Advancing Promising Monoclonal Antibody Therapies for Serious Infections

Jefferies Global Healthcare Conference

June 7, 2016
Advancing Monoclonal Antibodies to Address Serious Infections

• Clinical-stage biotechnology company focused on the discovery and development of mAbs for pre-emptive and post-infection therapy of the most serious infectious diseases

• ASN100 for *S. aureus*: initiating Phase 2 clinical trial in 2016
  – Large market potential where no current therapies exist for the prevention of *S. aureus* pneumonia in heavily colonized, high-risk, mechanically ventilated patients

• Deep pipeline of antibody-based infectious disease programs based on proven technologies

• Targeting areas of high mortality, high healthcare costs and high unmet need during an unprecedented time of globally heightened mandates to better manage infectious diseases
Global Action to Address Public Health Crisis with Innovative Anti-infective Therapies

• Antimicrobial resistance is a growing global public health crisis
  – According to the CDC, antibiotic resistance causes 23,000+ deaths and >2M illnesses per year in the U.S.

• Global policy makers, health care leaders, regulators around the world taking action to spark new innovation
  – Declaration by the pharmaceutical, biotechnology and diagnostics industries on combating antimicrobial resistance renews focus on anti-infective field

• New reimbursement paradigm and increased funding for innovation in this space prioritized globally

“If we fail to act...we are cast back into the dark ages of medicine.”
- David Cameron, UK Prime Minister

“Although previously unthinkable, the day when antibiotics don’t work is upon us.”
- Dr. Arjun Srinivasan, CDC
Uniquely Positioned to Lead Antibody-Solutions to Serious Infectious Diseases

• Fundamental shift in approach to anti-infectives

mAbs have been successfully applied to many therapeutic areas, but rarely to acute bacterial infections where they have the potential to address critical unmet medical needs and change the course of antibiotic resistance

✓ Selective, pathogen-specific vs. broad-spectrum
✓ Designed to preserve host microbiome
✓ Non-antibiotic approach intended to avoid resistance
✓ Pre-emptive therapy in colonized patients
### Experienced and Proven Team

<table>
<thead>
<tr>
<th>Management</th>
<th>Experience</th>
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<tbody>
<tr>
<td>Rene Russo, PharmD BCPS, President &amp; CEO</td>
<td>Cubist, Bristol Myers Squibb</td>
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<tr>
<td>Eszter Nagy, MD PhD, Co-founder &amp; Chief Scientific Officer</td>
<td>Intercell AG, BoD Wittycell S.A.S, University of Vienna</td>
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<tr>
<td>Michael Gray, MBA CPA, Chief Financial Officer &amp; Chief Business Officer</td>
<td>Curis, Reprogenesis, E&amp;Y LLP</td>
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<tr>
<td>David Mantus, PhD, Chief Development Officer</td>
<td>BIND, Seres, Cubist, Sention, Shire</td>
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<tr>
<td>Chris Stevens, MD, Chief Medical Officer</td>
<td>Millenium/Takeda, Alnara, Circe, Altus</td>
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<tr>
<td>Ed Campanaro, SVP Clinical Operations</td>
<td>bluebird bio, Cubist, AAI Pharma Services Corp.</td>
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<table>
<thead>
<tr>
<th>Board of Directors</th>
<th>Experience</th>
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<tbody>
<tr>
<td>Jan Adams</td>
<td>Managing Director, EMBL Ventures GmbH</td>
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<tr>
<td>Daniel Burgess</td>
<td>Venture Partner, SV Life Sciences, Prior CEO of Rempex and Mpex</td>
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<tr>
<td>Tillman U. Gerngross, Chairman</td>
<td>CEO, Adimab, Co-Founder, Arsanis</td>
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<tr>
<td>Carl Gordon</td>
<td>Partner, OrbiMed Advisors</td>
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<tr>
<td>Terry McGuire</td>
<td>Founding Partner, Polaris Venture Partners</td>
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<tr>
<td>Eszter Nagy</td>
<td>Co-founder and CSO, Arsanis</td>
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<td>Claudio Nessi</td>
<td>Partner, NeoMed Management</td>
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<td>Michael Ross</td>
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<td>Rene Russo</td>
<td>CEO, Arsanis</td>
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<tr>
<td>Amy Schulman</td>
<td>Venture Partner, Polaris Venture Partners</td>
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Deep Pipeline of Monoclonal Antibodies to Address the Most Serious and Problematic Infectious Diseases

<table>
<thead>
<tr>
<th></th>
<th>Lead identification</th>
<th>Lead optimization</th>
<th>Candidate selection</th>
<th>Pre-clinical development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Prevention</th>
<th>Treatment</th>
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<td><strong>ASN100</strong></td>
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<td><em>Klebsiella pneumoniae</em></td>
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<td><em>Streptococcus pneumoniae</em></td>
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Addressing a Critical Problem for Patients and the Healthcare System

