Single Dose IV Peramivir Treatment in Pediatric Influenza: Lack of Development of Susceptibility to Peramivir

Marie-Ève Hamelin PhD1, Yacine Abed PhD1, Julie Carbonneau MSc1, Rienk Jeeninga PhD2, Saskia Smits PhD2, Small Kulenovic BSc1, Katyna Borroto-Esoda PhD3, Ray Taylor MBA4, Phil Collis PhD4, Guy Boivin MD1

1Centre de Recherche en Infectiologie du CHUL, Laval University, Québec, Canada, 2ViroClinics BioSciences B.V, Rotterdam, Netherlands, 3KBE Consulting, LLC, Raleigh, NC, 4BioCryst Pharmaceuticals, Durham, NC

Background

- Influenza remains a significant cause of morbidity and mortality globally.
- Peramivir (PVR) is a potent neuraminidase inhibitor (NA) with in vitro activity against all influenza virus subtypes.
- Previous studies demonstrated the efficacy and safety of PVR as a single dose intravenous (IV) treatment for acute uncomplicated influenza and has been FDA-approved for patients 2 years and older who have been symptomatic for no more than two days under the trade name of Rapivab®.
- A single arm study previously demonstrated the safety and efficacy of PVR in pediatric influenza in Japan.

Methods

- Phase 3, open-label, randomized active control trial, initiated February 2015
- Eligible subjects:
  - Male/female, age 0-<18 years
  - Acute uncomplicated influenza symptom onset within 48 hours of Screening:
  - Fever: Oral ≥ 100.4°F Rectal ≥ 101.3°F and ≥ 2 respiratory symptom (cough/ rhinitis)
  - Parent/ guardian written informed consent and assent by subjects ≤ 7 years

Results

- 122 subjects enrolled up to a data cutoff of March 31, 2017

Virologic Analyses

- Influenza infection and subtype was confirmed by PCR.
- In vitro susceptibility of cultured virus to PVR, OSE and zanamivir (ZVR) from paired pre- and post-treatment nasopharyngeal (NP) swabs was performed with a MUNANA assay.

- Sequence analysis of NA and hemagglutinin (HA) genes was performed from uncultured virus.

Virologic Outcomes (ITT Population)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median IC50 nM (Min, Max)</th>
<th>PVR vs. OSE</th>
<th>PVR vs. ZVR</th>
<th>PVR vs. OSE vs. ZVR</th>
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<tbody>
<tr>
<td>A/H1N1 WT</td>
<td>30.20 (0.85, 2.22)</td>
<td>0.74 (0.31, 2.66)</td>
<td>0.83 (0.63, 1.46)</td>
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<tr>
<td>A/H3N2</td>
<td>1.63 (0.46, 6.95)</td>
<td>0.59 (0.38, 2.09)</td>
<td>0.61 (0.38, 1.04)</td>
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Conclusions

- Among the PVR treated subjects, positive viral titers persisted for half of these subjects (50%) at Day 3, reduced to 5% of subjects by Day 7 and Day 14, no viral shedding reported.

- PVR had the greatest potency of 3 tested for all baseline virus subtypes in the order: PVR < ZVR < OSE.

- Among PVR treated subjects, no changes were observed in median last post-baseline sample PVR median IC50 compared to baseline and no individual subject treated with PVR had an IC50 fold-change from baseline greater than 1.63.

- All post-Baseline viruses from treated subjects remained sensitive to PVR and other NAIs, with normal inhibitory levels. One H3N2 virus from an OSE treated subject developed reduced inhibition to OSE, although no genotypic changes in NA or HA were identified.

- Treatment with a single dose of IV PVR was not associated with development of resistance to the drug in this population.

Contact: qcollins@biocryst.com

Presented at 30th AID Week 2017, October 4-8, San Diego, CA