CTP-656 Tablet Confirmed Superiority Of Pharmacokinetic Profile Relative To Kalydeco® in Phase I Clinical Studies

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CTP-656: A Novel, Next-Generation CFTR Potentiator

- Deuterated analog of ivacaftor
  - Potential use as monotherapy and in combination with other CFTR modulators
- Phase 1 data show improved PK profile vs. Kalydeco
  - Longer half-life supports once-daily dosing
  - Greater exposure to parent, less exposure to metabolites
    - Potential to provide greater efficacy
    - Potential for reduced DDIs
- Next Step: Open IND for Phase 2 efficacy trial in 2016

Kalydeco® is a registered trademark of Vertex Pharmaceuticals, Inc.
Deuterium: Powerful Tool For Pharmaceutical R&D

- Increased chemical bond stability provides potential for unique properties
  - Possibility for enhanced ADME properties
  - No significant change to compound’s intrinsic biological activity
  - Potential to improve effectiveness, safety and tolerability
Deuterium Modification Impacts Metabolism; Not Pharmacology

- **Ivacaftor exposure is predominantly to less active metabolites**

Deuterium-labeled analogs (D-M1 and D-M6) show lower efficacy compared to their non-labeled counterparts (M1 and M6) due to metabolism by CYP3A4/5.

**Ivacaftor**
- AUC = 1
- EC50 = 336 nM

**M1**
- AUC = 6X
- EC50 = 960 nM

**M6**
- AUC = 2X
- EC50 = 11300 nM

**CTP-656**
- EC50 = 255 nM

**D-M1**
- EC50 = 1346 nM

**D-M6**
- EC50 = 15000 nM

*Reported at steady state in healthy volunteers NDA 203-188: normalized to ivacaftor AUC=1

*Isc increase in G551D/F508del hBE cells (Ussing assay), Robert Bridges, Rosalind Franklin Univ. of Medicine and Science
- Designed to evaluate safety, tolerability and pharmacokinetics in healthy volunteers
- Two-part design
  - Single dose PK comparison of tablet formulation of 150 mg CTP-656 and Kalydeco
  - Three doses for seven days compared to placebo
  - Dosed in fed state (high fat breakfast)
CTP-656 Has A Superior PK Profile Relative To Kalydeco

**Phase 1 Tablet Crossover**

- CTP-656 key exposure parameters $C_{24hr}$ and $AUC_{0-24hr}$ enhanced ~ 3-fold
- CTP-656 oral clearance ~ 1/3 that of ivacaftor
- CTP-656 average half-life of ~ 15 hrs is 40% longer than that for ivacaftor ~ 11 hrs
Deuterium Modification Greatly Increases Parent Drug To Metabolite Ratio With CTP-656

- CTP-656/metabolite exposure ratios >> ivacaftor/metabolite exposure ratios
  - CTP-656/D-M1 ratio ~ 1.5; ivacaftor/M1 ratio ~ 0.5
  - CTP-656/D-M6 ratio ~ 2-4.5; ivacaftor/M6 ratio ~ 1.0
CTP-656 Multiple Dose PK Profile Supports Once-Daily Dosing

- Steady-state achieved after ~ 3 days of dosing
- CTP-656/metabolite ratios >> 1
- CTP-656 and M1 accumulation ratio ~ 1.6-1.8 for key exposure parameters $C_{24hr}$ and $AUC_{0-24hr}$
- No serious adverse events reported
  - Majority of adverse events reported were mild in severity
CTP-656: Expand Options, Improve Outcomes

- Phase 1 results demonstrate CTP-656 has a superior PK profile relative to Kalydeco
- CTP-656 PK and safety profile support once-daily dosing
- Single, efficient Phase 2 trial planned
  - Phase 1 results enable dose selection
  - International study with fewer than 40 patients total (gating mutations)
  - Intended clinical endpoints include sweat chloride, FEV$_1$
- Assessing potential for combination therapies with other CFTR modulators
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