BCX4161, an Oral Kallikrein Inhibitor, is Effective and Safe in the Prophylaxis of Acute Attacks in Patients with Hereditary Angioedema:

Results of the Phase 2 Trial OPuS-1

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HAE is a rare disease with significant mortality

- Caused by a deficiency of the C1 inhibitor (C1 INH), a regulator of several inflammatory pathways
  - Type I: Synthesis reduced (80%-85%)
  - Type II: Functional impairment (~15%-20%)

- ~6,200 patients U.S. and ~10,000 in EU based on estimated prevalence of 1 in 50,000

- Women appear to have a more severe and frequent disease course

- Patients average 1 to 3 attacks/month with most episodes lasting 1-5 days that resolve spontaneously

- Most common swellings are asymmetric, cutaneous and affecting the hands, feet, face, genitals and GI tract

- 50% of patients have laryngeal swellings that are potentially fatal

- Mortality has been reported in up to 30% of patients with previously undiagnosed HAE

Role of Plasma Kallikrein in HAE

Factor XIIa, Plasmin

Prekallikrein

Kallikrein

High-Molecular-Weight Kininogen

Bradykinin

BK receptor

Vasodilatation, nonvascular smooth muscle contraction & edema
BCX4161

- BCX4161 is a potent, small-molecule inhibitor of human plasma kallikrein
  - $K_i$ of 0.26 nM on isolated enzyme
  - Inhibition of kallikrein in plasma from 51 normal subjects:
    Median $EC_{50}$ is 6 nM
  - Inhibition of kallikrein in plasma from 10 HAE subjects during the intercritical period:
    Mean $EC_{50}$ is 14 nM
- Orally available
- Safety, pharmacokinetics, and kallikrein inhibition data from first-in-human study supported further clinical development\(^1,2\)

\(^1\)Collis et al., AAAAI 2014, Poster #138, \(^2\)Babu et al., AAAAI 2014, Poster #143
OPuS-1: Oral Prophylaxis for Hereditary Angioedema

A Phase 2a, Double-Blind, Placebo-Controlled 2-Period Crossover Study To Evaluate the Safety and Efficacy of BCX4161 as a Prophylactic Treatment to Reduce the Frequency of Attacks in Subjects with Hereditary Angioedema
OPuS-1: Proof-of-Concept Prophylaxis Study in HAE

- Targeted 25 HAE Type I and II patients in Germany and UK
- Frequent HAE attacks (~1/ week) required for entry
- Subject-reported attacks were adjudicated by an independent, blinded panel of HAE-treating physicians
- Acute attacks were treated in accordance with the subject’s normal standard of care
- Primary efficacy endpoint:
  - Mean acute attack rate during each treatment period
- Key secondary endpoints:
  - Attack severity (AAS28)
  - Quality of life (AE-QoL)
  - Safety and tolerability
OPuS-1: Patient population & HAE characteristics

### Demographics
- 24 subjects received study drug and completed study
- 15 women and 9 men
- 23 subjects with HAE Type I
- Mean age 42.4 years (SD 11.4)
- Mean BMI 28.7 kg/m² (SD 5.1)

### Disease parameters
- Mean duration of illness from first symptoms of 31.8 yrs
- 83% have had ≥ 1 laryngeal attack
- 54% had ≥ 1 laryngeal attack in the past year
- 29% underwent laparotomy
- Mean of 1.2 ER visits in the last year required for HAE attacks

### HAE treatment experience
- On-demand Rx self-administered by 83% of subjects
- 46% had tried androgens but discontinued for intolerability, AEs, lack of efficacy or difficulty in use
- On-demand Rx of HAE attack used within a median of 1h of attack onset
  - 37.5% still have symptoms ≥ 1 day after treating a usual attack
OPuS-1: Overall Attack Summary

**Placebo Period**
- n = 138 attacks reported
- n = 123 attacks adjudicated
  - Mean attack duration 23.3 h (SD 14)
- n = 116 attacks treated
  - 108 treated with C1 INH
  - 12 treated with icatibant

