STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Not applicable
ACTIVE INGREDIENT: Not applicable

Study No: NIS-IEU-DUM-2010
Observational study to assess clinical management patterns in patients with hospitalized community-acquired pneumonia (CAP) or complicated skin and skin structure infections (cSSSI) – REACH Study Addendum to Clinical Study Report Dated 08 November 2011

Developmental Phase: Not applicable
Study Completion Date: 18 March 2013 (date of Last Patient Last Visit)
Date of Report: 11 July 2013

OBJECTIVES: The primary objective of the original REACH study was to provide accurate and reliable scientific data on the clinical management and burden of CAP and cSSSI across Europe; and to evaluate and quantify unmet needs of these diseases by understanding the patient and disease characteristics, current practice, and clinical outcomes.

The data collected through this study extension responded to the following secondary objectives of the REACH study:

- To identify and assess early response indicator variables in complicated skin and soft tissue infection (cSSTI) patients.
- To quantify the effect of early response on healthcare resource utilization variables in cSSTI patients.

METHODS: The original REACH study was a multinational, multicentre, observational, retrospective cohort study of hospitalised patients with cSSSI or CAP.
The current extension study collected data from the same cSSTI patients who participated in the original REACH study. As a Non-Interventional Study (NIS), no additional diagnostic or monitoring procedures were applied to the subjects, other than day-to-day practice. This NIS included all cSSTI patients enrolled in the original REACH study for whom relevant data were available.
A descriptive analysis approach (including frequency tables) was used to assess clinical management, clinical outcomes, and healthcare resources in patients showing an early response to treatment in comparison with patients without an early response, as assessed by the responses to the following questions:

Q1: Resolution of fever within the 72h period since initial antibiotic therapy (yes/no/unknown)
Q2: Documented indication of lesion improvement within the 72h period since initial antibiotic therapy (yes/no/unknown)
Q3: Cessation of spread of redness, oedema and/or induration of lesion within the 72h period since initial antibiotic therapy (yes/no/unknown)
Q4: Reduction in size of redness, oedema and/or induration within the 72h period since initial antibiotic therapy (yes/no/unknown)
Q5: Disappearance of local signs/symptoms present at admission within the 72h period since initial antibiotic therapy (yes/no/unknown)
Q6: Documented indication of patient improvement/readiness for IV to oral switch within the 72h period since initial antibiotic therapy (yes/no/unknown).

Definition 1 (Def 1) of early response to antibiotics (in line with FDA draft guidance for evaluation of antibiotics in cSSTI) required resolution (absence) of fever and some indication of lesion improvement or stability within 72h of treatment initiation; i.e. a positive response to Q1 AND Q2, Q3 or Q4.
Definition 2 (Def 2) of early response to antibiotics required evidence of lesion improvement or stability or resolution of signs and symptoms within 72h; i.e. a positive response to Q2, Q3, Q4 or Q5.

RESULTS:

A total of 1513 patients (76% of the total number of cSSTI patients who participated in the original REACH study) were included in this extension analysis. Six hundred patients were evaluable with Def 1 of early response (i.e., the information collected was sufficient to evaluate whether or not the criteria were met). A total of 363 (60.5%) patients were early responders, while 237 (39.5%) were not.
This population of 600 patients evaluable with Def 1 of early response and that of not evaluable patients were largely comparable in terms of baseline characteristics, although the former included a lower proportion of females (Def 1: 41.9% ER / 39.7% NotER vs. Not Eval with Def 1: 43.2%), a younger age (Def 1: 58.5 yrs ER / 58.2 yrs NotER vs. Not Eval with Def 1: 60.8 yrs), and a lower proportion of comorbidities (71.3% ER / 74.7% NotER vs. Not Eval with Def 1: 81.1%). Similarly, only minor differences were observed between the population of 600 patients evaluable with Def 1 of response and the whole REACH study population.
Of the 237 patients who did not show an early response, 54 became early responders when Def 2 of early response was used. This change in response outcome under the alternative definition was largely due to the fever resolution criterion in Q1 (47 patients [7.8% of the Def 1 population]) and due to symptom resolution in Q5 in just 7 patients (1.2% of Def 1 population). In other words, 553 of the 600 patients (92.2%) were included in the same classification regardless of the consideration of fever resolution. Therefore, including fever resolution restricted the number of patients who met the definition for early response, but the outcomes were largely unaffected.

