Presatovir (GS-5806) for Treatment of Respiratory Syncytial Virus Infection

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Disclosures

♦ I am an employee of Gilead Sciences, Inc.
Significant Unmet Medical Need of RSV Infection

- RSV is a significant cause of morbidity and mortality among children <5 years old
  - Worldwide: ~3.4 million hospitalizations with up to 200,000 deaths\(^1\)
  - US: ~60,000 hospitalizations among <24 month old infants\(^2\)
    - ~2 million annual outpatient and emergency visits
    - Among <1 year olds: 9-fold more respiratory deaths than influenza

- RSV infections also affect adults
  - Elderly with underlying cardiopulmonary disease (prevalence 5–8%)
    - Among >50 year olds: ~10,000 deaths each year\(^3\)
  - Immunocompromised: hematopoietic cell and lung transplant patients (prevalence 2–17%)
    - ~25% of upper tract infections progress to lower tract\(^4\)
    - Mortality rate among lower tract infected is ~30%\(^5\)

- No effective treatment for RSV infection is available

RSV, respiratory syncytial virus.
RSV Development Challenges

- No formal guidance available for development of agents to treat or prevent RSV
- Establishing definition for RSV disease severity
  - Lack of widely-accepted definition
- Defining appropriate patient population
  - Underlying patient factors, age and/or disease severity
- Clinical endpoints
  - Clinical outcome versus virologic endpoints
  - Need to avoid endpoints that are influenced by health care system (e.g., duration of hospitalization)
  - “MALRI”: medically attended lower respiratory illness endpoint (e.g., physician visits, urgent care and emergency visits, and hospitalization)
Agents in Development for RSV Treatment

Fusion inhibitors
Presatovir, VP-14637, JNJ-2408068, ALX-0171

Entry via fusion

RSV VIRAL PARTICLE

RSV POLYMERASE

Inhibitors
ALS-8176, T-705 (influenza polymerase)

Fusion inhibitors
Presatovir, VP-14637, JNJ-2408068, ALX-0171

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RSV POLYMERASE

Inhibitors
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Presatovir Preclinical Characteristics

- **Allosteric inhibitor of F protein**
  - Blocks viral entry by inhibiting fusion of the viral envelope with the host cell membrane

- **In vitro** antiviral effect
  - Mean EC$_{50}$ 0.4 nM for 75 clinical RSV (types A and B) isolates

- **In vivo** efficacy in a cotton rat model

- Concentrates in the lung in Sprague-Dawley rats
  - Lung tissue/plasma AUC ratio ~26, ELF/plasma AUC ratio ~9.4 in animal models

- Favorable safety profile in toxicology studies

AUC, area under concentration-time curve; EC$_{50}$, half-maximal concentration; ELF, epithelial lining fluid.
Presatovir Preclinical Characteristics

- Limited potential for clinically significant DDIs

- Rates of presatovir metabolism by CYPs 1A2, 2B6, 2C8, 2C9 and 2C19 below limit of quantification

- No appreciable Phase II metabolism (eg UGT1A1)

- Presatovir is not expected to be an inhibitor of CYP450- or UGT1A1 or an inducer via PXR or AhR-mediated pathways

<table>
<thead>
<tr>
<th>Transporters / Enzymes</th>
<th>Substrate</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp/BCRP and OATP1B1/3</td>
<td>✓</td>
<td>✓ (weak)</td>
</tr>
<tr>
<td>MATE1/MATE 2-K</td>
<td>—</td>
<td>✓ (weak)</td>
</tr>
<tr>
<td>CYP3A</td>
<td>✓</td>
<td>—</td>
</tr>
</tbody>
</table>

AhR, aryl hydrocarbon receptor; BCRP, breast cancer resistance protein; CYP, cytochrome p450; DDI, drug-drug interaction; MATE, multidrug and toxic compound extrusion protein; OATP, organic anion-transporting polypeptide; P-gp, P-glycoprotein; PXR, pregnane X receptor; UGT, uridine 5’-diphospho-glucuronosyltransferase.
Clinical Program Overview

