment response is linked to antibody potency and sustained exposure[6]
- VYD2311 is an investigational, half-life-extended, fully human immunoglobulin G1 (IgG1) mAb that functions as a human angiotensin-converting enzyme 2 (hACE2) competitor targeting the spike glycoprotein receptor-binding domain of SARS-CoV-2[7,8]
  - VYD2311 previously demonstrated potent *in vitro* neutralization of historical and contemporary SARS-CoV-2 variants, with a half-life of ~76 days[7]
  - In the Phase 3 LIBERTY study, VYD2311 met coprimary endpoints on safety/tolerability compared to an mRNA-based COVID-19 vaccine[8]

The SPEAR (Spike Protein Elimination and Recovery) Study Group was convened to develop a study-design recommendation for a future mAb trial using VYD2311

Methods

FLINTLOCK (NCT07899346)

Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Study

Key Inclusion Criteria

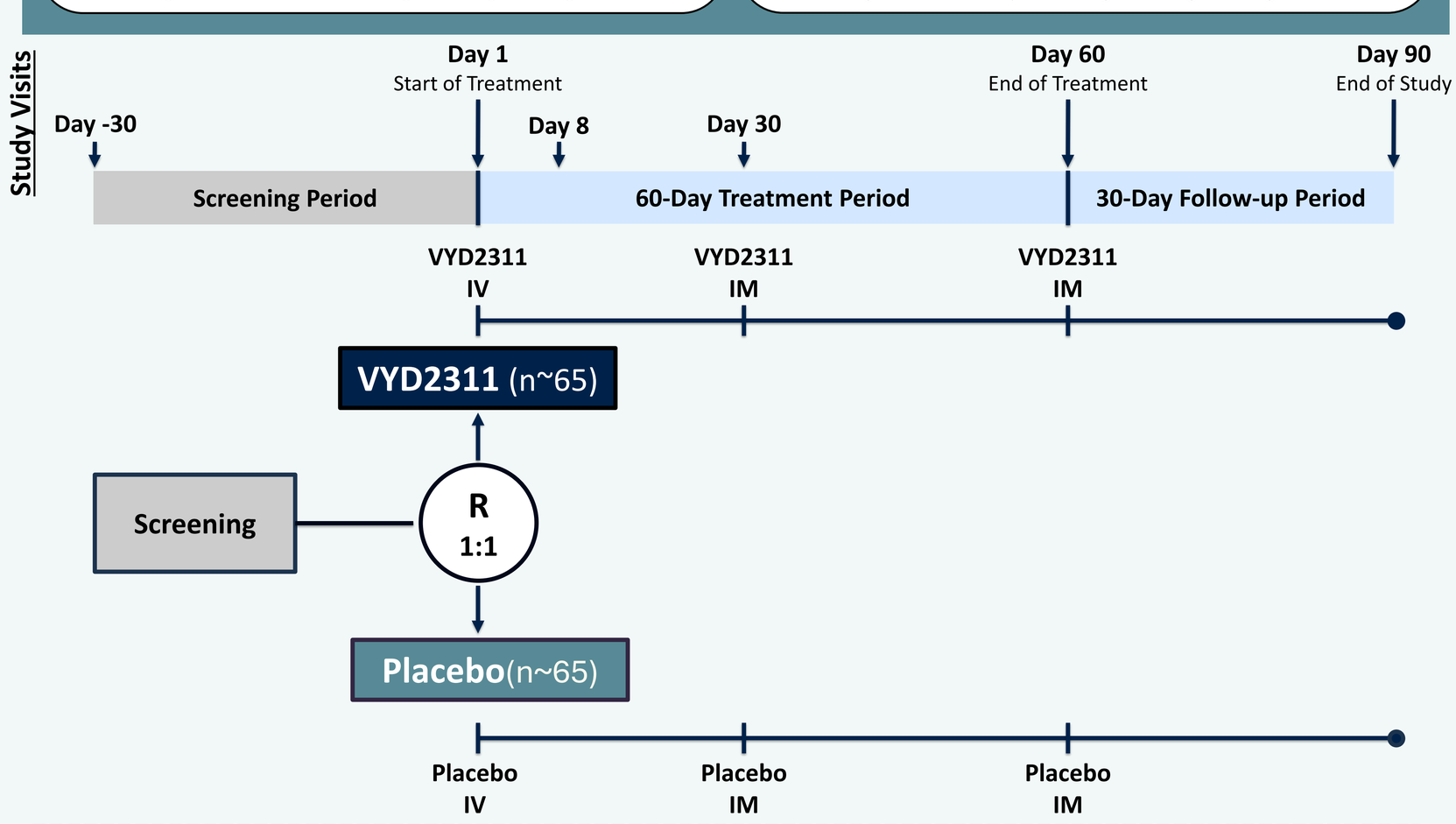
All participants

- Aged ≥18 to ≤65 years

Cohort-specific criteria

Long-COVID cohort: had a documented or highly probable acute SARS-CoV-2 infection prior to the onset of LC symptoms
- Has clinical evidence of at least 2 new or worsening LC symptoms with at least 1 such symptom considered Grade ≥3 in severity which:
  - Presented ≥6 months and <24 months after the inciting acute SARS-CoV-2 infection
  - Have been present (including waxing and waning if present more days than not) for at least 60 days prior to Screening
  - Are not primarily attributable to a pre-existing condition or alternative diagnosis confirmed by the investigator during screening

Post-Vaccination Syndrome (PVS) cohort: received ≥1 dose of a SARS-CoV-2 vaccine prior to the onset of symptoms. No known or suspected SARS-CoV-2 infection prior to vaccination and onset of PVS symptoms.
- Has clinical evidence of at least 2 new or worsening PVS symptoms with at least 1 such symptom considered Grade ≥3 in severity which:
  - Presented and persisted after the SARS-CoV-2 vaccine
  - Have been present (including waxing and waning if present more days than not) for at least 60 days prior to Screening
