1656-P

A Phase 2a Study to Evaluate the Safety of MEDI8852 in Outpatient Adults with Acute, Uncomplicated Influenza A

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Introduction

- MEDI8852 is a human IgG1κ monoclonal antibody (mAb) that binds to the conserved stalk region of the influenza hemagglutinin (HA) protein.
- MEDI8852 directly neutralizes type A influenza viruses, blocking viral cell entry, HA maturation, and cell-to-cell spread.
- MEDI8852 binds to all influenza A HA subtypes and neutralizes a large panel of influenza viruses, including seasonal H1N1 and H3N2 strains, and subtypes that have the potential to cause pandemics, such as H2, H5, H6, H7 and H9.[1]
- MEDI8852 also exhibits Fc receptor-mediated viral clearance through antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity.[1]
- MEDI8852 was highly protective in murine and ferret models of lethal influenza virus infection.[1]
- A previous, first-in-human study demonstrated that a single IV dose of up to 3000 mg of MEDI8852 had a safety profile comparable to that of placebo in healthy adult volunteers.[2]
- MEDI8852 is being developed for the treatment of influenza A in hospitalized patients.

Objectives

- The primary objective of this study was to evaluate the safety and tolerability of 1) a single IV dose of MEDI8852 (750 or 3000 mg) administered in conjunction with oseltamivir (OS), 2) OS administered alone, and 3) a single IV dose of MEDI8852 (3000 mg) alone, in adults with confirmed, acute, uncomplicated influenza A.
- A secondary objective was to characterize viral shedding in nasopharyngeal (NP) swab samples by quantitative reverse transcription polymerase chain reaction (qRT-PCR).
- An exploratory endpoint evaluated time to resolution of influenza symptoms.

Methods

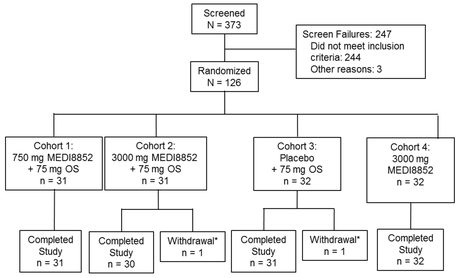
- This phase 2a, randomized, partial double-blind, active-controlled, dose-ranging study was conducted at 54 centers in 2 countries (United States and South Africa) during the 2015-16 Northern Hemisphere and 2016 Southern Hemisphere influenza seasons.
- Eligible subjects were male or nonpregnant female adults, age 18 to 65 years, with positive influenza rapid antigen test results at screening. Subjects also had symptomatic presumptive influenza A infection, with an onset of symptoms ≤ 5 days prior to study drugs administration, defined as the presence of fever ≥ 38.0 ˚C, ≥ 1 moderate systemic symptom (headache, malaise, myalgia, sweats and/or chills or fatigue) and ≥ 1 moderate respiratory symptom (cough, sore throat, or nasal symptoms).
- Subjects were randomized 1:1:1:1 into 4 cohorts:
  - Cohort 1: 750 mg MEDI8852 and 75 mg OS;
  - Cohort 2: 3000 mg MEDI8852 and 75 mg OS;
  - Cohort 3: placebo and 75 mg OS;
  - Cohort 4: 3000 mg MEDI8852
- In each cohort, MEDI8852 or placebo was administered as single IV infusion on day 1 and OS was administered as per the local standard of care (ie, orally twice a day for 5 days, beginning on day 1).
- Randomization was stratified by duration of illness (≤ 48 vs > 48 hours).

Results

Subjects

- A total of 373 subjects were screened and a total of 126 (of the planned 160) subjects who met eligibility criteria were randomized into the study (**Figure 1**).

Figure 1. Study Design



OS = oseltamivir.
Note: One subject who was randomized to Cohort 2 withdrew consent on day 2 (the subject did not have influenza A infection confirmed with a positive rapid antigen test at screening and therefore did not receive study drugs) and one subject who was randomized to Cohort 3 withdrew consent on day 78 (withdrawal of consent was not due to an AE). One subject who was randomized to Cohort 4 received the OS regimen in error and was counted as part of Cohort 2 for the purposes of the As-treated Population.

- Treatment groups were balanced with respect to most of the demographic and baseline characteristics, including age, body mass index, body temperature and solicited influenza symptoms (**Table 1**).

Safety

- Adverse events (AEs) occurred at a slightly higher rate in MEDI8852 compared to placebo recipients; investigational product-related AEs occurred at similar rates between MEDI8852 and placebo recipients.
- The most commonly reported AEs were bronchitis (11.8%; 11/93 all MEDI8852 subjects; 3.1%; 1/32 placebo) and nausea (4.3% and 6.3%, resp.) (**Table 2**).
- Most bronchitis events occurred in subjects from a single site (75.0%; 9/12) that enrolled 44 of 126 study subjects; nearly all events were grade 1 or grade 2 in severity (1 grade 3 event), which began around Day 7 and resolved by Day 15.
- All subjects with bronchitis had solicited influenza symptom scores that were either stable or decreasing at the time of onset (**Table 3**).

