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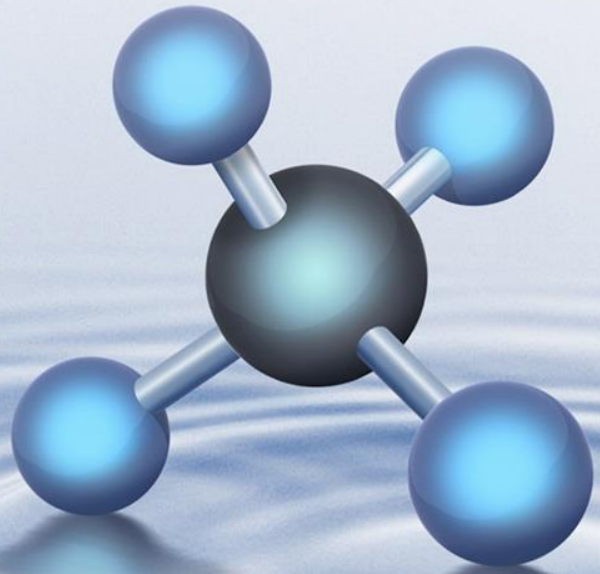
# CTP-656 Tablet Confirmed Superiority Of Pharmacokinetic Profile Relative To Kalydeco® in Phase I Clinical Studies

*39th European Cystic Fibrosis Conference*
*8-11 June 2016, Basel, Switzerland*



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

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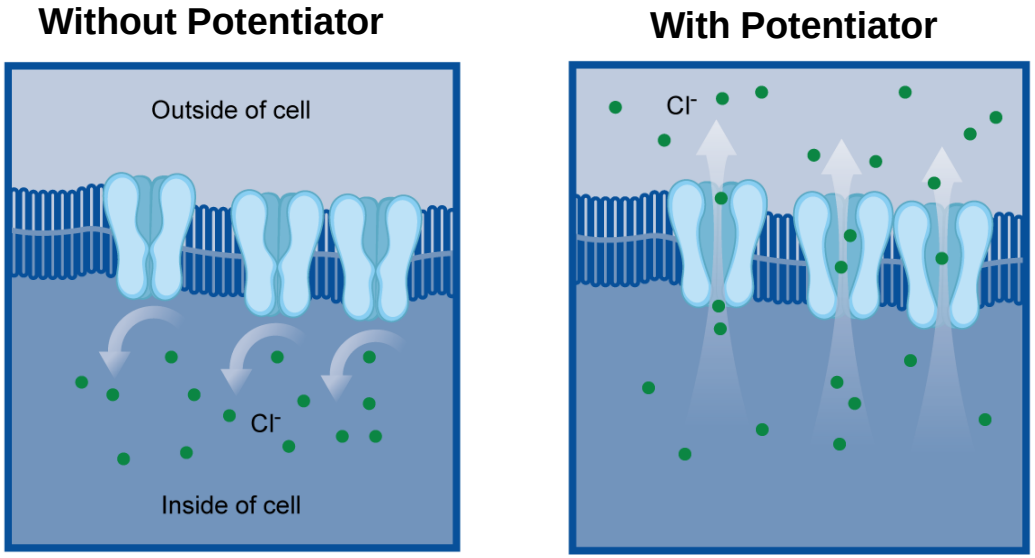


- Deuterated analog of ivacaftor
  - Potential use as monotherapy and in combination with other CFTR modulators
- Phase 1 data show improved PK profile vs. Kalydeco
  - Longer half-life supports once-daily dosing
  - Greater exposure to parent, less exposure to metabolites
    - Potential to provide 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

