A Phase 3, Randomized, Double-blind, Placebo-controlled, Single-dose Study to Evaluate the Efficacy and Safety of Suvratoxumab in Mechanically Ventilated Adults and Adolescents for the Prevention of Nosocomial Pneumonia

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Primary:- To evaluate the effect of suvratoxumab on reducing the incidence of nosocomial all-cause pneumonia.Secondary:- To evaluate the safety of a single IV dose of suvratoxumab.- To evaluate the effect of suvratoxumab on reducing the incidence of...

Ethical review	Approved WMO
Status	Pending
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON51453

Source
ToetsingOnline

Brief title
SAATELLITE-2

Condition

- Bacterial infectious disorders

Synonym
Staphylococcus aureus; prevention of pneumonia

Research involving

Human

Sponsors and support

Primary sponsor: Aridis Pharmaceuticals, Inc.
Source(s) of monetary or material Support: COMBACTE Group,Pharmaceutical Industry

Intervention

Keyword: Nosocomial Pneumonia, Single-dose, Staphylococcus aureus, Suvratoxumab

Outcome measures

Primary outcome

- Incidence of nosocomial all-cause pneumonia through 30 days post dose.

Secondary outcome

- Treatment emergent adverse events (TEAE) and clinical laboratory assessments through 30 days post dose, and treatment emergent serious adverse events (TESAE) and TEAE of special interest (TEAESI) through 90 days, and for a subset of subjects through 180 days post dose.

- Incidence of nosocomial all-cause pneumonia or death through 30 days post dose.

- Incidence of nosocomial S. aureus pneumonia through 30 days post dose.

- Incidence of nosocomial pneumonia caused by S. aureus through 90 days post dose.

- Magnitude of healthcare utilization (e.g., duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, number of and days of systemic antibiotic use) through 90 days post dose in all subjects and in a subset of subjects through 180 days post dose.

- Suvratoxumab serum concentration and PK parameters through 30 days post dose,

and in a subset of subjects through 90 days post dose.

- Suvratoxumab ADA response in serum through 30 days post dose, and in a subset

of subjects through 90 days post dose.

Study description

Background summary

Bacterial pneumonia, especially an event occurring within the hospitalized or intensive care unit (ICU) population, is a clinically significant and serious disease that contributes significantly to morbidity and mortality. These events constitute the second most common nosocomial infection and the leading cause of death from nosocomial infection in critically ill patients in Europe (Torres et a, 2017), in the United States (US; Spellberg and Talbot, 2010, Elliot et al, 2018), and worldwide (de Carvalho Baptista et al, 2018). In the European Union (EU), the mortality varies widely between European Countries with rates between 1% and 48% (Peyrani et al, 2019). Staphylococcus aureus (S. aureus) is a primary cause of nosocomial pneumonia. In both European and US ICUs, investigators found that 20% to 22% of their mechanically ventilated ICU patients developed pneumonia caused by S. aureus (Esperatti et al, 2010, Hurley 2018).

S. aureus pneumonia among mechanically ventilated ICU patients is associated with significant healthcare-associated costs (Paling et al, 2017). In a study conducted from 2002 to 2006, mean incremental costs of S. aureus pneumonia compared to non-pneumonia controls was reported to be $101,660 (Restrepo et al, 2010). Similarly, an analysis of privately insured patients admitted to an ICU between 2006 and 2012 suggests that S. aureus pneumonia was associated with a mean excess or incremental cost of $100,000 compared to the intubated (control) ICU patients (Kyaw et al, 2015).

There is limited data available for the incidence and prevalence of S. aureus pneumonia occurring in each specific patient population subgroup (Gaensbauer 2017). Estimates indicate that S. aureus pneumonia occurs most frequently in adults (83.2 to 84.3% of all cases in years 2012, 2009, 2006) followed by neonates/infants (birth up to 1 year) (11.2 to 12.5% of reported cases) and adolescents (12 years up to 17 years) (4.0 to 4.3% of all cases; HCUP 2017). Older pediatric patients (especially adolescents) are at risk for developing S. aureus pneumonia and ventilator associated pneumonia (VAP), which results in experiencing head and neck trauma, such as traumatic brain injury (Hamele et al, 2016).

