2 STUDY SYNOPSIS

<table>
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MedImmune</td><td rowspan="3">Individual Study Table
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<tr><td>Name of Finished Product:
Not applicable</td></tr>
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<tr><td colspan="3">Title
An Observational Study to Assess Respiratory Syncytial Virus (RSV)-associated Illness in Adults With Chronic Obstructive Pulmonary Disease (COPD) and/or Congestive Heart Failure (CHF)</td></tr>
<tr><td colspan="3">Principal Investigator(s)
Principal Investigator’s Study Center</td></tr>
<tr><td colspan="3">Rochester, NY 14621, USA
Publication (reference)</td></tr>
<tr><td colspan="3">Not applicable.</td></tr>
<tr><td colspan="2">Study Period (years)</td><td>Clinical Phase</td></tr>
<tr><td colspan="2">Oct 2011 – May 2014
Objectives</td><td>Not applicable</td></tr>
<tr><td colspan="3">Primary:
The primary objective of this study was to determine the incidence rate of medically-attended (inpatient or outpatient) acute respiratory illnesses (ARIs) or events leading to worsening cardiorespiratory status (ie, acute exacerbations of COPD [AECOPD] or worsening CHF) associated with RSV infections in high-risk adults (ie, those with severe COPD and/or advanced CHF) across multiple consecutive RSV seasons.
Secondary:
1. To determine the rate of all-cause medically-attended (inpatient or outpatient) ARI or events leading to worsening cardiorespiratory status in high-risk adults.
2. To determine the RSV-associated and all-cause mortality rate in high-risk adults.
3. To determine the magnitude of health care resource utilization for RSV-associated and all-cause medically-attended (inpatient or outpatient) ARI or events leading to worsening cardiorespiratory status.
4. To determine the incidence of RSV-related secondary bacterial pneumonia events and their association with antibiotic use.
Safety:
This was an observational study in which subjects did not receive investigational product; therefore, no safety endpoints were evaluated. However, adverse events (AEs) related to study procedures (hereafter referred to as protocol-related AEs) were collected.</td></tr>
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Methodology

This was a prospective, observational study conducted across multiple consecutive RSV seasons to determine the incidence rate of RSV-associated ARI or events leading to worsening cardiorespiratory status in adults with severe COPD and/or advanced CHF. Multiple sites in the Northern Hemisphere participated in the study.

Each RSV season was defined as 01 November through 30 April of the following year with the off-season occurring between 01 May and 31 October of the same year. Subjects had scheduled study visits every May and October to obtain blood, nasal swab, sputum, and clinical data through the May 2014 visit. Subjects enrolled in April or September had the first May or October scheduled visit waived, respectively. In addition, unscheduled visits to collect blood, nasal swab, sputum, and clinical data were conducted in cases where a subject sought outpatient, inpatient, or over-the-phone medical consultation for the onset (ie, Day 1) of a criteria-confirmed ARI or events leading to worsening cardiorespiratory status following enrollment through the May 2014 visit. Sample collection illness visits were conducted at the study clinic. Alternatively, a home collection visit to obtain biological specimens (blood, nasal swab, sputum) and clinical data was conducted if the subject was unable to visit the study site. Such visits occurred within 72 hours (but no greater than 14 days) after criteria-confirmed illness. For all subjects, a follow-up blood sample was collected in the clinic or at the subject's home approximately 30 days (± 4 days) after the onset of any medically-attended ARI or events leading to worsening cardiorespiratory status.

Between scheduled study visits, subjects were contacted by phone to ascertain if unscheduled medical treatment for an ARI or events leading to worsening cardiorespiratory status was sought outside the study site (eg, urgent care or emergency room [ER] visits). Calls were to take place bi-monthly through the end of the study. Subjects were followed for approximately 1.5 to 2.5 years depending on the time of enrollment.

Number of Subjects (Planned and Analyzed)

Termination of the study enrollment resulted in the enrollment of 453 subjects instead of the planned 750 subjects. The study enrollment was terminated per the sponsor's decision. Subjects who were already enrolled were followed for the duration of the study as described by the study protocol.