**BCX4161 Period**
- n = 89 attacks reported
- n = 79 attacks adjudicated
  - Mean attack duration 20.0 h (SD 13)
- n = 72 attacks treated
  - 68 treated with C1 INH
  - 9 treated with icatibant
OPuS-1: Primary efficacy endpoint outcome

<table>
<thead>
<tr>
<th>Adjudicated attacks</th>
<th>BCX4161 period n=24</th>
<th>Placebo period n=24</th>
<th>Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least Squares Mean</td>
<td>0.82</td>
<td>1.27</td>
<td>-0.45 (-0.67, -0.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Attack rate per week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Analysis was performed using a mixed effect model including sequence, period and treatment as fixed effects, and subjects within sequence as a random effect. Sequence and period were not significant.

Baseline characteristics including sex, age, weight, BMI, screening attack rate and on-demand HAE medication use were not predictors of response to BCX4161.
### OPuS-1: Subject-Reported Weekly Attack Rates

**Weekly attack rate mean (SD), all subjects:**

<table>
<thead>
<tr>
<th></th>
<th>Historical</th>
<th>Screening</th>
<th>Treatment Period</th>
<th>Washout</th>
<th>Treatment Period</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.50 (0.6)</td>
<td>1.91 (1.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Historical HAE Attack Rate**

- Screening Window
- 28 Day Dosing Period 1
- 28 Day Dosing Period 2
- 7 Day Washout
- 7 Day Follow-Up

**Sequence 1**
- BCX4161
- 0.91 (0.7)

**Sequence 2**
- Placebo
- 1.48 (0.7)

**Weekly attack rate mean (SD), n = 12/sequence:**

<table>
<thead>
<tr>
<th></th>
<th>Sequence 1</th>
<th>Washout Period</th>
<th>Sequence 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCX4161</td>
<td>0.91 (0.7)</td>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.48 (0.7)</td>
<td>Washout Period</td>
<td>BCX4161</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.38 (0.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.94 (0.7)</td>
</tr>
</tbody>
</table>
OPuS-1: Primary endpoint sensitivity analysis & key secondary analyses

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>BCX4161 period</th>
<th>Placebo period</th>
<th>By-subject Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least Squares Mean attack rate per week, All subject-reported attacks*</td>
<td>0.92</td>
<td>1.43</td>
<td>-0.50</td>
<td>0.002</td>
</tr>
<tr>
<td>(Sensitivity analysis of primary endpoint)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline in Angioedema Quality of Life score, weighted total†</td>
<td>-8.4</td>
<td>-0.5</td>
<td>-7.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Disease activity, mean Angioedema Activity Score (AAS28)</td>
<td>21.4</td>
<td>28.8</td>
<td>-7.35</td>
<td>0.022</td>
</tr>
</tbody>
</table>

* Analysis was performed using a mixed effect model including sequence, period and treatment as fixed effects, subjects within sequence as a random effect.
† Negative numbers represent improvement in AeQoL
OPuS-1: Overall adverse event summary

<table>
<thead>
<tr>
<th></th>
<th>BCX4161 (N=24)</th>
<th>Placebo (N=24)</th>
<th>Total (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any AE, n (%)</td>
<td>17 (71%)</td>
<td>20 (83%)</td>
<td>24 (100%)</td>
</tr>
<tr>
<td>Subjects with any Drug-Related AE, n (%)</td>
<td>12 (50%)</td>
<td>10 (42%)</td>
<td>17 (71%)</td>
</tr>
<tr>
<td>Subjects with AE Leading to Study Discontinuation, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with any Serious AE, n (%)</td>
<td>0</td>
<td>1 (4.2)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Subjects with any AE of Grade 3 or Grade 4, n (%)</td>
<td>3 (13%)</td>
<td>3 (13%)</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>Subjects with Drug-Related AE of Grade 3 or 4, n (%)</td>
<td>1*(4%)</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

