DRX-065: A Novel Mitochondrial Modulator for NASH
Pharmacokinetic (PK) Results & Modeling from Phase 1 Study

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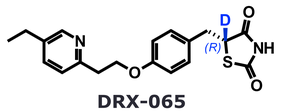
Aims

- Assess PK of DRX-065 in human
- Generate PK model
- Predict efficacious dose of DRX-065 for NASH
- Assess potential to avoid weight gain



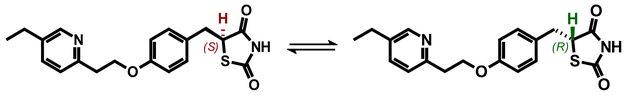
DRX-065
deuterium-stabilized R-pio

Background

Pioglitazone for NASH: Highly Efficacious <u>but</u> Causes Weight Gain

- Pioglitazone (pio) is most extensively studied drug for NASH[1]
- Only drug recommended off-label for treatment of NASH[2,3]
- Significant efficacy in recent Phase 4 in biopsy-proven NASH patients[4]
  - Pbo vs pio (30mg (2mos)→45mg), 18 mos+18 mos open label, 101 pts
  - 58% ≥ 2-point reduction in NAS without worsening of fibrosis
  - 51% resolution of NASH
  - Efficacious for both non-T2DM and T2DM NASH patients[5]
  - Efficacious in NASH patients with advanced fibrosis[6]
  - <u>But</u> weight gain of ~3.5% despite reduced calorie diet
- Weight gain & edema limit use: PPARγ agonist-related side effects

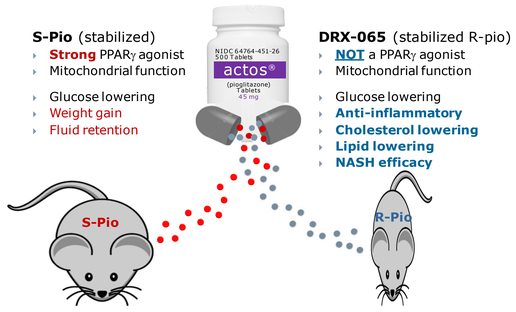
Pio is a Mixture: Interconverting R- & S-Enantiomers



- Single stereoisomeric drugs preferred – require stable stereocenter
- Characterization of pio enantiomers elusive due to interconversion
- New discovery – stabilization of pio stereocenter with deuterium
  - Enables elucidation of discrete mechanistic & functional properties[7,8,9]

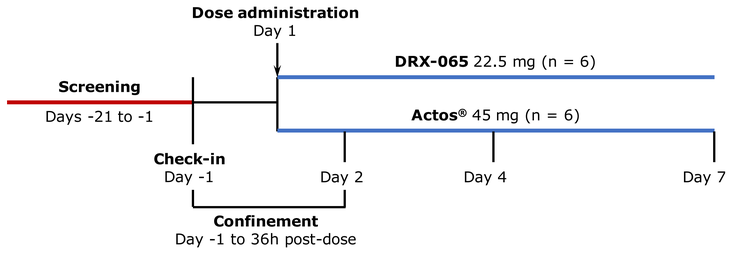
R-Pio Responsible for NASH Efficacy, Lacks PPARγ Activity

- DRX-065 is deuterium-stabilized R-pio
- Mitochondrial function modulator <u>without</u> PPARγ activity
- Pharmacological benefits ≥ racemic pio for NASH (rodent models)
- No PPARγ-associated side effects of weight gain & edema (rodent)
- S-pio: PPARγ agonist, limited NASH efficacy, weight gain (rodent)



Functional Parameters from Mouse Models of T2DM[10] or NASH[10]	Pio	d-S-Pio	DRX-065
⬇ Hepatic Triglycerides	✓	-	✓✓
⬇ Hepatic Free Fatty Acids	✓	-	✓
⬇ Hepatic Cholesterol	✓	-	✓
⬇ Hepatic Inflammation	✓	-	✓
⬇ Hepatic Ballooning	✓	-	✓
⬇ Hepatic Steatosis	✓	-	✓✓
⬇ Hepatic Fibrosis	✓	✓	✓
⬆ Weight Gain	✓	✓	—
⬆ Edema	✓	✓	—

Methods for Phase 1 Single Dose Study (Part 1)



- 45 mg Actos® (branded, racemic pio) or 22.5 mg DRX-065[11]
- Open label study in healthy volunteers (3 males & 3 females per group)
- Endpoints: Safety, tolerability, PK
- PK Analysis
  - GLP LC/MS-MS quantitative analysis of plasma samples collected
  - Concentrations of protonated & deuterated enantiomers of pio analyzed in Phoenix WinNonlin (Certara L.P.) (non-compartmental extravascular dosing approach)
  - Separate analysis for each volunteer (standard PK parameters averaged for both dose groups)

Note: Part 2 ongoing with additional dose(s) for dose proportionality evaluation

Safety, Tolerability & PK

Safety & Tolerability

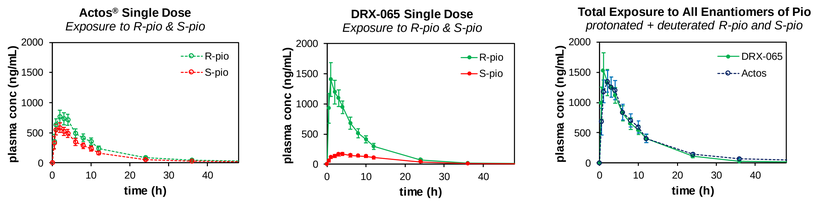
- DRX-065 was safe and well-tolerated

PK Results: Single Dose of Actos® (45 mg)