A total of 453 subjects were enrolled at 57 study sites in 9 countries in the Northern Hemisphere and were included in the Enrolled Population. Subjects were enrolled between 13 Oct 2011 and 15 May 2012 (last subject evaluation was on 31 May 2014). An additional 2 subjects who were entered into the study (n=455) did not meet the severe COPD or advanced CHF criteria at enrollment and were excluded from all populations and analyses.

Of these 453 subjects, 8 subjects were excluded from the Evaluable Population because they did not meet the study entry criteria (ie, ineligible due to < 50 years of age at screening [n=2], participation in another study [n=3], unstable condition for ≥ 2 weeks prior to screening [n=2], and had no direct contact with children [n=1]). A total of 445 subjects met the entry criteria and were considered evaluable (Evaluable Population).

Diagnosis and Main Criteria for Inclusion

The study population included clinically stable subjects ≥ 50 years of age with severe COPD (ie, Global Initiative for Chronic Obstructive Lung Disease Stage III/IV) and/or CHF (ie, New York Heart Association Class III/IV or American College of Cardiology-American Heart Association Stage C/D) who were at increased risk for events leading to worsening cardiorespiratory status as determined by previous medical history and expected exposure to children at least once a month.

Test Product Dose, Mode of Administration, and Batch Number(s)

Not applicable

Duration of Treatment

Not applicable

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Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

Not applicable

Disease Evaluation Methods

Acute Respiratory Illness:

Surveillance for ARI began following enrollment and continued through the end of the study. Two methods were used to determine whether criteria for an ARI were met:

- An ARI was defined as new onset or worsening of at least 2 of the following respiratory symptoms: sore throat, nasal congestion or discharge, hoarseness, cough, sputum, wheezing, dyspnea, and pleuritic chest pain.
- An ARI was also defined as 1 of the aforementioned respiratory symptoms and ≥ 1 of the following systemic symptoms: feverishness, fatigue, headache, and myalgia.

Worsening Cardiorespiratory Events:

Surveillance for AECOPD began following enrollment and continued through the end of the study. Upon contact from the subject, the study site confirmed the exacerbation onset by administering a brief exacerbation assessment based on the Anthonisen definition of an AECOPD:

- Worsening of ≥ 2 major symptoms (dyspnea, sputum volume, and sputum purulence) for ≥ 2 consecutive days; or
- Worsening of any 1 major symptom together with any 1 minor symptom (sore throat, cold, fever without other cause, or increased cough or wheeze) for ≥ 2 consecutive days

Surveillance for worsening CHF began following enrollment and continued through the end of the study. CHF worsening was defined as events during the natural course of the disease characterized by a change in ≥ 1 symptom (pulmonary edema, dyspnea, weight gain ≥ 5 pounds, pedal edema, jugular venous distension, and tachycardia and tachypnea) that was beyond normal day-to-day variation and may have warranted a change in medications (eg, angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, and others).

RSV-associated Medically-attended ARI, AECOPD, and CHF:

Subjects were considered to be RSV infected if they had a positive reverse transcriptase polymerase chain reaction (RT-PCR) during the acute phase of illness and/or ≥ 4-fold increase in serum antibody.

ARI, AECOPD, and worsening CHF were considered related to RSV infection if subjects were found to be RT-PCR positive or demonstrated serologic response in the period surrounding the healthcare visit.

Healthcare Resource Utilization:

Information was collected during each phone call to quantify the impact of disease and treatment on healthcare resource utilization (HRU). Information collected included COPD and/or CHF-related medical encounters (ie, phone calls to healthcare providers, physician office/outpatient visits, ER visits, hospitalizations, intensive care unit [ICU] stays, supplemental oxygen, and ventilator use). A questionnaire was provided to capture this information.

Statistical Methods

Statistical analyses were descriptive in nature. All data were provided in data listings sorted by subject number. Categorical data were summarized by the number and percentage of subjects in each category. In general, continuous variables were summarized by descriptive statistics, including mean, standard deviation, median, and range. Confidence intervals (CIs) were 2-sided unless otherwise stated.

