FT-4202, an Allosteric Activator of Pyruvate Kinase-R, Demonstrates Proof of Mechanism and Proof of Concept After a Single Dose and After Multiple Daily Doses in a Phase 1 Study of Patients with Sickle Cell Disease

SCD Pathophysiology

• Loss of oxygen promotes HbS polymers in the sickle RBC, resulting in RBC sickling and membrane damage, which lead to hemolysis and vaso-occlusion

• Sickle RBCs contain more 2,3-DPG\(^1\) than healthy RBCs, resulting in:
  o Decreased (↓) Hb O\(_2\) affinity [ie, increased (↑) \(P_{50}\)]
  o Early release of O\(_2\), leading to deoxygenation of HbS, polymerization, and sickling

• Sickle RBCs have insufficient energy (ATP)\(^2\) for membrane maintenance and repair, contributing to hemolysis and a reduced RBC lifespan

FT-4202 is an Oral Activator of Pyruvate Kinase R (PKR)

Hypothesis #1:
PKR activation decreases 2,3-DPG, reducing HbS polymerization and sickling.

Hypothesis #2:
PKR activation increases ATP, promoting RBC repair/health and reducing hemolysis.

Anticipated clinical outcomes:
- Increased Hb levels
- Decreased vaso-occlusion

FT-4202 is an Oral Activator of Pyruvate Kinase R (PKR)

Hb --> GLUCOSE -| 2,3-DPG | GLUCOSE
Deoxy-Hb -| PEP | HbS polymerization
ADP -| ATP | RBC membrane integrity
FT-4202 -| PKR | ATP
PYRUVATE

2,3-DPG
PKR
FT-4202
Hb
ADP
ATP
GLUCOSE
Deoxy-Hb
PEP
PYRUVATE

For more information, visit: https://epg-digital.com/u/ASH2020-brown

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Healthy Volunteers (Completed)

- Single Ascending Dose (Completed)
  - Randomization 6:2 vs. placebo
    - 100 mg
    - 700 mg
    - 400 mg
    - 200 mg
- Multiple Ascending Dose (Completed)
  - Randomization 9:3 vs. placebo; 14 days treatment
    - 400 mg QD
    - 300 mg BID
    - 200 mg BID
    - 100 mg BID
- Patients with SCD
  - Single Dose (Completed)
    - Randomization 5:2 vs. placebo
      - 700 mg (n = 7)
  - Multiple Ascending Dose (Completed)
    - 14 days blinded treatment
      - Block Randomization of 7:2 or 9:3 vs. placebo
      - 600 mg Daily (n = 9 - 12)
      - 300 mg Daily (n = 9 - 12)
  - Multiple Ascending Dose (Enrolling)
    - 12-weeks open label treatment
      - 400 mg Daily for 12-weeks (n = 12 – 20)
      - Roll-over

Presented by Kalfa et al., ASH 2019

Presented by Estepp et al., EHA 2020
Predicted PD Response in HV RBCs: Defines an Exposure : Response Threshold

- In healthy volunteers, 90% maximal response:
  - ATP ≥ 150 mg QD
  - 2,3-DPG ≥ 400 mg QD
- A single dose of 700 mg of FT-4202 was tolerated
- 300 mg daily in patients with SCD can be expected to confirm proof of mechanism
  - Results of the MAD will inform a Phase 2 dose range
## Patients with Sickle Cell Disease: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>700 mg FT-4202 or Placebo Single Dose Cohort (N = 7)</th>
<th>300 mg FT-4202 or Placebo 14-Day Dose Cohort (N = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>34.7 (15, 48)</td>
<td>29.7 (19, 43)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>2 (29%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td><strong>Hb SS genotype</strong></td>
<td>7 (100%)</td>
<td>8 (89%)</td>
</tr>
<tr>
<td><strong>Hb, g/dL</strong></td>
<td>8.6 (7.4, 10.1)</td>
<td>8.9 (7.1, 10.1)</td>
</tr>
<tr>
<td><strong>ARC, 10⁹/L</strong></td>
<td>224.6 (148.2, 369.3)</td>
<td>242.8 (125.6, 329.3)#</td>
</tr>
<tr>
<td><strong>MCV</strong></td>
<td>108.7 (96.5, 125)</td>
<td>112.9 (75.0, 131.5)#</td>
</tr>
<tr>
<td><strong>Total bilirubin, mg/dL</strong></td>
<td>3.61 (2.10, 6.60)</td>
<td>3.31 (0.60, 11.30)</td>
</tr>
<tr>
<td><strong>LDH, U/L</strong></td>
<td>385.9 (308.0, 576.0)</td>
<td>364.8 (180, 610)</td>
</tr>
<tr>
<td><strong>Hydroxyurea Use</strong></td>
<td>7 (100%)</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>% HbS</td>
<td>79.4 (70.0, 89.1)</td>
<td>81.0 (67.0, 92.9)</td>
</tr>
<tr>
<td>% HbF</td>
<td>14.2 (5.5, 27.5)</td>
<td>12.1 (3.5, 20.1)</td>
</tr>
<tr>
<td>% F cells</td>
<td>50.6 (33.3, 91.8)</td>
<td>41.3 (30.1, 67.2)##</td>
</tr>
</tbody>
</table>