During infection, S. aureus releases a number of toxins, and S. aureus alpha toxin (AT) is a key virulence factor leading to immune evasion, tissue invasion and necrosis (Wilke and Bubeck Wardenburg, 2010, Wu et al, 2019). The pivotal role of AT in S. aureus pathogenesis is supported by animal models (dermonecrosis, pneumonia, sepsis, endocarditis, and mastitis) (Bramley et al, 1989; Bayer et al, 1997; Bubeck Wardenburg et al, 2008; Kobayashi et al, 2011; Powers et al, 2012) and by observational studies in humans in which the presence of anti-AT antibodies during severe infections was associated with improved outcome (Adhikari et al, 2012; Jacobsson et al, 2010; Ruotsalainen et al, 2008, Wu et al, 2018). AT expression level by colonizing methicillin susceptible S. aureus (MSSA) has been reported to be a marker for progression to VAP, thereby implicating a role for AT in VAP.

Antibiotics are the only intervention available for treating S. aureus diseases. Despite the introduction of new antibiotics against S. aureus, emergence of resistance requires new approaches for combatting S. aureus diseases. While prevention of healthcare-associated infections caused by S. aureus is an important public health goal, no vaccines or passive immunization therapies are commercially available (Argondizzo et al, 2021). Prevention currently focuses on infection control practices and limited prophylactic use of antibiotics (e.g., pre-surgery). Indeed, antimicrobial prophylaxis should be limited to specific, well-accepted indications to avoid excess cost, toxicity, and antimicrobial resistance (Enzler et al, 2011). In a recent study, systemic antibiotics were determined to be ineffective in patients colonized with S. aureus to reduce colonization burden and prevent S. aureus VAP (Stulik et al. 2017). Topical decolonization regimens have been proposed for S. aureus carriers based on anecdotal data, given that nasal carriage is a risk factor for hospital-acquired infection (Muñoz et al, 2008; Bode et al, 2010, Hantisch et al, 2020). However, decolonization efforts have not been consistently effective and are not universally implemented (Kluytmans et al, 1996; Perl et al, 2002; Kalmeijer et al, 2002, Kuraitis and Williams 2018). Several antibiotic prophylactic treatment options are shown to be ineffective in preventing S. aureus VAP, which underscores the urgent need for better therapeutic alternatives for the prevention of S. aureus pneumonia (Burnham 2017; Stulik et al 2017).

Study objective

Primary:
- To evaluate the effect of suvratoxumab on reducing the incidence of nosocomial all-cause pneumonia.

Secondary:
- To evaluate the safety of a single IV dose of suvratoxumab.
- To evaluate the effect of suvratoxumab on reducing the incidence of nosocomial all-cause pneumonia or death.
- To evaluate the effect of suvratoxumab on reducing the incidence of

nosocomial S. aureus pneumonia.
- To evaluate the effect of suvratoxumab on reducing the incidence of long-term nosocomial pneumonia caused by S. aureus.
- To measure the effect of suvratoxumab on the magnitude of healthcare utilization.
- To evaluate the serum PK of suvratoxumab.
- To evaluate the serum ADA responses to suvratoxumab.

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy of a single IV dose of suvratoxumab (5000 mg) in mechanically ventilated subjects in the ICU who are at high risk for S. aureus infections and who are currently free of active S. aureus-related disease but are colonized with S. aureus in the LRT. Approximately 564 subjects will be enrolled and randomized at about 200 centers worldwide. Subjects in this study will be adult (18 to 65 years of age) and adolescent subjects (12 to < 18 years of age) in the ICU, who require mechanical ventilation for * 3 days and who are colonized with S. aureus in the LRT, but currently free of active S. aureus-related disease. Subjects will be randomly assigned in a 1:1 ratio (282:282) to receive a single IV dose of suvratoxumab (5000 mg) or placebo. Randomization will be stratified by whether or not subjects received systemic anti-S. aureus systemic antibiotic treatment, and by geographic region. Following investigational product administration on Day 0, subjects will be followed through Day 90 (and for a subset of approximately 100 subjects for PK and ADA through Day 90 and followed for safety through Day 180).

Intervention

Single-dose of 5000 mg suvratoxumab or placebo intravenously administered at D0 of V2.

Study burden and risks

Potential benefits from participating to the trial:
- Suvratoxumab may prevent development of pneumonia, but that is not certain.
- In this study the participant can also get a placebo. In case the participant is getting a placebo no preventative treatment will be given (prevention currently focuses on infection control practices, however, there are no preventive treatments that prove to be effective).
- Research will help doctors to learn more about the study drug. This may help others with a similar health problem in the future.