Given there were subjects who clearly had RSV illness in months outside the protocol-defined RSV season (01 Nov – 30 Apr, with off-season occurring 01 May – 31 Oct), the analyses were based on redefined RSV seasons (Season 1: 01 Oct2011 – 31 May 2012; Season 2: 01 Oct 2012 – 31 May 2013; Season 3: 01 Oct 2013 – 31 May

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2014) and off-seasons (non-RSV Season 1: 01 Jun 2012 – 30 Sep 2012; non-RSV Season 2: 01 Jun 2013 – 30 Sep 2013) as described in the SAP.

Summaries to Support the Primary Objective (Primary Endpoint):

The primary endpoint of the study was the incidence rate of inpatient RSV-associated ARI or events leading to worsening cardiorespiratory status across multiple consecutive RSV seasons. The incidence rate was summarized separately for inpatient and outpatient events and for inpatient and outpatient events combined through all RSV seasons of follow-up. Subgroup analyses were used to summarize this endpoint by RSV season and risk factors. Primary endpoint analysis was performed with adjustment for individual subject follow-up time.

In order to provide more details on the follow-up time calculation as was provided in the SAP, individual follow-up time was calculated through discontinuation, end of season, or RSV event date, whichever was earlier. Follow-up time was calculated separately for each RSV season and RSV event type (ie, [1] RSV inpatient ARI or events leading to worsening cardiorespiratory status, [2] RSV outpatient ARI or events leading to worsening cardiorespiratory status, or [3] RSV inpatient or outpatient ARI or events leading to worsening cardiorespiratory status). Similar calculations were used for each non-RSV season.

Summaries to Support the Secondary Objectives (Secondary Endpoints):

<u>All-cause ARI or events leading to worsening cardiorespiratory status</u>

All-cause inpatient ARI or events leading to worsening cardiorespiratory status was summarized for all 3 RSV seasons combined and for each RSV season separately. The incidence rate was also summarized separately for outpatient events and for both inpatient and outpatient events combined through all seasons of follow-up. Analyses for all-cause medically-attended (inpatient or outpatient) ARI or events leading to worsening cardiorespiratory status endpoints were performed with adjustment for individual subject follow-up time and by the same subgroups as described for the primary endpoint.

<u>RSV-associated and all-cause mortality</u>

Mortality through all follow-up, during the RSV season, and during the non-RSV season was summarized for RSV-associated deaths and all-cause deaths. Analyses for all-cause and RSV-associated mortality were performed with adjustment for individual subject follow-up time as described for the primary endpoint.

<u>Healthcare resource utilization</u>

HRU for RSV-associated medically-attended (inpatient or outpatient) ARI or events leading to worsening cardiorespiratory status was summarized. In addition, HRU for all-cause medically-attended events was summarized overall and separately for subjects who had an RSV-associated event and for subjects who did not have an RSV-associated event. Information summarized included COPD and/or CHF-related medical encounters including hospital duration, incidence and duration of ICU stay, supplemental oxygen use, and number of outpatient visits (eg, ER visit, and physician office/outpatient visits). Results from the EQ-5D and Lawton-Brody IADL Scales were provided for the beginning and end of each RSV season.

<u>RSV-related secondary bacterial pneumonia and antibiotic-usage</u>

The incidence of RSV-related secondary bacterial pneumonia events (ie, bacterial pneumonia on the Healthcare Visit case report form of "confirmed" or "suspected") was summarized for all 3 RSV seasons combined and for each RSV season separately. Analyses were performed with adjustment for individual subject follow-up time as described for the primary endpoint. In addition, the incidence of non-RSV-related secondary bacterial pneumonia events was summarized for all 3 RSV seasons combined and for each RSV season separately. Similarly, incidence rates were summarized for the non-RSV seasons combined and for each non-RSV season separately.

