Influenza viruses cause annual epidemics during autumn and winter. Influenza A and B cause 
34 TEAEs in 12/14 (86%) subjects.

Methods

Two randomized, double-blind, placebo-controlled, single ascending-dose studies to investigate the safety, tolerability, and pharmacokinetics of an Anti-Influenza A Monoclonal Antibody, MHAA4549A, in Healthy Volunteers


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Aims

- Influenza A virus can cause significant morbidity and mortality.
- MHAA4549A, a human monoclonal IgG1 (IgG) antibody that binds to the hemagglutinin protein of influenza A, is being examined as a novel therapeutic for influenza A patients with severe disease.

Methods

Two randomized, double-blind, placebo-controlled, single ascending-dose studies were conducted to assess the safety, tolerability, and pharmacokinetics of MHAA4549A in healthy volunteers.

- The first study randomized 21 healthy male and female volunteers ≥ 18 (25–70) years into two cohorts receiving a single IV dose of 1.5, 5, 15, or 45 mg/kg MHAA459A or placebo (4 active:1 placebo, except first cohort [4:2]). The second study randomized 14 healthy male and female volunteers (15-75 years) into two cohorts receiving in single IV fixed doses of 45 mg/kg (MHAA4549A) or placebo (in the 45 mg/kg cohort in 4.60 mg/kg and 4.10 mg/kg dose) for two days after dosing.

Results

- No subject discontinued either study. No dose-limiting adverse events, or serious adverse events were reported. No anti-MHAA4549A antibodies were detected in any volunteer.

Conclusions

- MHAA4549A is safe and well-tolerated in healthy volunteers up to a single IV dose of 10,800 mg and demonstrated linear serum pharmacokinetics consistent with those of a human IgG1 antibody lacking endogenous target engagement in humans.

INTRODUCTION

Influenza

- Influenza viruses cause annual epidemics during autumn and winter, and are associated with significant human disease.

- Respiratory illness with a broad clinical spectrum that typically results in mild symptoms, such as fever and cough, from which most people recover without requiring medical attention.

- Each year, seasonal influenza affects approximately three to five million cases of severe illness and up to 200,000 deaths worldwide.

- Caused an estimated average of 19,100 deaths between 1997 and 2009 in the U.S. states.

- Caused considerable mortality and morbidity in European countries.

- A significant unmet medical need still exists in those at high-risk of developing influenza complications.

- Children

- Elderly patients

- Pregnant women

- Patients with underlying chronic medical conditions

- Patients with weakened immune systems

MHAA4549A

- Human monoclonal IgG1 antibody that binds to the Influenza A virus.

- Derived from a single human plasmablast isolated from an influenza-vaccinated donor.

- Mechanism

- Binding is highly conserved epitope on the influenza A hemagglutinin stalk region.
- Blocks fusion of the viral envelope with the host target cell membrane.
- Prevents viral genome entry into the host cell.
- Neutralizes all seasonal influenza A strains tested in vitro and in vivo in models of influenza A infection, both alone and in combination with oseltamivir.

OBJECTIVES

Primary Objective

- Evaluate the safety and tolerability of single intravenous doses of MHAA4549A as compared to placebo when administered to healthy volunteers.

Secondary Objectives

- Characterize the pharmacokinetic (PK) profile of single intravenous doses of MHAA4549A.

- Determine the incidence of anti-therapeutic antibodies (ATAs) in healthy volunteers.

METHODS

Study Design

- GV28916: Phase 1, randomized, double-blind, placebo-controlled, single ascending-dose study
- GV26069: Phase 1, randomized, double-blind, placebo-controlled, single ascending-dose study

- GV28916: 21 healthy male and female volunteers total, ≥ 18 years of age
- GV26069: 10 healthy male and female volunteers total, ≥ 18 years of age

- Cohorts: A (1.5 mg/kg), B (5 mg/kg), C (15 mg/kg), D (45 mg/kg)

RESULTS

Safety

- No DLTs, AESI, severe AEs, or SAEs were reported.
- No safety issues were observed.
- No subjects developed treatment-induced ATAs. One subject (10,800 mg MHAA4549A) tested positive for ATAs at baseline.

Pharmacokinetics

- MHAA4549A concentrations exhibited a biphasic disposition, with an initial rapid distribution phase followed by a slow elimination phase in GV28916 and GV29609.
- Mean terminal half-life for MHAA4549A: approximately 23 days (23–24 days).
- Changes in vital signs, clinical laboratory results, and electrocardiograms were monitored during and following GV29609 administration.

Key Inclusion Criteria

- Age ≥ 18 years
- Body mass index (BMI) < 32 kg/m²
- No history of chronic disease
- No evidence of significant findings from medical history, 12-lead ECG, clinical labs, or vital signs compared to placebo.

Key Exclusion Criteria

- History or clinically significant manifestations of metabolic, hepatic, renal, hematologic, immunodeficiency, pulmonary, cardiovascular, gastrointestinal, urologic, neurologic, or psychiatric disorders.
- History of anaphylaxis, hypersensitivity, or drug allergies, except to tobacco smoke.
- Positive pregnancy test result at screening or breastfeeding during the study.

REFERENCES


CONCLUSIONS

- MHAA4549A was safe and well-tolerated in healthy subjects following a single IV administration of up to 10,800 mg, and demonstrated linear serum pharmacokinetics consistent with the expected profile of an IgG1 antibody in humans.

- No anti-MHAA4549A antibodies were detected in any volunteer.

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Monoclonal Antibody of Influenza A Virus (GV28916) as a New Therapeutic for Influenza, A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Single Ascending-Dose Study: Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending-Dose Studies to Investigate the Safety, Tolerability, and Pharmacokinetics of an Anti-Influenza A Monoclonal Antibody, MHAA4549A, in Healthy Volunteers


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