CAL02: A BROAD-SPECTRUM ANTI-TOXIN AGENT

Development of Non-Traditional Therapies for Bacterial Infections

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LIPOSOMES

>10 liposomal formulations approved for human use in EU and the USA since 1995

- drug delivery vehicles in medicine
- adjuvants in vaccination
- signal enhancers/carriers in diagnostics
- penetration enhancer in cosmetics

- No pharmacological activities of their own
- Benign safety profile, no major adverse finding related to empty liposomes reported
**CAL02**

**APPROACH**

Lipid microdomains on cell membrane are used as docking stations by many bacterial toxins.

CAL02: Specific mixture of empty liposomes engineered to mimic these docking stations to irreversibly trap toxins.

- Empty liposomes composed of cholesterol and sphingomyelin
- Empty liposomes composed of sphingomyelin only

**DRUG COMPOSITION**

Concentrated mixture of empty liposomes composed of cholesterol and sphingomyelin and of sphingomyelin only.

**MECHANISM OF ACTION**

Acts as a winning decoy by mimicking domains targeted by toxins.
Neutralizes a large panel of toxins.
A NON-TRADITIONAL APPROACH TO ADDRESS URGENT MEDICAL NEEDS

Antibiotics kill the pathogen but fail to neutralize toxins

CAL02 neutralizes bacteria’s most deadly weapons

BACTERIAL GROWTH AND DISSEMINATION
IMPEDED IMMUNE DEFENSE
PRO-INFLAMMATORY BURST
ORGAN FAILURE
DEATH

CAL02:
- Unique broad-spectrum MOA (Gram+ & Gram-)
- Active regardless of resistance profile
- MOA complementary to antibiotics
- Independent from antibiotic’s class & MIC
- Does not prompt resistance
- No impact on commensal flora
- Good safety profile
- Wide therapeutic impact
**Toxins neutralized by CAL02 include** all CDCs (e.g. pneumolysin, streptolysins), beta-PFTs (e.g. alpha-hemolysin, Panton–Valentine leukocidin), phospholipases, virulent appendages

**In vivo studies:**
- Pneumonia & bacteremia models
- Treatment hours after infectious challenge / start of antibiotics
- Infections caused by *S. pneumoniae* / *S. aureus* (incl. MRSA, USA300) / *P. aeruginosa*

**Results highlighted that:**

mmatory responses
DEVELOPMENT STEPS

- Non-clinical pharmacology – Efficacy studies (survival, organ protection, bacterial load, inflammation)
- Pilot PK / biodistribution
- Two-weeks expanded acute toxicology in rats and dogs (non-GLP)
- **Scientific Advice Meeting with MHRA** : Discuss preclinical package and FIM directly in patients
- PK / biodistribution in healthy and infected mice
- Safety pharmacology: Respiratory, CNS, Cardiovascular (GLP)
- Expanded single/double-dose toxicity in rats and dogs (GLP)
- **CTA via VHP** : Clinical Trial Application via Voluntary Harmonization Procedure (FR, BE, UK)
- First-in-human trial in patients
A randomized, multicentre, double-blind, placebo-controlled study
to assess the safety, tolerability, efficacy and pharmacodynamics after the intravenous administration of CAL02
in severe community-acquired pneumonia due to Streptococcus pneumoniae

- CAL02 in addition to standard of care
- 3 arms:
  - CAL02 Low Dose (4 mg/kg)
  - CAL02 High Dose (16 mg/kg)
  - Placebo (saline)
- Primary objective: Safety & Tolerability
- Secondary objectives: Efficacy & Pharmacodynamics

Severe pneumococcal CAP:
- Rapid diagnosis
- Well-defined acute phase and complications
- Standard antibiotic treatments
- Homogeneity of toxin/toxic profile
- Patients evolve into serious condition:
  - 10-20% hospitalized CAP patients end up in the ICU*
  - Average ICU stays: 13 days**
  - 30-35% ICU patients develop septic shock***
  - Mortality of ICU patients surpasses 30%***

ClinicalTrials.gov code NCT02583373

* Mandell et al. CID (2007)
** Mongardon et al. Crit Care (2012)
FIRST-IN-HUMAN TRIAL

- 10 ICUs, 2 countries
  Study Coordinators: Bruno François (Limoges, France) and Pierre-François Laterre (Brussels, Belgium)

- Study design

<table>
<thead>
<tr>
<th>RANDO</th>
<th>FOLLOW-UP &amp; TEST-OF-CURE</th>
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<tr>
<td>D -1</td>
<td>D 1</td>
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<tr>
<td>D 2</td>
<td>D 8</td>
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<td>D 15-22</td>
<td>D 29</td>
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  CAL02 (i.v.) + SOC

- Randomization

  - Jean Chastre, Chairman (FR)
  - Prof. Steven Opal (USA)
  - Prof. Jérôme Pugin (CH)
  - Dr. Philippe Eggimann (CH)
FIRST-IN-HUMAN TRIAL

BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>TOTAL (n = 19)</th>
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<tbody>
<tr>
<td>Age</td>
<td>59.2 (15.9)</td>
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<tr>
<td>CURB-65</td>
<td>3.5 (0.8)</td>
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<tr>
<td>APACHE II</td>
<td>21.5 (4.9) *</td>
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<tr>
<td>SOFA</td>
<td>7.7 (3.3)</td>
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<tr>
<td>Septic shock (need of vasopressors)</td>
<td>11 (58%)</td>
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<td>Invasive mechanical ventilation</td>
<td>8 (42%)</td>
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<tr>
<td>Bacteremia</td>
<td>5 (26%)</td>
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<tr>
<td>PAO2/FiO2</td>
<td>144.5 (84.7)</td>
</tr>
<tr>
<td>CRP</td>
<td>300.8 (151.1)</td>
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<tr>
<td>Procalcitonin</td>
<td>27.8 (34.3)</td>
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* APACHE II distribution across treatment arms (mean):
  - CAL02 Low dose: 25.3
  - CAL02 High dose: 22.1
  - Placebo: 17.4

OUTCOME – PRIMARY OBJECTIVES

SAFETY & TOLERABILITY

- Equal distribution of TEAEs and SAEs between arms
- No difference in the frequency and severity grade
- Nature of AEs consistent with profile of study population

CAL02 was considered safe and well tolerated
OUTCOME – SECONDARY OBJECTIVES: EFFICACY

- One death in each arm
- All surviving patients cured at TOC (Day 15-22)
- More patients cured at early TOC (Day 8) in CAL02 High Dose arm (56% vs. 20% in placebo arm), translated in a shorter time to cure (8 vs. 10 days in placebo arm)
- Shorter duration of IMV in ventilated patients treated with CAL02 High Dose (4.5 vs. 12 days in other arms)
- Faster improvement of organ dysfunction (50% reduction in SOFA score achieved by Day 5 in the CAL02 arms vs. 12.5% in the placebo arm)
- Hemodynamic protection and stabilization in CAL02-treated arms vs. no improvement or cases of worsening in the placebo arm
- Faster normalization of inflammatory biomarkers in CAL02-treated patients
- Shorter ICU stay in CAL02 High Dose arm (5 vs. 12 days for placebo arm)
What’s next?

- Profile:
  - Broad-spectrum activity
  - Good safety profile
  - Does not prompt resistance
  - Has the potential to improve SOC

  - Superiority trial for SOC + CAL02 versus SOC alone → in severe rather than mild infection

- Priority: Discuss devel plan with Health Authorities
  - Study populations (origin of infection and causing pathogen(s))
  - Sample size & Endpoints
  - Address and include MDR strains
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