♦ 7 Phase 1 studies in healthy subjects
  – SAD, MAD, mass balance, food effect, ethnic bridging, QT, ECHO, DDI studies with inhibitors/inducers

♦ Phase 2a challenge study in healthy subjects infected with RSV

♦ 4 Phase 2b efficacy and safety studies in adults with RSV
  – Hospitalized adults with RSV
  – HCT recipients with upper respiratory tract infection
  – HCT recipients with lower respiratory tract infection
  – Lung transplant recipients with RSV infection

ECHO, environmental influences on child health outcomes; HCT, hematopoietic cell transplantation; MAD, multiple ascending dose.
Presatovir PK Data in Healthy Adults

- Dose-proportional exposure increases across 25 mg to 800 mg
- Low variability in PK (CV% 30–40%)
- $t_{1/2}$ ~33–35 hours

%CV, % coefficient of variation; plasma-binding-adjusted effective concentration required for 95% inhibition.
Jin et al. ICAAC. September 2-6, 2014, Washington DC, USA.
**Clinical Pharmacology**

**In vivo DDI Potential**

- Presatovir may be administered with inhibitors of P-gp/BCRP, OATP1B1/1B3 or CYP3A
- Moderate/strong CYP3A inducers should not be administered with presatovir

<table>
<thead>
<tr>
<th>Object</th>
<th>Perpetrator</th>
<th>AUC</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presatovir</td>
<td>Cyclosporine OATP/P-gp/BCRP inhibitor</td>
<td>↑26%</td>
<td>↑11%</td>
</tr>
<tr>
<td></td>
<td>Cobicistat CYP3A inhibitor</td>
<td>↑122%</td>
<td>↑13%</td>
</tr>
<tr>
<td></td>
<td>Rifampin Strong CYP3A/P-gp inducer</td>
<td>↓80%</td>
<td>↓40%</td>
</tr>
<tr>
<td></td>
<td>Efavirenz Moderate CYP3A/P-gp inducer</td>
<td>↓56%</td>
<td>↓12%</td>
</tr>
</tbody>
</table>

90% CIs of the GLSM ratios extended above (↑) or below (↓) the predetermined equivalence boundaries of 70 to 143%.

- Presatovir may be administered with inhibitors of P-gp/BCRP, OATP1B1/1B3 or CYP3A
- Moderate/strong CYP3A inducers should not be administered with presatovir

- Presatovir may be administered without regard to food

- Lack of effect of race on the PK of presatovir

GLSM, geometric least-squares mean.
1. Xin et al. IDWeek 2015, abstr 765.
The 5d 50/25 mg regimen targeted $C_{min} \sim 4x \text{paEC}_{95}$

Doses and regimens for Cohorts 5–7 (adaptive regimens) informed by interim efficacy/safety analyses of Cohorts 1–4 (prespecified regimen)

*Included in safety but not efficacy analysis.
Results: Reduction in Viral Load and Symptoms

Reduced Viral Load

![Graph showing reduced viral load over time.

Reduced Respiratory Symptoms

![Graph showing reduced respiratory symptoms over time.

Reduced Nasal Mucus Production

![Graph showing reduced nasal mucus production over time.