Table 1. Demographics and Baseline Characteristics

Parameter	Cohort 1: 750 mg MEDI8852 + OS n = 31	Cohort 2: 3000 mg MEDI8852 + OS n = 31	Cohort 3: Placebo + OS n = 32	Cohort 4: 3000 mg MEDI8852 n = 32	Cohorts 1, 2 and 4 combined: Total MEDI8852 n = 94
Hemisphere, n (%)					
Northern	23 (74.2)	25 (80.6)	24 (75.0)	23 (71.9)	71 (75.5)
Southern	8 (25.8)	6 (19.4)	8 (25.0)	9 (28.1)	23 (24.5)
Age, median (range), years	40.0 (21-61)	43.0 (19-64)	42.0 (18-59)	44.5 (22-65)	43.0 (19-65)
Sex, n (%)					
Female	13 (41.9)	18 (58.1)	20 (62.5)	15 (46.9)	46 (48.9)
Male	18 (58.1)	13 (41.9)	12 (37.5)	17 (53.1)	48 (51.1)
Race, n (%)					
Asian	0	0	1 (3.1)	0	0
Black or AA	8 (25.8)	3 (9.7)	5 (15.6)	5 (15.6)	16 (17.0)
White	23 (74.2)	28 (90.3)	26 (81.3)	27 (84.4)	78 (83.0)
Ethnicity, n (%)					
Hispanic/Latino	17 (54.8)	20 (64.5)	16 (50.0)	17 (53.1)	54 (57.4)
Non-Hispanic/Latino	14 (45.2)	11 (35.5)	16 (50.0)	15 (46.9)	40 (42.6)
Duration of illness at baseline, n (%)					
≤ 48 hours	15 (48.4)	18 (58.1)	14 (43.8)	18 (56.3)	51 (54.3)
> 48 hours	16 (51.6)	13 (41.9)	18 (56.3)	14 (43.8)	43 (45.7)
Body temperature, median (range), ˚C	38.00 (36.1-39.6)	38.15 (35.8-39.7)	38.10 (36.5-39.3)	38.00 (36.1-39.6)	38.00 (35.8-39.7)
Solicited influenza symptoms, median (range), total score	17.0 (7-21)	16.0 (7-21)	16.0 (6-21)	17.0 (10-21)	17.0 (7-21)
Viral subtype via RT-PCR					
A/H1N1, n	22	21	26	20	63
A/H3N2, n	5	2	4	3	10

AA, African American

Table 2. Summary of Adverse Events

Type of Adverse Event, n (%)	Cohort 1: 750 mg MEDI8852 + OS n = 31	Cohort 2: 3000 mg MEDI8852 + OS n = 31	Cohort 3: Placebo + OS n = 32	Cohort 4: 3000 mg MEDI8852 n = 31	Cohorts 1, 2 and 4 combined: Total MEDI8852 n = 93	Total n = 125
Any	11 (35.5)	16 (51.6)	10 (31.3)	12 (38.7)	39 (41.9)	49 (39.2)
Investigational product-related	4 (12.9)	6 (19.4)	5 (15.6)	4 (12.9)	14 (15.1)	19 (15.2)
Grade 3	0	3 (9.7)	2 (6.3)	0	3 (3.2)	5 (4.0)
Serious	0	1 (3.2)	1 (3.1)	0	1 (1.1)	2 (1.6)
Special interest (ie, infusion-related reaction)	0	1 (3.2)	0	0	1 (1.1)	1 (0.8)
Occurring in ≥ 4% of subjects in any cohort						
Bronchitis	4 (12.9)	5 (16.1)	1 (3.1)	2 (6.5)	11 (11.8)	12 (9.6)
Nausea	2 (6.5)	1 (3.2)	2 (6.3)	1 (3.2)	4 (4.3)	6 (4.8)
Diarrhoea	0	2 (6.5)	0	2 (6.5)	4 (4.3)	4 (3.2)
Upper respiratory tract infection	1 (3.2)	3 (9.7)	0	0	4 (4.3)	4 (3.2)
Pharyngitis	2 (6.5)	0	1 (3.1)	1 (3.2)	3 (3.2)	4 (3.2)
Dysgeusia	1 (3.2)	2 (6.5)	1 (3.1)	0	3 (3.2)	4 (3.2)
Bronchial hyperreactivity	2 (6.5)	0	0	0	2 (2.2)	2 (1.6)
Paraesthesia	0	0	2 (6.3)	0	0	2 (1.6)

- All subjects with bronchitis were afebrile (<30˚C) at the time of onset or prior to onset per temperature measurement.
- Most subjects with bronchitis (90.9%; 10/11) who had confirmed influenza A at baseline/Day 1 with RT-PCR had viral loads <LLOQ or undetectable at the time of bronchitis onset or prior to bronchitis onset.
- Two subjects reported serious AEs during the study, including 1 subject who had a grade 3 investigational-product related event of infusion-related reaction (which was also an AE of special interest) and 1 subject who had a grade 3 event of syncope. These events resolved and the subjects completed the study.