- AEs were balanced between BCX4161 and placebo periods
- 1 Serious Adverse Event - HAE abdominal attack (placebo)
- Grade 3 events on BCX4161 were nasopharyngitis (2), thirst, and pruritus*; grade 3 events on placebo were musculo-skeletal pain, neck pain, headache and HAE attack
- No grade 4 events
### OPU-S-1: Treatment-emergent adverse events occurring in $\geq 3$ subjects

<table>
<thead>
<tr>
<th>MedDRA System Organ Class / Preferred Term</th>
<th>BCX4161 (N=24)</th>
<th>Placebo (N=24)</th>
<th>Total (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least one TEAE, n (%)</td>
<td>17 (71%)</td>
<td>20 (83%)</td>
<td>24 (100%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>3 (13%)</td>
<td>0</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Splenomegaly*</td>
<td>3 (13%)</td>
<td>0</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>9 (38%)</td>
<td>10 (42%)</td>
<td>18 (75%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4 (17%)</td>
<td>6 (25%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>Diarrhea‡</td>
<td>3 (13%)</td>
<td>5 (21%)</td>
<td>8 (33%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>3 (13%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>7 (29%)</td>
<td>8 (33%)</td>
<td>14 (58%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (17%)</td>
<td>7 (29%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>6 (25%)</td>
<td>4 (17%)</td>
<td>9 (38%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (17%)</td>
<td>4 (17%)</td>
<td>7 (29%)</td>
</tr>
</tbody>
</table>

* In 2 subjects, spleen size was found to be normal on ultrasound. The third subject was 197 cm tall. There were no lab abnormalities and enlarged spleen persisted through 3 months post-study follow-up without symptoms. Splenic length correlates to height\(^1\). The large spleen in this subject is likely an incidental finding.

‡ No increase in frequency of defecation – represents soft or pasty stools, generally grade 1.

OPuS-1: Conclusions

• All study objectives were met
• All 24 subjects completed the trial
• Mean study drug dosing compliance was 98%
• Attack rates on BCX4161 were significantly lower than on placebo ($p<0.001$)
• Quality of life was significantly improved ($p=0.004$)
• The safety and tolerability profile of BCX4161 was similar to placebo
• The efficacy and safety profile from OPuS-1 supports continued development of BCX4161
Acknowledgements

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  Inmaculada Martinez-Saguer
  Hilary Longhurst
  Murat Bas

• Clinical trial staff at each participating OPuS-1 center

• HAE patients who graciously participated in OPuS-1
Backup Slides
OPuS-1: PK, PK-PD and PK-efficacy relationships

- Drug exposure was generally similar to that seen in healthy subjects in the phase 1 study.
- Plasma kallikrein inhibition was correlated with plasma drug level, $r = 0.73$.
- Higher drug exposure was associated with a better clinical outcome.
## Correlation Analysis: Attack Rate and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Adjudicated attack rate difference</th>
<th>Screening attack rate</th>
<th>Weight</th>
<th>BMI</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjudicated attack rate difference</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening attack rate</td>
<td>-0.35 ( p = 0.10 )</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>0.11 ( p = 0.61 )</td>
<td>0.15 ( p = 0.49 )</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.29 ( p = 0.17 )</td>
<td>-0.16 ( p = 0.45 )</td>
<td>0.83 ( p &lt; 0.001 )</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.33 ( p = 0.11 )</td>
<td>-0.09 ( p = 0.69 )</td>
<td>-0.01 0.95</td>
<td>0.17 ( p = 0.42 )</td>
<td></td>
</tr>
</tbody>
</table>

Data are Pearson Correlation Coefficients and associated p values, n = 24
Influence of Covariables on Attack Rate

<table>
<thead>
<tr>
<th></th>
<th>R-Square (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Attack Medication (C1 INH, Icatibant or Icatibant + C1 INH)</td>
<td>7.4% (0.43)</td>
</tr>
<tr>
<td>Sex</td>
<td>13.4% (0.08)</td>
</tr>
</tbody>
</table>

Calculated from generalized linear model of attack rate with gender and screening attack medication as explanatory variables for the dependent variable, attack rate.