**Results: Viral Load With Shorter/Lower-Dose Regimens**

- **Post-Treatment, days**
- **Mean VL, log_{10} PFU/mL (SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=27)*</td>
<td></td>
</tr>
<tr>
<td>Placebo (n=36)†</td>
<td></td>
</tr>
<tr>
<td>Presatovir 3d 50/25 mg (n=13)</td>
<td></td>
</tr>
<tr>
<td>Presatovir 5d 10/5 mg (n=11)</td>
<td></td>
</tr>
<tr>
<td>Presatovir 5d 50/25 mg (n=27)</td>
<td></td>
</tr>
<tr>
<td>Presatovir SD 100 mg (n=10)</td>
<td></td>
</tr>
</tbody>
</table>

*Cohorts 1–4; †Cohorts 5–7; p <0.05 for all arms vs placebo.
SE, standard error; VL, viral load.
Results: Similar Effects With Shorter/Lower-Dose Regimens

Mucus Weight

Total Symptom Diary Score

<table>
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<tr>
<th>Placebo (n=27)*</th>
<th>Placebo (n=36)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presatovir</td>
<td></td>
</tr>
<tr>
<td>5d 50/25 mg (n=27)</td>
<td>3d 50/25 mg (n=13)</td>
</tr>
<tr>
<td>SD 100 mg (n=10)</td>
<td>5d 10/5 mg (n=11)</td>
</tr>
</tbody>
</table>

p <0.05 for all arms vs placebo, except GS-5806 5d 10/5 mg vs placebo for Mucus Weight (p=0.20).
Mechanistic Modeling

♦ Characterization of the dynamics between viral load (VL), clinical symptom score (CSS) and presatovir dose

♦ Presatovir dosing simulations (N=100 subjects):
  – 100 mg SD, 2 to 200 mg ascending QD dosing, 200 mg Q4D, and 200 mg LD then 100 mg QD
  – Dosing regimens modeled to initiate from 24 to 120 hours post-infection to examine effect of time of drug initiation post-infection

Lutz J, et al. RSV Symposium 2016,
Presatovir Effect as a Function of Dose

Maximum VL and CSS suppression is predicted to occur at doses as low as 50 mg QD

Minimal VL and CSS suppression is predicted if presatovir is administered greater than 72 hrs post inoculation

Mechanistic Modeling: Presatovir Efficacy Intermittent Dosing

- Administration of two 200 mg doses, staggered by 4 days, is predicted to achieve maximal viral suppression

Phase 2b Hospitalized Adult Study

- 200 RSV+ hospitalized adults
- Single-dose regimen
- Primary endpoint: daily average change in VL (Day 5)
- Secondary endpoints: symptoms, healthcare utilization
- 190 subjects enrolled (May 2017)
Phase 2b Bone Marrow Transplant Upper and Lower Respiratory Tract Studies

Day 1

- Presatovir 200 mg q4d x5
- Placebo q4d x5

Optional Extended Viral Follow-up

Viral Load
Symptoms

Upper Respiratory Tract
Lower Respiratory Tract

<table>
<thead>
<tr>
<th>RSV+ patients</th>
<th>200 outpatients</th>
<th>60 inpatients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>Multidose</td>
<td>Multidose</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Daily average change in VL (Day 9)</td>
<td>Daily average change in VL (Day 9)</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td>Progression, respiratory failure, mortality</td>
<td>Respiratory failure, mortality</td>
</tr>
<tr>
<td>Subjects enrolled</td>
<td>188 (June 2017)</td>
<td>60 (May 2017)</td>
</tr>
</tbody>
</table>
Phase 2b Lung Transplant Study

- 60 RSV+ lung transplant patients
- Primary endpoint: daily average change in VL (Day 7)
- Secondary endpoints: lung function, symptoms
- 48-wk follow-up for development of BOS/graft failure after Day 28
- 61 subjects enrolled

BOS, bronchiolitis obliterans syndrome.
Conclusions

- Presatovir is a fusion inhibitor for treatment of RSV infection
- Favorable clinical pharmacology profile (healthy volunteers)
- Favorable safety profile (healthy adults and patients)
- Potent antiviral effect that reduces clinical signs and symptoms of RSV infection in challenge study
- Currently being evaluated in 4 ongoing Phase 2b studies in both outpatient and inpatient settings
We extend our thanks to the study participants and study team. This study was funded by Gilead Sciences, Inc.