Sponsor: Sanofi **Drug substance(s):** Pristinamycin (PYOSTACINE®)	**Study Identifiers:** U1111-1160-6001; EudraCT Number: 2013-000420-34; NCT02332577 **Study code:** PRISTL06562

Title of the study:

A Multi-center, Non-inferiority, Randomized, Open-Label, Phase IV Study Comparing Pristinamycin (2 g x 2 Per Day for 2 Days Then 1 g x 3 Per Day for 5 to 7 Days) to Amoxicillin (1 g x 3 Per Day) for 7 to 9 Days in Adults with Acute Community Acquired Pneumonia with a PORT Score of I, II or III

Study center(s):

This study was conducted at 16 centers that screened 165 patients and randomized 161 patients in France, Morocco and Tunisia.

Study period:

First Patient First Visit (FPFV): 30-Apr-2015

Last Patient Last Visit (LPLV): 27-Mar-2020

Study Status: Terminated (The sponsor stopped the study due to low recruitment with no safety concerns)

Phase of development: IV

Objectives:

Primary

To assess the clinical efficacy of pristinamycin at a dose of 2 x 2 g/day for 2 days then 3 x 1 g/day for 5 to 7 days versus amoxicillin 3 x 1 g/day for 7 to 9 days, 5 to 9 days after the end of treatment.

Secondary

To assess the clinical efficacy in the subpopulation with microbiological documentation at enrolment and according to baseline levels of procalcitonin (PCT).

To assess the effectiveness of the treatments against pneumococci

To evaluate the rate of relapse and mortality after 30 ± 2 days of treatment

To document failures

To record and follow-up adverse events (AE)

Methodology:

International, multi-center, randomized, open-label, parallel-group phase IV non-inferiority study stratified by Pneumonia patient Outcome Research Team (PORT) score and country. Due to recruitment issues, the study design, initially double-blind, double-dummy, was amended in early 2019. The study was then early terminated in 2023.

Number of study participants:

A total of 500 patients were planned to be included as per protocol. When the study prematurely terminated, a total of 161 patients had been included.

The Full Analysis Set (FAS) study population consisted of 159 patients (79 in the pristinamycin arm and 80 in the amoxicillin arm). These same patients were in the safety population.

Diagnosis and criteria for inclusion:

- Male or Female ≥18 years
- Suspected bacterial CAP defined by CXR obtained within 48 hours before randomization showing new lobar or multilobar infiltrates. For patients included in primary care, this X-ray could be performed within 24 hours after patient enrolment/randomization (up to 48 hours at the latest).
- Different predefined functional and/or clinical signs
- PORT score of I, II or III (Fine I, II or III)

Study products:

- Study drug: Pristinamycin/PYOSTACINE®, 500-mg film-coated tablets. Oral administration, swallowed with a glass of water during meals.
- Control drug: Amoxicillin, 500-mg capsules. Oral administration, swallowed with a glass of water before or during meals.
- Pristinamycin placebo: same appearance as the active product, given as a scored film-coated tablet. Oral administration, swallowed with a glass of water during meals.
- Amoxicillin placebo: same appearance as the active medication as capsules. Oral administration, swallowed with a glass of water before or during meals.

Duration of study intervention:

The original double-blind double-dummy regimen was:

Pristinamycin/PYOSTACINE® or pristinamycin placebo: 4 tablets twice daily for 2 days (48 hours), then 2 tablets three times daily for 5 to 7 days. The first five doses were to be taken 12 hours apart.

Amoxicillin or amoxicillin placebo: 2 capsules three times daily for 7 to 9 days.

The study was switched to open-label, in early 2019 with the following regimen:

Pristinamycin/ PYOSTACINE®: 4 tablets twice daily for 2 days (48 hours), then 2 tablets three times daily for 5 to 7 days. The first five doses were to be taken 12 hours apart.

Amoxicillin: 2 capsules three times daily for 7 to 9 days.

Criteria for evaluation:

Primary:

Cure (or success) assessed 5 to 9 days after treatment (Test Of Cure, TOC). Patients were classified into one of the following categories, based on radiological and clinical evolution: success or failure.

Secondary:

Cure (or success) at V4 (TOC) in patients with bacteriological documentation and according to baseline levels of PCT

Cure rate at V4 (TOC) in patients with bacteriological documentation for pneumococci

Relapse and mortality rates at V5

Documentation of failures

Serious and non-serious AE report

Statistical methods:

The premature termination of the study meant that the statistical power necessary for analyses of primary and secondary efficacy objectives could not be achieved. As a result, the findings are presented using descriptive statistics.

The primary analysis was performed on the FAS population:

• Assessment of cure at V4 by the Adjudication Committee and the investigator,

• The comparison of these two assessments (Cohen Kappa coefficient).

The secondary criteria are described on the FAS population:

• Assessment of cure at V4 in patients with microbiological documentation,

• Relapses and mortality at V5,

• Documentation of failures.

Safety is presented on the Safety Population using especially the following parameters: treatment exposure, deaths, AEs, treatment discontinuation, AEs of Special Interest (AESI), the blood laboratory parameters, vital signs.

Summary Results:

Demographic and other baseline characteristics:
The population was slightly predominantly male (58.5%). The majority of patients was in PORT II class (69.0%); the others were in PORT III class. The majority of enrollments occurred in the hospital (81.1%).

Exposure:

The mean duration of exposure to study treatments was 10.8 days. A total of 26 patients (16.8%) discontinued treatment early at Visit 4.

Efficacy results:

Cure was assessed in 71.6% of patients by the investigator and 40.3% of patients by the Adjudication Committee. The coefficient assessing concordance between the two cure assessments is relatively low (0.39). Five patients relapsed at V5 (4 in amoxicillin group and 1 in pristinamycin group).

Safety results:

A total of 64 AEs were reported in 46 patients (28.9%) considering both treatment arms (pristinamycin and amoxicillin). Thirteen (13) of these AEs were serious, reported in 13 patients, and 3 patients died of SAEs (two patients due to cancers and one patient due to a pneumonia). None of these SAEs were related to treatment. Six (6) AEs led to treatment discontinuation, 3 in each treatment group.

Changes in laboratory and clinical variables were comparable between the two treatment arms.

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