Potential disadvantages from participating to the trial:
- Possible side effects of suvratoxumab
- Possible discomfort from the measurements during the study

- Participant can lose additional time
- (additional) testing
- Appointment that the participant need to attend

Conclusion:
Antibiotics are the only intervention available for treating S. aureus diseases. Despite the introduction of new antibiotics against S. aureus, emergence of resistance requires new approaches for combatting S. aureus diseases. While prevention of healthcare-associated infections caused by S. aureus is an important public health goal, no vaccines or passive immunization therapies are commercially available (Argondizzo et al, 2021). Prevention currently focuses on infection control practices and limited prophylactic use of antibiotics (e.g., pre-surgery). Indeed, antimicrobial prophylaxis should be limited to specific, well-accepted indications to avoid excess cost, toxicity, and antimicrobial resistance (Enzler et al, 2011). In a recent study, systemic antibiotics were determined to be ineffective in patients colonized with S. aureus to reduce colonization burden and prevent S. aureus VAP (Stulik et al. 2017).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

1. Adult (18 [unless otherwise specified by local Country laws] to 65 years of age) or Adolescent (12 to < 18 years of age [unless otherwise specified by local Country laws]) at the time of screening.
2. Written informed consent and written informed assent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act [HIPPA] in the United States [US], European Union [EU] Data Privacy Directive in the EU) obtained from the subject/legally acceptable representative (LAR) prior to performing any protocol-related procedures, including screening evaluations.
3. Females of childbearing potential (inclusive of adolescents) who are sexually active with a non-sterilized male partner must have evidence of not being pregnant upon enrolment and have a negative pregnancy test prior to administration of investigational product.
- Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral oophorectomy, or complete hysterectomy), premenarchal or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
4. Tracheal or bronchial sample positive by polymerase chain reaction (PCR) for S. aureus within 36 hours prior to randomization. Note: the 36-hour window will be determined by the time of sample collection.
5. Currently intubated and on mechanical ventilation in the ICU.
6. Expected to remain intubated and mechanically ventilated for * 3 days based on investigator estimate.
7. No diagnosis of new-onset pneumonia within 72 hours prior to randomization (subjects with evidence of resolved pneumonia will be eligible).

Exclusion criteria

1. The study subject is moribund or unlikely to survive for a week post randomization despite delivery of adequate antibiotics and supportive care based on clinical judgement by the Principal Investigator (PI).
2. Acute confirmed or suspected active S. aureus disease at study enrolment and investigational product dosing (colonization is acceptable as per inclusion criterion #4).
3. Active pulmonary disease that would impair the ability to diagnose

pneumonia, such as active tuberculosis or fungal disease, obstructing lung cancer, large empyema, cystic fibrosis, or acute respiratory distress syndrome with lung "white out".
4. Receipt of anti- S. aureus systemic antibiotics for > 48 hours within 72 hours prior to randomization that are considered active against the S. aureus strain with which the subject is colonized or anticipated ongoing receipt of anti- S. aureus systemic antibiotics.
5. Acute Physiology and Chronic Health Evaluation (APACHE)-II score >= 25 (if Glasgow Coma Scale [GCS] score is > 5) or >= 30 (if GCS score is <= 5), or SOFA score >= 9 at time of randomization.
- Note: Vasopressors only used to improve cerebral perfusion pressure (e.g., subarachnoid hemorrhage) will not be entered in the calculation of the cardiovascular component of the SOFA score.
6. Receipt of any investigational drug therapy within 30 days prior to randomization.
7. Previous receipt of a mAb within 60 days prior to randomization.
8. Subjects with a CD4 count of < 200 due to advanced human immunodeficiency virus (HIV) infection. Subjects with a history of HIV infection who have been on highly active antiretroviral therapy and asymptomatic from HIV infection for at least 6 months may be enrolled.
9. History of allergic disease or reactions likely to be exacerbated by any component of the investigational product.
10. Not able to complete long-term follow-up for at least 90 days post dose based on investigator judgment.
11. Pregnant female or nursing mother.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	10-11-2022
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Suvratoxumab

Ethics review

Approved WMO Date:	08-06-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-08-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	5331885
EudraCT	EUCTR2021-004979-14-NL
CCMO	NL81137.028.22