- Higher exposure to R-pio vs S-pio
  - Enantiomer exposure differences also observed with other racemic drugs

PK Results: Single Dose DRX-065 (22.5 mg) vs. Actos® (45 mg)

- Relative exposure (AUC) to R-pio/S-pio increased ~3x
- No change in elimination half-life
- Some loss of deuterium (D/H exchange), then formation of S-pio
- Surprising 2x increase in C_{max} of R-pio
  - Increases in AUC and/or C_{max} also observed after dosing of other single stereoisomers vs. parent racemic drugs (e.g. Lexapro® vs. Celexa®)
  - Suggests dosing DRX-065 <22.5 mg to match R-pio in 45 mg Actos®
- Same overall exposure to "Total racemic pio" at ½ the dose



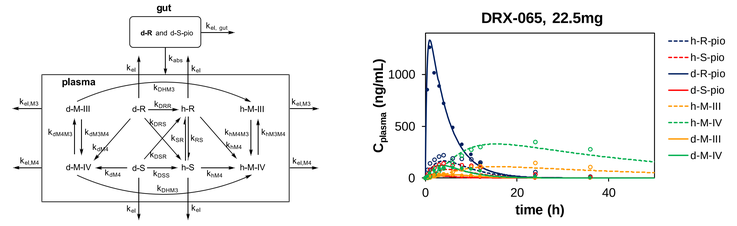
Data presented as sum of concentrations of protonated and deuterated enantiomers for DRX-065

PK Parameter	R-pio/S-pio Ratio After Dosing:	
	Actos® (45 mg)	DRX-065 (22.5 mg)
AUC_{last}	1.5	4.2
C_{max}	1.4	8.5

PK Model of Enantiomers & Metabolites

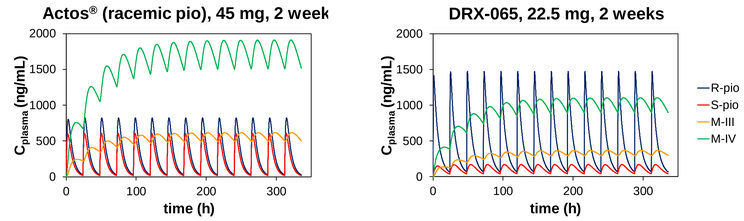
PK Model Created to Predict Steady State PK Properties

- Created from average experimental PK data (concentration vs. time)
- Simulate absorption, distribution, elimination of protonated and deuterated R-pio and S-pio and of metabolites M-III and M-IV[12].
- Fitted rate constants used to predict
  - Time to steady state
  - Dose of DRX-065 for same exposure to R-pio as 45 mg Actos®
- Fit shown for DRX-065 only



PK Model Predicts 15 mg DRX-065 Efficacious Without Weight Gain

- No accumulation of R-pio or S-pio with daily dosing
  - Results consistent with published data with racemic pio[13]
- 15 mg DRX-065: Predicted same R-pio exposure as 45 mg Actos®
- 15 mg DRX-065: Predicted ~4x lower S-pio exposure vs. 45 mg Actos®
  - Levels of S-pio in human similar to 7.5 mg Actos® (no weight gain[14])
- Supporting experimental data with DRX-065
  - In mouse, no weight gain but excellent NASH efficacy[8,9]
  - In human, relative exposure to R-pio vs S-pio similar to mouse[8,9]



Conclusions

- Deuterium stabilizes pio enantiomers & enables characterization[8,9]
  - DRX-065 is deuterium-stabilized R-pio
- R-pio responsible for NASH efficacy, <u>lacks</u> PPARγ activity[8,9] (preclinical)
- DRX-065 human PK: Relative exposure to R-pio increased >3x
- PK model predicts 15 mg DRX-065 efficacious for NASH, no weight gain
  - R-pio exposure similar to 45 mg racemic pio (efficacious for NASH[4])
  - S-pio exposure similar to 7.5 mg racemic pio (no weight gain[14])

Notes & References

1. Hardy, et al., Curr Opin Gastroenterol. 2015, 31(3),175–183.
2. Chalasani, et al., Hepatology 2018, 67(1), 328-357.
3. European Association for the Study of the Liver (EASL), J Hepatol. 2016, 64(6),1388-1402.
4. Cusi, et al., Ann Intern Med. 2016, 165(5), 305-315.
5. Bril, et al., Clin Gastroenterol Hepatol. 2017, accepted for publication, online Dec 7, 2017 doi:/10.1016/j.cgh.2017.12.001.
6. Musso, et al., JAMA Intern Med. 2017, 177(5), 633-640.
7. DeWitt, et al., Hepatology. 2015, 62(1), 281A-282A (AASLD Abstract 143).
8. Prosecution history for DeuteRx International Appl. WO 2015/109037.
9. Jacques, et al., Hepatology. 2016, 64(6), 1137A-1138A (AASLD Abstract LB-32).
10. Models were selected based on literature data where pio had shown efficacy: *db/db* mouse model of T2DM (Endocrinol. 2009, 150, 3457-3464) & choline deficient diet model of NASH (Lab Investig. 2007, 87, 56-65).
11. Actos®, racemic pio, is a 1:1 mixture of R-pio & S-pio. Therefore, DRX-065 is dosed at 1/2 the dose.
12. Model used non GLP experimental data for 2 major active human metabolites of pio, M-III and M-IV.
13. Budde, et al., Br J Clin Pharmacol. 2003, 55(4), 368-374.
14. Rajagopalan, et al., Diabetes Res Clin Pract. 2015, 109(3), e32-e35.

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