Lead Clinical Program: ASN100
The Impact of *S. aureus* Infection

- >1M patients mechanically ventilated in US each year (1.6M predicted by 2020)

| Trauma to healthy person | Surgery and treatment with advanced technology and highly-trained medical specialists, ventilated during recovery ($10,000s+ of healthcare dollars) | Patient that should recover dies after developing *S. aureus* infection despite antibiotic treatment |
Therapeutic Paradigm for *S. aureus*: Pneumonia in Mechanically Ventilated Patients

**Prevention**

- ASN100

**Colonization period**

- 0

**S. aureus pneumonia**

- 7

- 14+

**Days on mechanical ventilation**

**Treatment**

- vancomycin
- telavancin
- tedizolid
- ceftaroline
- ceftobiprole
- linezolid
- nafcillin

Mortality: 30%

Cost: $25->100K

20 excess days in hospital

(6 in ICU)
Addressing Extreme Burden on the US Healthcare System

Hundreds of thousands of patients at risk for SA VAP in the US each year

- 1.2 million ventilated patients in US each year\(^1\)
- ~240,000 heavily-colonized patients\(^2\) (20% of ventilated patients)
- ~80,000 patients progress to SA VAP\(^2\)

\(S.\ aureus\) pneumonia in mechanically ventilated patients puts tremendous pressure on the US healthcare system

- Extends days on ventilation
- Leads to longer hospital and ICU stays
- Increases risk of re-hospitalization

\(S.\ aureus\) pneumonia is caused by methicillin-resistant SA

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\(^1\) Wunsch, 2010
\(^2\) Stulik, 2014
ASN100: A Monoclonal Antibody Product
Uniquely Designed to Address *S. aureus* Pneumonia

**Compelling Features of ASN100**

- Combination of 2 human monoclonal antibodies (mAbs) that neutralize 6 clinically-important *S. aureus* cytotoxins
- ASN 100 is the only mAb product that addresses all clinically important toxins associated with pneumonia development and progression

**Benefits of ASN100**

- Unlike other mAbs, ASN100 protects both lung epithelium from toxin effects and preserves human immune cells to combat infection
- Designed to have no impact on the patient’s microbiome
- Intended to have no risk for resistance development (toxin target)
- ASN100 offers a novel, non-antibiotic approach to pre-emptive therapy, with the potential to break the cycle of antimicrobial resistance

**TRANSLATION**

ASN100 dramatically improves outcomes in multiple animal models of *S. aureus* infection compared to other single-toxin *S. aureus* mAbs
S. aureus Activates an Arsenal of Cytotoxins to Invade Human Tissue and Destroy Immune Cells

Alpha-hemolysin (Hla) destroys epithelial cells (airway)

Leukocidins lyse phagocytic cells (immune system)
ASN100 Neutralizes Six *S. aureus* Cytotoxins Critical to Human Pathogenesis
ASN100 Achieves Complete Toxin Neutralization

alpha-hemolysin (Hla)

HlgAB

HlgCB

LukSF (PVL)

LukED

LukGH

• ASN-1: An antibody identified with the Adimab platform targets the only region of Hla that is shared with and highly conserved in other toxins
• Three rounds of optimization achieved high affinity binding to all four toxins that share only 25% amino acid identity

• ASN-2: An antibody that preferentially binds to the LukGH dimer
• All LukGH variants expressed by different S. aureus strains tested are neutralized

conserved amino acids among Hla and F-components indicated with black spheres
Unlike other *S. aureus* mAbs, ASN100 Protects Both Lung Epithelial Cells & Human Immune Cells In Vitro

**ASN100** neutralizes alpha-hemolysin (Hla) with high efficacy compared to Hla-only mAbs

**ASN100** inactivates leukocidins and preserves phagocytic cells, unlike Hla-only mAbs

### Hla-neutralization: human lung cells

![Graph showing Hla-neutralization: human lung cells](image)

### Leukocidin neutralization: human phagocytes

![Graph showing Leukocidin neutralization: human phagocytes](image)

Rouha, 2015
Data on file
**In Vitro Synergy of ASN100 mAbs Provides Complete Protection of Human Phagocytes**

- All 5 leukocidins must be neutralized to avoid killing of phagocytes
- Both mAbs (ASN-1 and ASN-2) are needed for full efficacy
- Synergy demonstrated across diversity of strains and toxin expressions

![Bar chart showing live phagocytes exposed to CA-MRSA USA300](image)

*Data on file*
Superior Prophylactic Efficacy Achieved in Rabbit Model of Necrotizing Pneumonia Compared to other *S. aureus* mAbs

- ASN-1 has superior efficacy compared to Hla-specific mAbs in rabbits, the most relevant animal species that is susceptible to the leukocidins.