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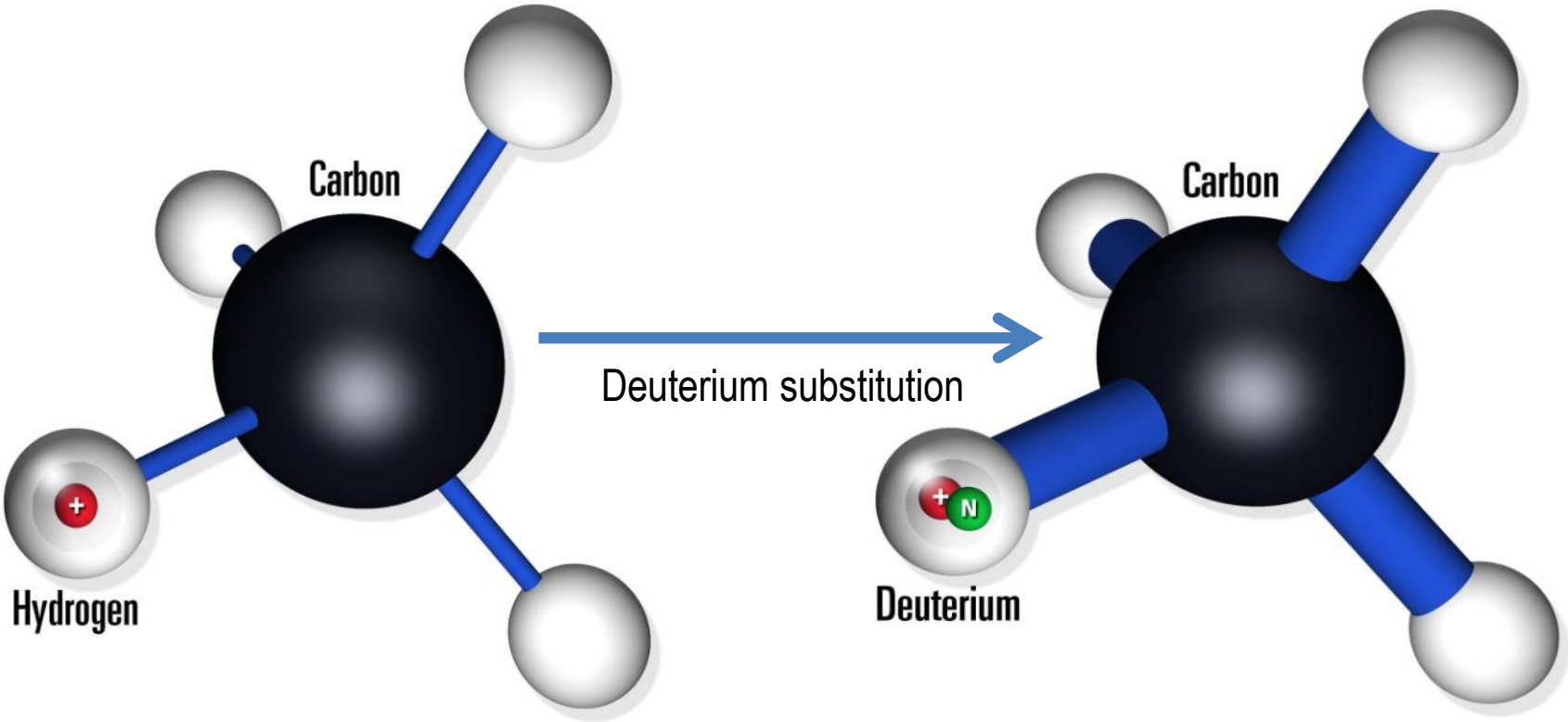
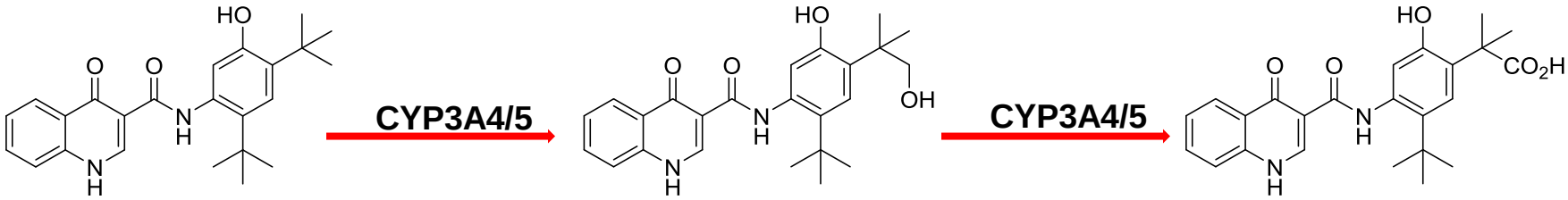



