Combioxin

Innovative anti-virulence approach for severe bacterial infections

CAL02: A BROAD-SPECTRUM ANTI-TOXIN AGENT

Development of Non-Traditional Therapies for Bacterial Infections

FDA Public Workshop

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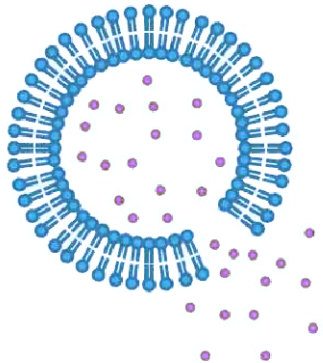
LIPOSOMES

Combioxin

>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

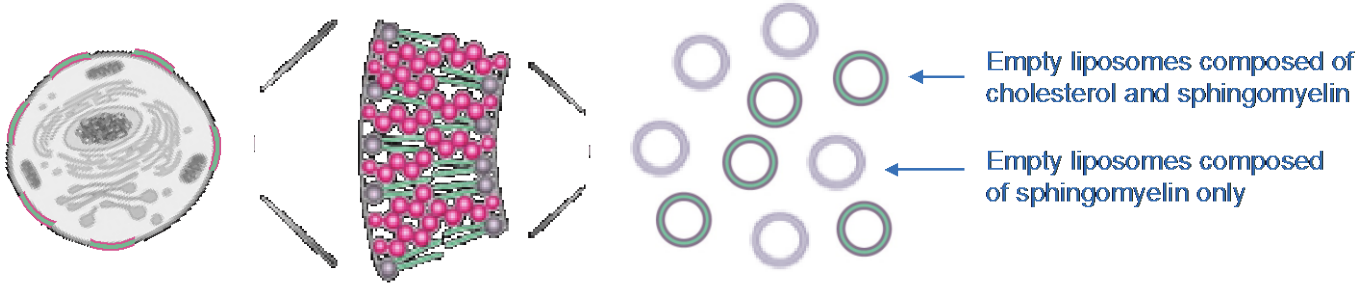
- **No pharmacological activities of their own**
- Benign safety profile, no major adverse finding related to empty liposomes reported

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



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

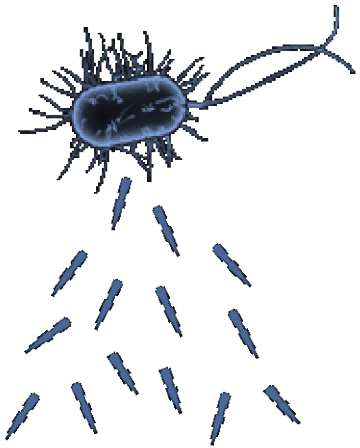
Neutralizes a large panel of toxins

CAL02

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

PRECLINICAL DATA

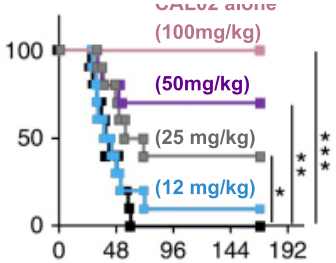
Toxins neutralized by CAL02 include all CDCs (e.g. pneumolysin, streptolysins), beta-PFTs (e.g. alpha-hemolysin, Panton–Valentine leukocidin), phospholipases, virulent appendages

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

FIRST-IN-HUMAN TRIAL

Combioxin

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

ClinicalTrials.gov code NCT02583373

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%***

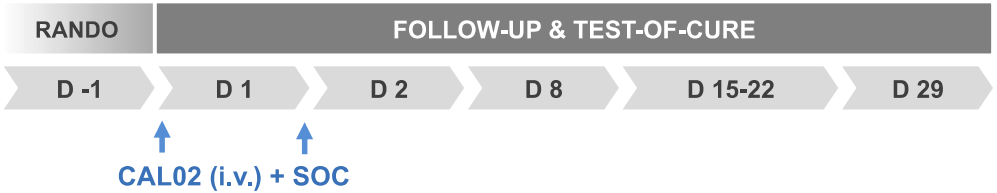
* *Mandell et al. CID (2007)*
** *Mongardon et al. Crit Care (2012)*
*** *Welte et al. Thorax (2012); Torres. Community Acquir Infect (2014); Lynch and Zhanel. Curr Opin Pulmonary Med (2010)*

FIRST-IN-HUMAN TRIAL

- 10 ICUs, 2 countries

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

- Study design



- Randomization

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

FIRST-IN-HUMAN TRIAL

BASELINE CHARACTERISTICS

PARAMETERS		TOTAL (n = 19)
Age	Mean (SD)	59.2 (15.9)
CURB-65	Mean (SD)	3.5 (0.8)
APACHE II	Mean (SD)	21.5 (4.9) *
SOFA	Mean (SD)	7.7 (3.3)
Septic shock (need of vasopressors)	n (%)	11 (58%)
Invasive mechanical ventilation	n (%)	8 (42%)
Bacteremia	n (%)	5 (26%)
PAO2/FiO2	Mean (SD)	144.5 (84.7)
CRP	Mean (SD)	300.8 (151.1)
Procalcitonin	Mean (SD)	27.8 (34.3)

* 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)

CLOSING COMMENTS

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 Autorities
  - Study populations (orginin of infection and causing pathogen(s))
  - Sample size & Endpoints
  - Address and include MDR strains

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