The average number of antibiotics administered (indicated for "pneumonia") per RSV-related secondary

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bacterial pneumonia event per subject was also summarized. The average number of antibiotics per RSV-related secondary bacterial pneumonia event was calculated as the total number of antibiotics administered during the study divided by the total number of RSV-related secondary bacterial pneumonia events. Only subjects with an RSV-related secondary bacterial pneumonia event were included in the analysis.

Summary of Results

Subject Disposition:

Of the 453 enrolled subjects, 445 met the entry criteria and were considered evaluable. In the Evaluable Population, 345 (77.5%) subjects had severe COPD, 72 (16.2%) subjects had advanced CHF, and 28 (6.3%) subjects had both severe COPD and advanced CHF. A total of 330 (74.2%) subjects from the Evaluable Population completed the study. The main reasons for not completing the study were death and withdrawal of consent (10.6% each).

Demographic and Baseline Characteristics:

The majority of subjects in the Enrolled Population (N=453) were male (66.4%) and White (95.1%); mean (SD) age was 66.1 (8.4) years and mean (SD) weight of 80.66 (19.43) kg. Demographics of subjects with severe COPD, advanced CHF, and both severe COPD and advanced CHF were largely similar. The main differences were slightly higher mean weight in the advanced CHF population (88.29 kg) compared with the severe COPD and combined severe COPD and advanced CHF populations (79.08 kg and 80.55 kg, respectively), and a higher proportion of males in the advanced CHF population (76.7%) compared with the severe COPD and combined severe COPD and advanced CHF populations (64.5% and 64.3%, respectively).

Primary Outcome:

Incidence of medically-attended RSV-associated ARI or events leading to worsening cardiorespiratory status:

For the RSV seasons combined, the incidence of medically-attended (inpatient or outpatient) RSV-associated ARI or events leading to worsening cardiorespiratory status was 4.68 events per 100 patient-seasons (1.32 inpatient and 3.32 outpatient events per 100 patient-seasons). By RSV season, the highest incidence of medically-attended events was observed for RSV Season 1 (6.37 events per 100 patient-seasons) followed by RSV Season 2 (5.41 events per 100 patient-seasons) and RSV Season 3 (2.80 events per 100 patient-seasons). Of note, the inpatient and outpatient incidence was identical for RSV Season 1 (3.15 and 3.16 events per 100 patient-seasons, respectively), whereas the outpatient incidence was higher than the inpatient incidence for both RSV Season 2 (4.61 vs 0.76 events per 100 patient-seasons, respectively) and RSV Season 3 (1.86 vs 0.93 events per 100 patient-seasons, respectively).

For the RSV seasons combined, 42 subjects had an RSV-associated inpatient or outpatient ARI or events leading to worsening cardiorespiratory status. Of these subjects, 12 were positive by RT-PCR only, 14 had a 4-fold increase in serology only, and 16 were positive by RT-PCR and had a 4-fold increase in serology.

In addition, 28 subjects (6 inpatient and 22 outpatient) had a 4-fold increase in RSV serology and a medically-attended illness, but there were insufficient data to connect the seroresponse to a specific medically-attended illness visit. These were considered as probable RSV-associated illnesses but were not included in the incidence rate determinations since they did not meet the defined criteria for inclusion.

As expected, for the non-RSV seasons combined, the incidence of medically attended (inpatient or outpatient) RSV-associated ARI or events leading to worsening cardiorespiratory status was low with 0.25 events per 100 patient-seasons (0.13 inpatient and 0.13 outpatient events per 100 patient-seasons).

Medically-attended RSV events were categorized by the level of serum RSV antibody levels at the beginning at each RSV season. In general, an inverse relationship between anti-RSV antibody levels and RSV-associated medically-attended events was observed. Higher RSV antibody levels were associated with a lower incidence of RSV-associated medically-attended events.