- Increased chemical bond stability provides potential for unique properties
  - Possibility for enhanced ADME properties
  - No significant change to compound's intrinsic biological activity
  - Potential to improve effectiveness, safety and tolerability

# Deuterium Modification Impacts Metabolism; Not Pharmacology

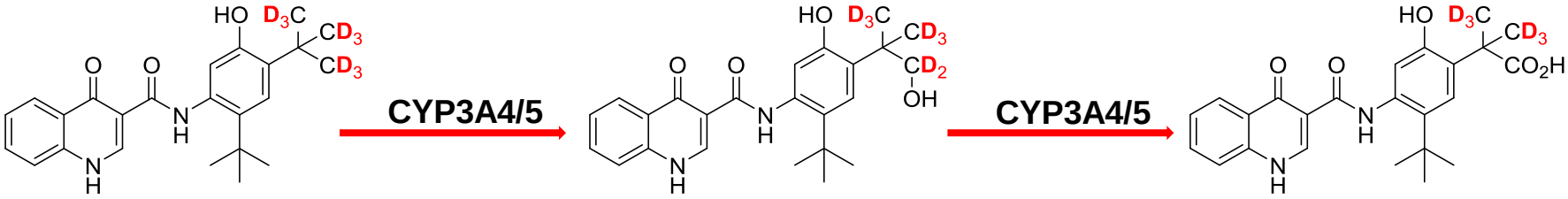
- *Ivacaftor exposure is predominantly to less active metabolites*