Demographics and Baseline Characteristics: for the Def 1 analysis population, data was available from 30 hospitals with early responders and 10 hospitals with not early responders. No relevant differences were observed in the type of hospitals where early

responders and not early responders were managed. The majority of sites were university hospitals and almost all hospitals were publicly funded, large institutions (i.e., >600 beds).
Within the Def 1 analysis population, there were more male patients than female patients. The mean patient age was approximately 58 years, with about 62% of patients <65 years of age. The majority of patients (>80%) were of white ethnic origin.

Main Results: early responders were more likely than not early responders to come from sites where an infectious disease specialist (251 [69.1%] patients *vs*. 147 [62.0%] patients, respectively) or a surgeon (37 [10.2%] patients *vs*. 16 [6.8%] patients, respectively) treated the patients.
Comorbidities (relevant medical conditions upon hospitalisation) were less frequent among early responders (71.3%) than among not early responders (74.7%). This difference was particularly marked for diabetes (22.9% *vs*. 31.6%). On the contrary, cancer was more frequent among early responders (17.1%) than among not early responders (12.2%).
The mean time from symptom start to index visit was similar for early and not early responders. However, early responders were diagnosed with cSSTI approximately 2.5 days earlier than not early responders.
Skin infection lesions in early responders were less frequently those typical of a poorer prognosis than in not early responders: diabetic leg ulcers (2.8% *vs*. 3.4% of patients), peripheral vascular disease lesions (3.9% *vs*. 8.4%), large (>50 cm^2 extension) lesions (16.8% *vs*. 20.7%), lesions affecting the fascia (11.3% *vs*. 25.7%), lesions in lower extremities (62.5% *vs*. 75.9%), lesions with swelling/induration (65.8% *vs*. 73.0%), and lesions with skin necrosis (7.7% *vs*. 14.8%). This suggests that patients showing these lesion characteristics at presentation may be at higher risk to show a later response to antibiotic treatment.
Difficult-to-treat microorganisms such as MRSA, some gram-negative bacteria, strict anaerobic bacteria, etc., were less frequently isolated in early responders than in late responders. Correspondingly, easier-to-treat bacteria were more frequently isolated from early responders than from not early responders.
Recurrent cSSTI episodes and infections of nosocomial origin were less frequent among early than among not early responders (8.3% vs. 9.3%).
Regarding clinical outcomes, and as expected, the proportion of patients requiring initial treatment modification was lower among early responders (34.2%) than among not early responders (48.1%). Early responders also showed a lower proportion of re-infection or recurrence than not early responders (8.0% vs. 10.1%). The mortality rate was also lower for early responders compared with not early responders (1.4% vs. 3.8%).
The most frequently used first-line antibiotic (or combination of antibiotics) therapy was similar for early responders and not early responders, suggesting that no consideration seems to be given to the possibility of different treatment for potential longer term responders, based on the patient profile. Beta-lactamic antibiotics in combination with beta-lactamase inhibitors were the most frequently used agents (amoxicillin–clavulanate: 18.2% in ER, 12.2% in NotER, ampicillin/sulbactam or sultamicillin: 6.9% in ER, 19.8% in NotER, piperacillin- tazobactam (5.5% in ER, 8.4% in NotER, etc.).
An association was found between early response to antibiotics and a reduced use of healthcare resources. For example, compared to not early responders, early responders

had shorter hospital stays (median of 9.0 days *vs*. 16.0 days, for early and not early responders, respectively), fewer admissions to ICU (4.1% *vs*. 16.0%, respectively) and for shorter durations (median of 3.5 days *vs*. 5.0 days, respectively), lower incidence of septic shock (0.8% *vs*. 6.3%, respectively), etc., than not early responders.
Taken together, these results allowed identification of cSSTI patient profiles with lower chances of showing an early response: patients with lesions typical of a poorer prognosis (e.g., diabetic leg ulcers, large lesions, fascia affected, etc.), patients with difficult-to-treat microorganisms (MRSA, some gram-negative bacteria, strict anaerobic bacteria), patients with recurrent infections, etc., although the data suggests first line treatment was similar for all patients. In addition, an association was found between early response to initial antibiotic treatment and improved clinical outcomes and a reduced use of healthcare resources.

Safety Results: due to the non-interventional character of this study, no pro-active safety data collection took place. Only spontaneously mentioned safety events were reported as required by the post-marketing pharmacovigilance regulations.