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Secondary Outcomes:

All-cause ARI or events leading to worsening cardiorespiratory status

For the RSV seasons combined, the incidence of all-cause ARI or events leading to worsening cardiorespiratory status was 63.85 events per 100 patient-seasons, including 19.82 inpatient and 48.24 outpatient events per 100 patient-seasons. By RSV season, the highest incidence of inpatient or outpatient all-cause ARI or events leading to worsening cardiorespiratory status was observed for RSV Season 1 (93.94 events per 100 patient-seasons), followed by RSV Season 2 (62.66 per 100 patient-seasons) and RSV Season 3 (50.28 per 100 patient-seasons). For each of the 3 RSV seasons, the outpatient incidence of all-cause events was higher than the inpatient incidence.

For the non-RSV seasons combined, the incidence of all-cause ARI or events leading to worsening cardiorespiratory status was 22.11 events per 100 patient-seasons (6.12 inpatient and 17.21 outpatient events per 100 patient-seasons). By non-RSV season, the highest incidence of inpatient or outpatient all-cause ARI or events leading to worsening cardiorespiratory status was observed for non-RSV Season 1 (23.82 events per 100 patient seasons), followed by non-RSV Season 2 (20.26 per 100 patient-seasons). For each of the 2 non-RSV seasons, the outpatient incidence of all cause events was higher than the inpatient incidence.

RSV-associated and all-cause mortality

The total number of deaths was 2.68 per 100 patient-seasons, with none of the deaths considered to be RSV related. The mortality rate was higher during the RSV season than during the non-RSV season (3.63 vs 1.59 per 100 patient-seasons, respectively).

Health care resource utilization

Healthcare resource utilization for subjects with inpatient or outpatient RSV-associated ARIs or events leading to worsening cardiorespiratory status was low. For inpatient RSV-associated HRU, 2.9% of subjects were hospitalized, 0.6% were admitted to the intensive care unit (ICU), 1.3% had supplemental oxygen initiated, and 0.4% required increased supplemental oxygen. For outpatient RSV-associated HRU, 0.4% of subjects visited the emergency department, 0.8% visited a primary care physician, 3.5% visited a specialist, and 2.0% had a phone consultation; none of the subjects visited other outpatient centers.

Healthcare resource utilization for all-cause inpatient ARIs or events leading to worsening cardiorespiratory status for subjects without an RSV event were higher. A total of 28.6% of subjects were hospitalized, 3.7% were admitted to the ICU, 2.4% required mechanical ventilation, 9.7% had supplemental oxygen initiated, and 2.4% required increased supplemental oxygen. Healthcare resource utilization for all-cause outpatient ARIs or events leading to worsening cardiorespiratory status for subjects without an RSV event were higher; 9.9% of subjects visited the emergency department, 17.4% visited a primary care physician, 33.8% visited a specialist, 6.7% visited other outpatient centers, and 18.1% had a phone consultation.

RSV-related secondary bacterial pneumonia and antibiotic usage

For the RSV seasons combined, the incidence of RSV-associated inpatient or outpatient secondary bacterial pneumonia events was 0.22 per 100 patient-seasons; event rates were identical for the inpatient and outpatient settings (0.11 per 100 patient-seasons each). Analysis by RSV season showed that RSV-associated inpatient or outpatient secondary bacterial pneumonia events were observed only during RSV Season 2 (0.50 per 100 patient-seasons), with no events reported during RSV Season 1 or RSV Season 3.

A total of 2 subjects were diagnosed with RSV-related secondary bacterial pneumonia for all RSV seasons combined (both subjects had COPD and diagnosed in Season 2). The average number of antibiotics per RSV-related secondary bacterial pneumonia event per subject was 3.50.

Adverse Events:

Protocol-related AEs are summarized for the Enrolled Population (N=453). Overall, 9 subjects (2.0%)

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experienced a total of 16 protocol-related AEs. Events reported in more than 1 subject were vessel puncture site bruise (6 subjects, 1.3%) and epistaxis (3 subjects, 0.7%). The incidence of protocol-related AEs was slightly higher in subjects with advanced CHF (4.1%) than those with severe COPD (1.7%) or both severe COPD and advanced CHF (0%). All 16 protocol-related AEs resolved.		
Date of Original Report: 20 Oct 2016		