**Ivacaftor**
**AUC=1***
**$EC_{50}$ = 336 nM#**

**M1**
**AUC=6X**
**$EC_{50}$ = 960 nM**

**M6**
**AUC=2X**
**$EC_{50}$ 11300 nM**



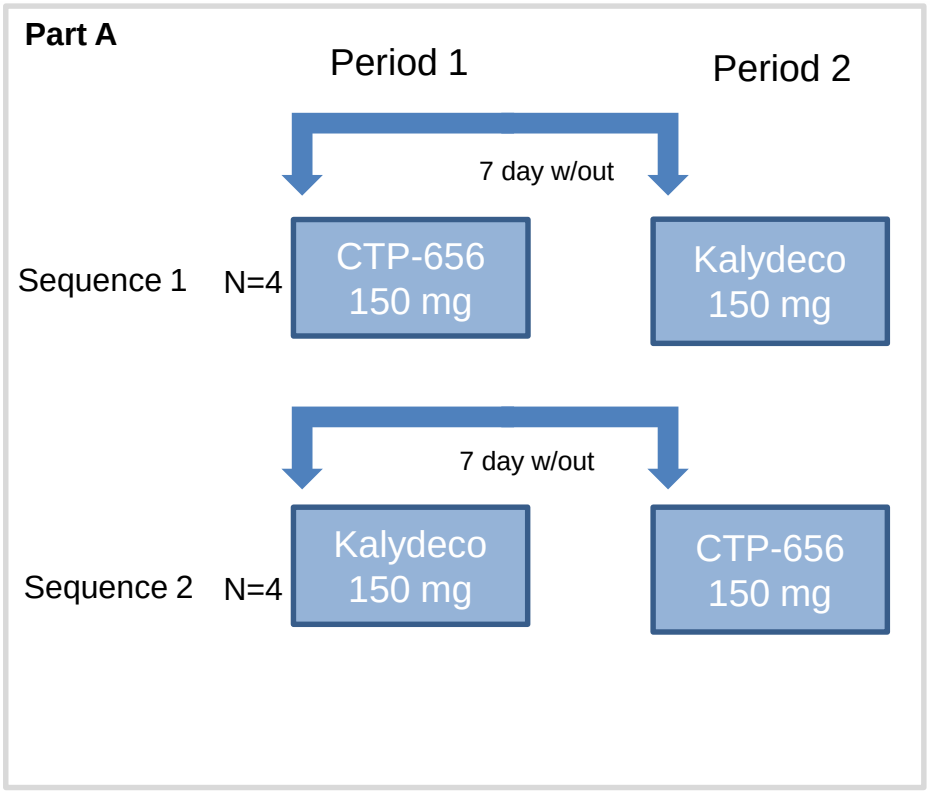

**CTP-656**
**$EC_{50}$ = 255 nM**

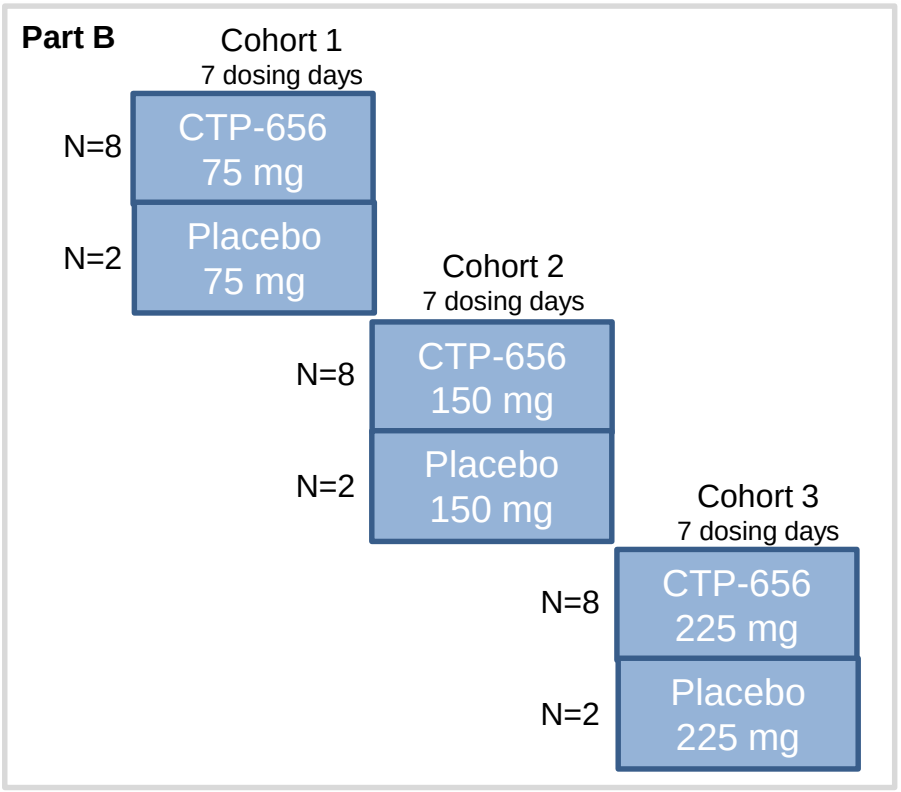
**D-M1**
**$EC_{50}$ = 1346 nM**

**D-M6**
**$EC_{50}$ = 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*

# CTP-656 Phase 1 Multiple-Ascending Dose Trial




- 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

