**TG-2349, a Novel HCV PI**

**A proof-of-concept study to evaluate the safety, tolerability, PK, and antiviral activity of multiple oral doses of TG-2349 in genotype 1, 2, 3, 4, 5, and 6 HCV–infected treatment naïve patients.**

**Study Methods**

- GT-1a & GT-1b: randomized, double blind, placebo controlled study in treatment naïve East Asian and Caucasian subjects.
- 3 dosage groups of 200, 400, 600 mg were included. 8 subjects per group with active-to-placebo ratio of 6:2.
- GT-2 to GT-6: open-label, parallel-panel design with single dose group of 600 mg.
- Samples with HCV RNA titer > 1,000 IU/mL were analyzed by population sequencing and/or deep sequencing using illumina MiSeq technology.
- In addition to sequence changed from baseline, variations in 17 potential protease inhibitor-related RAVs were interrogated. They are residues 36, 41, 43, 55, 58, 60, 72, 107, 122, 132, 138, 155, 168, 170, and 175 of the NS5 protease (based on GT-1a H77 numbering).

**Safety Findings**

- More than 3 logs of HCV RNA decline were observed in genotype-1, -2b, -4a, and -6e subjects after 3 doses of TG-2349.
- Lower reduction in GT-2a (1.73 log) & limited antiviral activity observed for GT-3a except 1 Hispanic subject with -1.52 log decline.
- All AEs were grade 1 or 2 except 1 SAE of bacteremia (GT-1b, 200 mg) that was drug not related.
- No deaths or discontinuations due to AEs.
- Most common reported AEs were dizziness, headache, and dehydration.

**Conclusions & Discussions**

- TG-2349 was generally safe and well-tolerated.
- Results of this phase IIA proof-of-concept study in treatment-naïve patients suggested that TG-2349 is effective in GT-1/2/4/6 subjects.
- A phase II study of TG-2349 in combination with Peginterferon and ribavirin is ongoing. Preliminary results indicated that 12 weeks of triple therapy is highly effective in GT-1b subjects with > 92% RVR (SAT-219, 2016 EASL).
- TG-2349-based regimen could provide a high response rate, short-duration, and affordable option.

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**Higher Genetic Barrier in GT-1b/2/4/6**

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**No RAV found in GT-1b/2/4/6 subjects. No RAV is not expected since limited efficacy observed.**

**No RAV found in GT-3a/4a/6a patients.**

**6aR-VAS, well-known for macrocyclic PI, appeared in GT-1b/4a/6a samples at 12-28 days after treatment.**

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**Higher Genetic Barrier Revealed in HCV-GT-1b/2/4/6 Subjects than GT-1a Patients – a Proof-of-Concept Trial of TG-2349 (Furaprevir)**

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