*Analysis as of 16-Nov-2020

# n = 8;  ## n = 6
FT-4202 is Well Tolerated in Patients with SCD*

Single dose of 700 mg FT-4202 or placebo treatment group (unblinded, EHA)
- Six TEAEs (AEs occurring after study treatment or in follow-up) in 4 of 7 patients;
  - All TEAEs were grade 1 and transient
    - One possibly related AE: palpitations, lasting < 1 minute, no other symptoms

14-days of 300 mg FT-4202 or placebo treatment group (analysis remains blinded)
- Fifteen TEAEs were reported in 7 of 9 patients;
  - Eight Grade 1 TEAEs: 3 patients c/o headache, 1 each of nausea, constipation, somnolence, increased LDH and increased AST
    - Possibly related AEs: 1 AE of headache and 1 AE of nausea
  - Six Grade 2 TEAEs: 3 uncomplicated sickle pain events (in 2 patients), 1 patient with N/V and 1 increased reticulocytes
    - No AEs were considered related to study treatment
    - All AEs of pain event considered unrelated and consistent with each patient’s SCD pain history
    - All treated with patient’s standard home pain medications (no SAE/no hospitalization)
  - One Grade 4 TEAE of elevated creatine kinase, unrelated to study treatment

Based on acceptable safety, SCD MAD 2 cohort (600 mg FT-4202 or placebo) opened and patients dosed

* Analysis as of 16-Nov-2020
PK/PD of the 300 mg SCD MAD cohort supports dose range of 200 mg to 400 mg once daily for the planned phase 2/3 study.
FT-4202 Increases Oxygen Affinity in Both HV and Sickle RBCs

- SCD RBCs have higher $P_{50}$ at baseline compared to HV RBCs.
- Normal $P_{50}$ values observed in SCD RBCs 24-hrs after a single dose or after 14-days of FT-4202.

Change in oxygen affinity correlates with 2,3-DPG response.

* $P=0.063$; ** $P=0.031$

# Based on FT-4202 PK analysis, $n=9$

$P$-values based on Wilcoxon matched-pairs signed rank test

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FT-4202 Increases Oxygen Affinity in Both HV and Sickle RBCs

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$P_{50}$ (mmHg)

- Change in oxygen affinity correlates with 2,3-DPG response
- HbS oxygen affinity appears more sensitive to 2,3-DPG levels

$P$-values based on Wilcoxon matched-pairs signed rank test

* Based on FT-4202 PK analysis, n=9
FT-4202 Improves Measures of Sickle RBC Health

Patient with SCD before and after a single dose of FT-4202 (700 mg)

Oxygen Affinity
Increased oxygen affinity post dose

Oxygen-Scan
Improved O₂-dependent change in deformability post dose

Osmo-Scan
Improved osmolality-dependent membrane function post dose

Healthy RBC:

SCD RBC (pre):

SCD RBC (post):

FT-4202 Improves Measures of Sickle RBC Health
Proof of Concept: Improved Hematologic and Hemolytic Parameters after 14-days of 300 mg FT-4202 Once Daily

• In patients receiving FT-4202: 6 of 7 had a > 1 g/dL ↑ in hemoglobin and all 7 had ↓ in reticulocytes
  • Median 1.2 g/dL Hb increase (range 0, 2.3) and median 60% reticulocyte decrease (range -39%, -81%) over baseline
• In patients receiving FT-4202: 6 of 7 had ↓ in LDH and all 7 had ↓ in total bilirubin
  • Median 36% LDH decrease (range +18%, -57%) and median 35% bilirubin decrease (range -7%, -63%) over baseline

# Based on FT-4202 PK analysis, n=9
Conclusions

- FT-4202 has a favorable safety profile in patients with SCD
- FT-4202 ↓2,3-DPG and ↑ATP, resulting in improved RBC functional studies:
  - ↓2,3-DPG: Normalizes HbS O₂ affinity curve to a HbA affinity curve
  - ↓2,3-DPG: ↑ O₂ affinity with ↓ HbS polymerization shifting PoS to lower O₂ pressure
  - ↑ATP: Improves RBC membrane function across an osmotic gradient
- Proof of concept demonstrated with FT-4202 daily for 14 days
  - PKR activation ↑ hemoglobin > 1 g/dL in 6/7 patients and 7/7 had ↓ reticulocytes and ↓ hemolysis
    - Median Hb increase of 1.2 g/dL; median reduction %reticulocyte of -60%
    - Median reduction in total bilirubin of -35%; median reduction of LDH of -36%
  - 600 mg FT-4202 or placebo daily for 14 days followed by 12 weeks 400 mg FT-4202 (open label) daily is ongoing to further evaluate the safety, PK/PD, and biological activity of FT-4202 in pts with SCD

These results support further evaluation of FT-4202 once daily in a Phase 2/3 study in patients with SCD (NCT04624659; FPI in early 2021 anticipated)
  - See Wood et al., Poster 2622, Session 114, ASH 2020 for details on the Phase 2/3 Design
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