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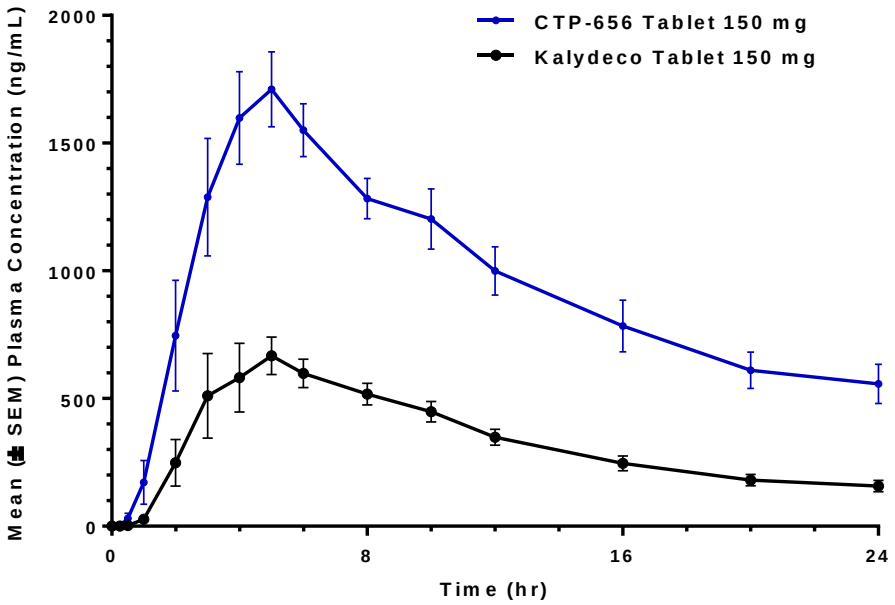
***Phase 1 Tablet Crossover***




- CTP-656 key exposure parameters $C_{24hr}$ and $AUC_{0\text{-}24hr}$ 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

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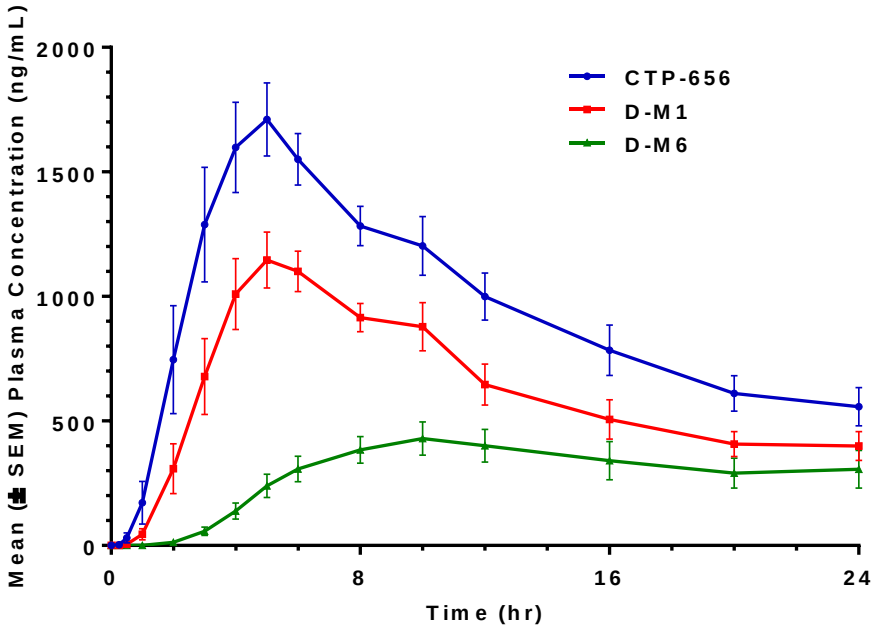
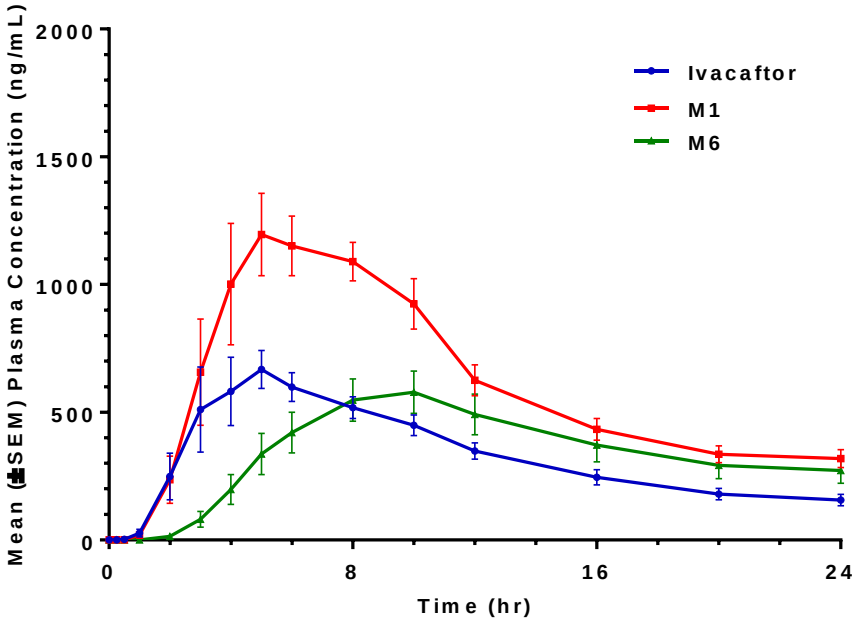
**CTP-656 (single dose 150 mg Tablet)**




