Multiple human cancers harbor alterations in FGFRs that drive tumor growth, including mutations, fusions and amplifications. There is mounting data from many Phase 1 and 2 studies demonstrating encouraging utility of FGFR inhibitors for the treatment of cancers that harbor various FGFR alterations across a broad range of tumor types. PRN1371 is a potent, covalent, highly selective FGFR1, 2, 3 and 4 inhibitor, which targets a cysteine residue within the kinase domain. This approach enables highly selective (Figure 1, Tables 1 & 2) and sustained inhibition of FGFR without the necessity to maintain systemic exposure of the drug.

Figure 1. Graphical representation of PRN1371 kinase selectivity against 250 kinases at 1 μM and enzymatic IC₅₀ potency. Table 1. Biochemical IC₅₀s.

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGR1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>FGR2</td>
<td>1</td>
</tr>
<tr>
<td>FGR3</td>
<td>4</td>
</tr>
<tr>
<td>FGR4</td>
<td>20</td>
</tr>
<tr>
<td>VEGFR</td>
<td>&gt; 500</td>
</tr>
</tbody>
</table>

Table 2. Cell proliferation in Ba/F3 cells transfected with wild type or mutant FGFR and cancer cell lines harboring FGFR alterations. PRN1371 maintains cellular potency against multiple FGFR alterations.

Study Subjects and Disposition
- 26 patients enrolled to date in five cohorts
- 10 males, 16 females
- The average age was 48 years (range 26 - 69)

Study Design
- **Part A**: “3+3” dose-escalation; adults with advanced solid tumors who have received at least one prior treatment for metastatic and/or locally advanced disease, and for whom no standard therapy options are available. To date cohorts have enrolled patients without an FGFR alteration or with alterations that mostly have an unknown likelihood of response. Doses safely administered are 15 mg, 20 mg, 25 mg, 35 mg daily in continuous 28-day cycles. Current cohort dosing is at 25 mg twice daily.
- **Part B**: Adults with solid tumors with FGFR1, 2, 3, or 4 mutations, translocations or truncations
- **Both Parts**: Administration of phosphate binders commenced as clinically indicated, tumor status reviewed every two months

Pharmacokinetics
- Intensive samples for determination of PRN1371 concentrations in plasma were collected on Days 1 and 15 over 8 hours, and assayed by a validated LC/MS method
- PK parameters determined by non-compartmental methods

Pharmacodynamics
- Intensive samples for determination of phosphate and FGFR23 levels in plasma were collected on Days 8 and 15
- FGFR23 was assayed by an immunotoxins ELISA assay (data not shown)

PRN1371 is well absorbed orally, exhibits rapid clearance (as intended), and does not accumulate with multiple days of dosing

PRN1371 exhibits low PK variability, and approximate dose proportionality between 15 and 35 mg daily doses

Conclusions
- PRN1371 is a covalent, selective inhibitor of FGFR1-4 exhibiting high potency against cancer cell lines harboring FGFR alterations
- PRN1371 is well absorbed following oral administration, with rapid clearance (by design) and low PK variability
- PRN1371 has been well-tolerated, without off-target safety signals, consistent with the findings in earlier animal toxicology studies
- Pharmacodynamic effects on phosphate have been observed at doses of ≥ 15 mg per day and, at ≥ 35 mg/day, are at the level associated with efficacy reported by other FGFR inhibitors
- Of six cases of stable disease, the best result to date is for a salivary cancer patient (SD 11 months)
- The study continues to enroll additional patients in dose-escalation cohorts and will expand to enroll subjects in the dose-expansion phase