Background

- The family of fibroblast growth factor receptors (FGFRs) consists of four transmembrane receptor tyrosine kinases, FGFR1-FGFR4.
- Ligand binding leads to receptor dimerization and phosphorylation to activate downstream signaling.
- FGFR signaling impacts key cellular processes including cell survival, proliferation, migration and differentiation.
- FGFR2 alterations are well-established oncogenic drivers across tumor types (Figure 1).
- These alterations are present in ~25% of all cancers, 80% of which are activating mutations.2

Table 1. Clinical Features and Clinical Coverage of Pan-FGFR Inhibitors

<table>
<thead>
<tr>
<th>Clinical Compound</th>
<th>Dose Schedule</th>
<th>ORR</th>
<th>Hyperphatemia</th>
<th>Stomatitis</th>
<th>Indication Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemigatinib3, 4</td>
<td>2 wk on/1 wk off</td>
<td>36%</td>
<td>94%</td>
<td>35%</td>
<td>Adv/met</td>
</tr>
<tr>
<td>Infigratinib</td>
<td>3 wk on/1 wk off</td>
<td>23%</td>
<td>95%</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Futibatinib</td>
<td>Daily Monitor Tolerance</td>
<td>32%</td>
<td>76%</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>CGT3103*</td>
<td>Daily Monitor Tolerance</td>
<td>42%</td>
<td>83%</td>
<td>35%</td>
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</tr>
</tbody>
</table>

- Table 2 compares mechanistic cellular IC50's for CGT3103 to approved and clinical stage FGFR2 inhibitors.

- Table 2. FGFR2 Mutations are not Addressed by Approved Inhibitors

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<table>
<thead>
<tr>
<th>FGFR2 Mutation</th>
<th>pERK Inhibition (IC50)</th>
<th>Target</th>
<th>Pemigatinib</th>
<th>Infigratinib</th>
<th>Futibatinib</th>
<th>RLY-4008*</th>
<th>CGT1672*</th>
<th>CGT3103*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR2-V564I</td>
<td>&lt;250X</td>
<td>29X</td>
<td>&gt;250X</td>
<td>1x</td>
<td>11x</td>
<td>4x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGFR2-V564E</td>
<td>&lt;250X</td>
<td>29X</td>
<td>&gt;250X</td>
<td>1x</td>
<td>11x</td>
<td>4x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGFR2-N549K</td>
<td>&lt;250X</td>
<td>29X</td>
<td>&gt;250X</td>
<td>1x</td>
<td>11x</td>
<td>4x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Table 2 shows CGT3103’s selectivity over FGFR1 and FGFR3.

- Figure 1. FGFR2 Alteration Frequency by Tumor Types

- Figure 2. CGT3103 Maintains Mutant Activity Due to Less Steric Bulk Near the V564 Gatekeeper Residue in the ATP Binding Pocket

- Figure 3. CGT3103 Showed FGFR2 Target Coverage in Mouse and Rat PK Studies

- Figure 4. CGT3103 Shows 12h inhibition of pERK in the Clinically Relevant A83 CA (K310R/N549K) Mouse Model

- Figure 5. CGT3103 Does Not Cause Hyperphosphatemia at Efficacious Plasma Concentrations

- Figure 6. CGT3103 Retains Enzymatic Activity vs. the c491A Cysteine Mutation

Conclusions

The CGT3103 FGFR2 inhibitor exhibits:

- Less steric clash near the Va564 gatekeeper residue in the ATP binding pocket.
- Inhibition of FGFR2 primary and acquired gatekeeper V564X and molecular brake (N549X) mutations.
- Coverage of FGFR2 IC50 with a window for selectivity over FGFR1 dosed PO at 30 mg/kg in both mouse and rat PK studies.
- Minimal PK effect in the A83 CA (K310R/N549K) model when dosed PO at 15 mg/kg.
- No increase serum phosphate levels when dosed to efficacious concentrations in rats.
- No shift in activity in an FGFR2 c491A enzyme assay, a potential mutation of concern for covalent inhibitors.

- This series of analogs are the first publicly disclosed FGFR1 sparing, reversible FGFR2 inhibitors that address all the major activating and resistance mutations.
- Work continues to identify a clinical candidate.