Pharmacokinetic Studies of Deuterated Isotopologs of Ivacaftor in Preclinical Models and Healthy Volunteers

**Introduction**

- Deuterium can positively impact the metabolic properties of a drug while preserving the intrinsic pharmacology.
- Ivacaftor (Kalydeco) is extensively metabolized in humans to less active metabolites (Fig. 1).
- Ivacaftor was deuterated to assess the impact on metabolism and PK.
- Two isotopologs, D9- and D18-ivacaftor (Fig. 2), were prepared and tested preclinically and clinically.
- Both isotopologs had reduced metabolism in preclinical tests (data not shown).
- A human crossover study was conducted to identify the development candidate (Fig. 3).
- CTP-656 was selected for further clinical development.

**Methods**

- D9- and D18-ivacaftor were prepared in a site-selective manner with high deuterium isotopic purity.
- *In vitro* CFTR potentiation was assessed in Ussing chamber assays in FRT cells (G551D) or F508del homozygous HBE cells (Fig. 2).
- A crossover isotopolog selection study (dosed as aqueous suspension) (Fig. 3).
- A single ascending dose study was conducted under fed (high fat breakfast) conditions. The study included a crossover of Kalydeco (150 mg tablet) and CTP-656 (150 mg aqueous suspension) (Fig. 4).
- Quantitative metabolite profiles for CTP-656 and Kalydeco were generated using LC-MS/MS; metabolite standards were utilized (Fig. 5).

**Results and Discussion**

- D9-, D18-ivacaftor and ivacaftor provided equivalent *in vitro* CFTR potentiation (Fig. 2).
- D9-ivacaftor showed a superior PK profile compared to D18-ivacaftor; D9-ivacaftor (CTP-656) was selected for further evaluation (Fig. 3).
- PK profile for 150 mg CTP-656 was superior to Kalydeco 150 mg; CTP-656 demonstrated a linear dose-exposure relationship (Fig. 4).
- Exposure to less active metabolites was substantially lower for CTP-656 compared to Kalydeco (Fig. 5).
- Treatment-related adverse events were mild in severity with no apparent differences between CTP-656 and Kalydeco.