**Kalydeco (single dose 150 mg Tablet)**




- 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

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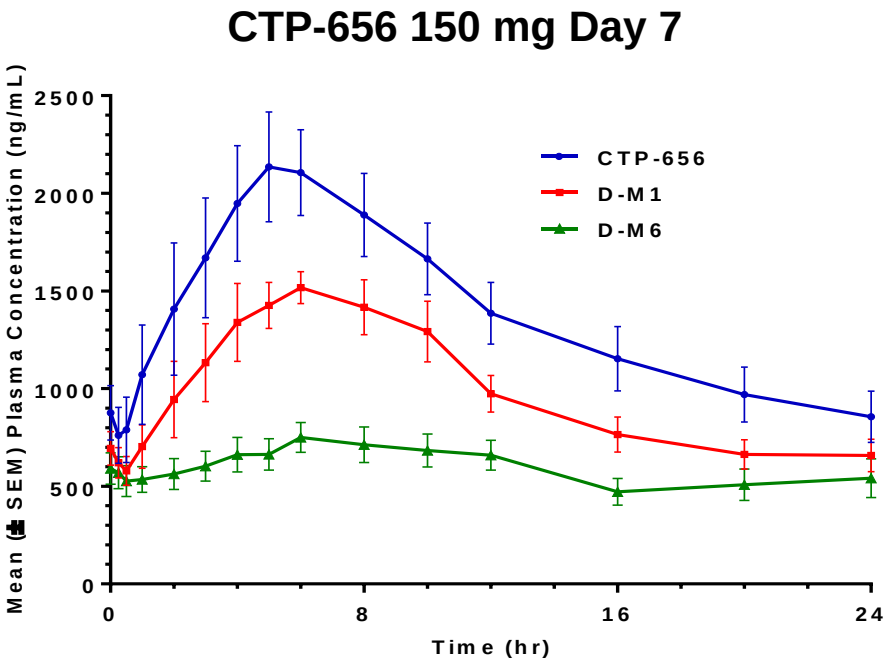


- Steady-state achieved after ~ 3 days of dosing
- CTP-656/metabolite ratios >> 1
- CTP-656 and M1 accumulation ratio ~ 1.6-1.8 for key exposure parameters $C_{24hr}$ and $AUC_{0\text{-}24hr}$
- No serious adverse events reported
  - Majority of adverse events reported were mild in severity

# CTP-656: Expand Options, Improve Outcomes

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- 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

# Acknowledgments


- Lana Pilja
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