  - Are not primarily attributable to a pre-existing condition or alternative diagnosis confirmed by the investigator during screening



Primary Objectives
- Evaluate the safety and tolerability of VYD2311 (compared with placebo) in adults with a confirmed diagnosis of LC or PVS symptoms through Day 90
- Evaluate the pharmacokinetics of VYD2311 through Day 90

Secondary Objectives
- Evaluate the clinical activity of VYD2311 (compared with placebo)
- Evaluate the immunogenicity of VYD2311 through Day 90

- Approximately 130 adults (aged 18 to 65 years) with LC or PVS will be enrolled
- Secondary outcome measures include changes in physician/participant-reported assessments (PROMIS-29+2, PCFS, PGI-C, PGI-S, and SDMT), and incidence of ADAs through Day 90
- Exploratory outcome measures, including serum spike antigen (pending assay availability), incidence of laboratory-confirmed COVID-19 infection, sit-to-stand testing, and hand grip strength are also evaluated through Day 90
- Estimated total study duration is up to 14 months; baseline and outcome data will be reported

Key Points



FLINTLOCK is among the first prospective, placebo-controlled trials to test whether sustained, high-titer anti-spike mAb therapy is safe and clinically active in adults who have confirmed LC or PVS



The study is designed to generate interpretable evidence on the role of antigen persistence in LC and PVS irrespective of the clinical result, and to inform the design of subsequent efficacy trials

LIMITATIONS

VYD2311 is an investigational agent for SARS-CoV-2. Its safety and efficacy have not been established, and it is not approved or authorized for any use by any regulatory authority.

DISCLOSURES

MP declares grants or contracts from NIH and PolyBio Research Foundation; consulting fees from Gilead Sciences, BioVie, BioNTech, and TechImmune; travel support from Invivyd; and research support from Aerium Therapeutics, Shionogi, and ImmunityBio; DP: no competing interests; MM is an employee of Invivyd, Inc, and may own stock.

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