**Survival in rabbit USA300 CA-MRSA pneumonia model**

- Infection with USA300 MRSA strain intrabronchially 24 hr after treatment with mAbs intravenously.

Rabbit pneumonia model (according to Diep, 2010)

Data on file
ASN100 Potentiates Antibiotics Commonly Used for MSSA (Oxacillin) or MRSA (Vancomycin, Linezolid) Infections

- ASN-1 significantly increases survival as an add-on treatment to sub-therapeutic doses of antibiotics in mouse pneumonia models.

Murine pneumonia model:
- Infection with lethal dose of *S. aureus* intranasally
- Treatment with sub-therapeutic doses of ASN-1 & antibiotic alone and in combination post-infection

Data on file
ASN100 Development Strategy: Pre-empting *S. aureus* Pneumonia in Mechanically Ventilated Patients

- *S. aureus* pneumonia: high mortality, high cost, and toxin-mediated

25% of All hospital pneumonia cases are confirmed positive for *S. aureus*

Pathology is driven by *S. aureus* cytotoxin damage to both the lung epithelium cells and immune cells

Endotracheal tubes are easily cultured, minimizing non-evaluable rates in clinical trials and allowing identification of high-risk patients

Lack of preventative therapies for heavily colonized patients allows for definitive, placebo controlled *superiority* design
## ASN100 Definitive Phase 2: Placebo-Controlled Superiority Trial Initiates in 2016

<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
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<tbody>
<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
<td>Q2</td>
</tr>
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### IND-enabling CMC and nonclinical

#### Phase 1 SAD

**Double-blind, placebo controlled (n=52)**

- Objectives: Safety and PK
- Dosing completed
- Two unblinded cohorts to determine mAb levels in BAL fluid

#### Phase 2 Prevention Study (Proof-of-Concept Study)

**Double-blind, placebo-controlled, superiority design (n≈300)**

- Objectives: Safety, PK, Efficacy

  **Inclusion:**
  - Mechanically ventilated patients
  - Heavily colonized patients (>10^5 cfu/ml ETA)
  - Patients on anti-staphylococcal antibiotics allowed

  **Endpoints:**
  - Progression to *S. aureus* pneumonia
  - Days on mechanical ventilation
  - Days in ICU

  1:1 Randomization

#### Phase 3

*complete in 2021*
ASN100 Phase 2 vs. “Traditional” VAP Studies

- Prevention design allows for highly executable clinical development

<table>
<thead>
<tr>
<th></th>
<th>ASN100 Phase 2</th>
<th>VAP Treatment Study</th>
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<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Superiority</td>
<td>Non-inferiority</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Placebo</td>
<td>Standard-of-care antibiotic</td>
</tr>
<tr>
<td><strong>Identifying patients</strong></td>
<td>Heavily colonized=at-risk</td>
<td>VAP diagnosis</td>
</tr>
<tr>
<td><strong>Prior antibiotics allowed?</strong></td>
<td>Yes</td>
<td>No (excludes &gt;90% of patients)</td>
</tr>
<tr>
<td><strong>Clinical endpoint</strong></td>
<td>Disease incidence</td>
<td>All cause 30-day mortality</td>
</tr>
<tr>
<td><strong>HEOR endpoints</strong></td>
<td>Reduced hospital stay, Reduced ICU stay, Reduced days on ventilation</td>
<td>Unclear</td>
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ASN100 Market Opportunity by 2022

ASN100 value proposition: a safe and effective option for the prevention and treatment of high-mortality, high-cost *Staphylococcus aureus* pneumonia without inducing pathogen resistance or altering the patient’s microbiome

### Indications

- **SA-VAP Prevention**
  - 320K ventilated, heavily colonized SA patients in US (~20% of 1.6M ventilated patients)
  - Potential Use: ~75%
  - Potential Price Point: Range: 60-90%
  - Revenue Potential (US, 2022): ~$3B+

- **SA-HAP and SA-VAP Treatment**
  - 85K SA-HAP and SA-VAP patients in US (~11% of total HAP + VAP patients)
  - Potential Use: ~50%
  - Potential Price Point: Range: 40-60%
  - Revenue Potential (US, 2022): ~$0.5B+

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$3B+$ Potential for a novel biologic in US alone
Arsanis is Redefining the Practice of Medicine for Serious Bacterial Infections

**Pre-empting Disease**

- No Available Therapies
- Arsanis’ targeted mAbs uniquely address this need
- Breaking the cycle of antibiotic resistance

**Post Disease Treatment**

- Majority treated with generic antibiotics
- New small molecule antibiotics & “potentiators” reserved for generic failures and niche MDR pathogens

**Colonization period**

- Days on mechanical ventilation

**S. aureus pneumonia**

- Mortality: 30%
- Cost: $25-100K
- Excess days in hospital (6 in ICU)