Table 3. Influenza Symptom Scores for Subjects with AEs of Bronchitis, By Cohort

Gender/Age	D1 AM	D1 PM	D2 AM	D2 PM	D3 AM	D3 PM	D4 AM	D4 PM	D5 AM	D5 PM	D6 AM	D6 PM	D7 AM	D7 PM	D8 AM	D8 PM	D9 AM	D9 PM	D10 AM	D10 PM
Cohort 1 (750 mg MEDI8852 and oseltamivir)																				
Female/42	18	14	15	15	12	12	13	15	14	10	12	9	7	5	3	3	1	2	2	2
Male/47	15	21	17	15	10	10	9	9	7	7	6	10	5	6	5	5	5	4	5	5
Female/54	20	14	14	11	12	10	7	7	8	11	11	10	7	4	2	0	0	0	0	0
Male/58	19	18	17	17	15	15	15	12	14	15	16	13	8	7	1	1	1	1	1	0
Cohort 2 (3000 mg MEDI8852 and oseltamivir)																				
Male/39	13	14	8	9	7	10	10	11	9	9	9	9	9	5	7	8	7	1	1	1
Male/43	20	17	19	16	16	11	8	5	6	5	1	1	1	4	3	1	0	0	0	0
Female/43	21	21	21	21	21	21	21	21	17	17	16	13	12	12	6	6	4	4	4	4
Male/30	19	19	21	21	17	10	11	11	10	8	8	9	11	10	7	6	6	4	4	2
Female/45	18	9	9	8	6	4	4	4	2	2	2	2	2	2	1	1	1	2	2	2
Cohort 3 (Placebo and oseltamivir)																				
Male/38	17	17	3	3	3	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Cohort 4 (3000 mg MEDI8852)																				
Female/63	18	18	15	11	10	7	4	4	3	3	2	3	1	2	2	2	3	3	3	3
Female/25	12	4	17	15	12	3	9	9	4	3	3	3	3	4	5	5	4	3	2	2

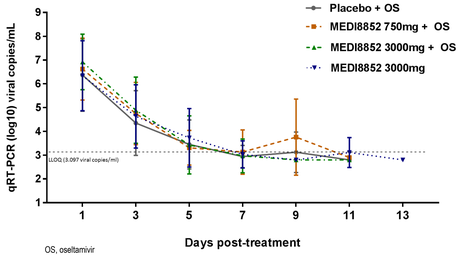
Note: Days during which subjects had AEs of bronchitis are highlighted in gray. For the last subject (Female/25), the onset of bronchitis was on day 12, which was after the period (days 1 to 10) during which influenza symptom scores were collected.

- There were no deaths or AEs leading to treatment discontinuation during the study.
- There were no clinically meaningful differences in routine chemistry and hematology results between MEDI8852 and placebo recipients.
- Solicited influenza symptoms occurred at similar rates between the MEDI8852 and placebo recipients (each 100%, respectively).
- Similarly, the median (range) number of days that subjects had any solicited symptoms were similar between MEDI8852 and placebo recipients (each 10.0 [2 to 13] days, respectively).
- Median (range) time to resolution of solicited influenza symptoms were similar across groups (93/94 MEDI8852, 111.3 [92.4, 130.8] hours; 32/32 placebo, 108.8 [71.2, 161.8] hours).

Virology

- Viral loads were determined for all influenza A confirmed baseline and corresponding follow-up NP samples by qRT-PCR. Similar decreases in viral loads were observed for all treatment groups (**Figure 2**).

Figure 2. Quantitation of Viral Shedding over Time as Measured by qRT-PCR (Log_{10} viral copies/mL)



OS, oseltamivir

Conclusions

- MEDI8852 demonstrated an acceptable safety profile in outpatient adults with acute, uncomplicated influenza A.
- Adverse events occurred at a higher rate in MEDI8852 compared to placebo recipients. Investigational product-related AEs occurred at similar rates between MEDI8852 and placebo recipients.
- The most common AE was bronchitis, which occurred at a slightly higher rate in MEDI8852 compared to placebo recipients. Nearly all bronchitis events were grade 1 or grade 2 in severity and occurred in afebrile subjects whose solicited influenza symptom scores were either stable or decreasing at the time of event diagnosis. Given the low-grade severity of these events and the associated influenza symptoms, as well as the general lack of an increase in influenza shedding during the events, these findings are not consistent with antibody-dependent enhancement of influenza infection.
- Decreases in mean viral loads (through Day 7) were similar between the treatment groups.
- The safety and tolerability profile of MEDI8852 in this study supports continued development for treatment of adults who are hospitalized with influenza A.

References

[1] Kallewaard NL, et al. *Cell*. 2016;166(3):596-608.

[2] Mallory RM, et al. *Biologicals*. 2017, http://dx.doi.org/10.1016/j.biologicals.2017.08.007.

Acknowledgements

The study (NCT02603952) was supported by MedImmune.

Presented at IDWeek 2017, San Diego, CA, Friday, October 6, 12:30 PM – 2:00 PM.