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Immunogenicity and Safety of Vaccines for the ICU

Nosocomial infections are an increasing problem as patients admitted to hospitals are, on average, older, multimorbid, immunocompromised and increasingly vulnerable to antibiotic-resistant bacteria circulating in hospitals.

Pseudomonas aeruginosa is one of the most common causes of nosocomial infection in intensive care unit patients and are a major cause of morbidity and mortality for ICU patients. Preventive vaccinations against the pathogen are a clinically relevant approach, and a reduction in mortality rate in ventilated ICU patients was observed in a Phase II trial for the *P. aeruginosa* vaccine employed in this case study.

Study Design

The primary objective of this study was to show the superiority of a *P. aeruginosa* vaccine with regard to overall mortality on Day 28 after first vaccination in mechanically ventilated ICU patients when compared to placebo.

Secondary objectives included assessment of various overall and sepsis-related mortalities. Moreover, incidence rates of invasive *P. aeruginosa* infection, immunogenicity of the experimental vaccine and seroconversion rates, and length of stays at the ICU and the hospital were evaluated versus placebo.

The trial was designed as a confirmatory, randomized, placebo-controlled, double-blinded phase II/III study



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that was conducted in 800 ICU patients requiring mechanical ventilation for at least 48 hours. *The sample size was powered to detect a treatment effect of 10% on Day 28 mortality as based on Phase II study results.*

Main criteria, in addition to the need for mechanical ventilation for at least 48 hours, were a high probability of survival for at least 48 hours, and exclusion of patients if sequential organ failure assessments (SOFA) scored below 4, if they had been admitted to the ICU <2 days after surgery or due to

trauma, or if they underwent organ transplantation less than 6 months prior to inclusion.

Informed consent from the patient or from the patient's legally authorized representative or waiver were obtained according to regional requirements.

Patients were randomized to receive two immunizations of either Pseudomonas aeruginosa vaccine or placebo administered seven days apart (on Days 0 and 7) by intramuscular injection. The non-adjuvanted vaccine contained 100 mcg recombinant Pseudomonas aeruginosa fusion protein construct

in 1 mL and placebo consisted of 1 mL PBS. Immunization was performed at the hospital ward if patients were discharged from ICU before Day 7.

Patients attended study visits on Days 0, 7, 14, 28, 56 and 180, during which general health status and safety were assessed (including AE's, SOFA scores, routine labs, *P. aeruginosa* infection etc.). In addition, blood samples were collected for the assessment of immunogenicity.

Study Approval and Conduct

Following the first submission of the study for ethical and regulatory review it took approximately 3.5 months until last approval of first submissions was obtained. Execution of the entire trial took approximately 45 months from First Patient In (FPI) to Last Patient Out (LPO).

A number of sites were selected by the Sponsor, but the majority of sites were identified and recruited by Celerion. To increase commitment of investigators and recruitment of patients, communication with investigators received special attention during the entire study. For instance, weekly calls were organised between the Celerion study team and the investigator & site staff and country-specific investigator meetings were held, during which lessons learnt were shared. Moreover, participating sites were supported with extra budgets to cover staff for on-site data entry support and, if applicable, special equipment and training.

Effectively, 812 patients were enrolled at 52 study centers across 6 EU countries (Austria, Belgium, Czech Republic, Germany, Hungary and Spain). A total of 800 patients were randomised (67% males, 33% females), 421 of which were early terminated. Early terminations were mainly due to patient deaths (338), loss to follow-up (52) and withdrawn consent (19).

Incapacitated Patients

A couple of aspects around incapacitated patients deserve special attention.

Typically, for incapacitated patients the ICF had to be signed by their legal representative. Subsequent to that, inclusion often had to be supported by the investigator and the patient's legal representative to

help provide data on medical history and concomitant medications relevant for inclusion.

Moreover, subtle differences existed in local law with regard to the Informed Consent Form and the consent procedure. Some examples of country-specific aspects are the following:

- In Hungary, signing of the ICF for the legal representative was highly dependent upon the investigator's opinion;
- Austrian investigators were allowed to decide on inclusion of comatose patients without requiring consent from the patient's legal representative.
- For incapacitated patients in Germany, an additional ICF had to be signed by an independent medical doctor if no legal representative were available.

Another noteworthy aspect is withdrawal of consent. In case patients had not consented themselves and, after regaining consciousness during the study, chose to withdraw consent, all data collected until withdrawal were likely to be discarded retrospectively.

SAE Reporting and Monitoring

Studies conducted in a population of critically ill ICU patients tend to generate large quantities of data due to high morbidity and mortality rates. Indeed, the current study population showed a substantial mortality rate (\pm 42% overall) and was characterised by high numbers of (S)AEs. An approximate 59% of patients had at least one SAE.

There was no requirement to submit individual SAE reports to Ethics Committees (Annual Report only).

Nevertheless, the involvement of such vulnerable patients and the consequent the high numbers of SAEs and co-medications generated a massive data set. Together with strict Sponsor guidance towards recording of co-medications and AEs as well as challenges around follow-up of AEs complicated Source Data Verification. Initially, the Sponsor expressed a preference of 100% SDV of ICU patients' medical records, but following discussions between Celerion and the Sponsor it was agreed that a reduction on % SDV would facilitate monitoring and be more realistic.

STUDY VISIT SAFETY ASSESSMENT

	Day 0	Day 7	Day 14	Day 28	Day 56	Day 180
Survival						
P.ae. Infection/SOFA						
Immunogenicity	X	X	X	X	X	X
Safety	X	X	X	X	X	X



Study Outcomes

The vaccine was well tolerated and not associated with safety concerns, and the seroconversion rate (i.e., proportion of patients with a ≥ 4 -fold increase in specific IgG titer compared with baseline) was significantly higher in the active vaccination group than placebo on all study visits.

Yet, the Day 28 all-cause mortality rate did not differ significantly between the groups.

Moreover, rates of *P. aeruginosa* infections did not differ significantly between both treatment groups.

Length of ICU stay as well as length of hospital stay after first vaccination were similar between the active vaccine and placebo groups.

CHALLENGES AND CELERION SOLUTIONS

Challenge	Celerion Capabilities
Informed Consent procedure for studies involving (incapacitated) ICU patients can be complex and different per country	Celerion has strong experience with international enrolment of ICU patients
Extensive morbidities and co-medications for ICU patients can complicate protocol adherence and data entry at site	Celerion experienced towards solutions to educate, motivate and support sites
Intensity of study monitoring can be challenging for studies in ICU patients	Celerion offers one of the industry's most experienced project management and monitoring teams
Variability in regulatory & ethical procedures	Celerion has experience with submissions to all required authorities in ICU patient studies
Communication between Sponsor, CRO and clinical site are pivotal	Celerion maintains regular communication with sites and sponsor to ensure compliance and commitment