Safety, Tolerability & PK of PXL065*, the Stabilized R-Stereoisomer of Pioglitazone:
A Mitochondrial Function Modulator for NASH without PPARγ Agonism & Related Side Effects

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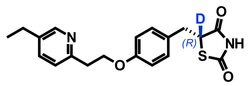
Aims

- Assess PK of PXL065 in human
- Generate PK model
- Predict efficacious dose of PXL065 for NASH
- Assess potential to avoid weight gain

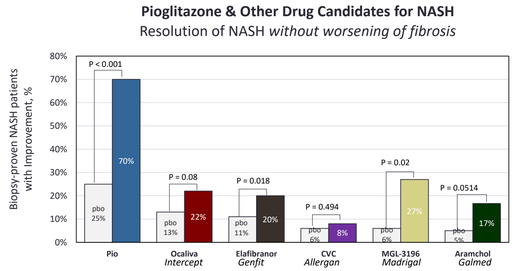


PXL065
deuterium-stabilized R-pio

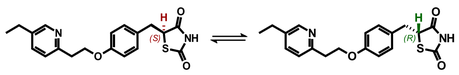
Background

Pioglitazone for NASH: Highly Efficacious[1] but Limited by PPARγ Effects

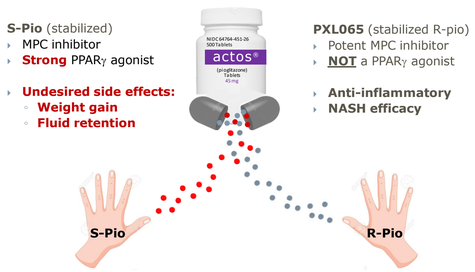
- Achieved "Resolution of NASH without worsening of fibrosis" (Phase 4 trial[2])
- Reduces incidence of hepatocellular carcinoma and other cancers[3]
- Recommended off-label for NASH by AASLD & EASL Practice Guidelines[4]
- Better efficacy than other drug candidates for NASH



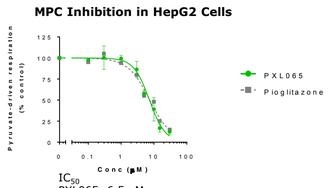
- Currently prescribed by ~14% of physicians for biopsy-proven NASH patients[5]
- Limited use due to PPARγ effects (weight gain, fluid retention, bone fracture)
- Complicated as a mixture of two interconverting stereoisomers



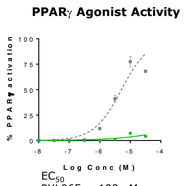
Discovery: R-Pio Responsible for NASH Efficacy, Lacks PPARγ Activity



- Stabilization of stereoisomers with deuterium identified discrete properties[6,7,8]
- R-pio is mitochondrial pyruvate carrier (MPC) inhibitor without PPARγ activity
- Pharmacological benefits ≥ racemic pio for NASH (rodent)
- No PPARγ-associated side effects of weight gain & edema (rodent)

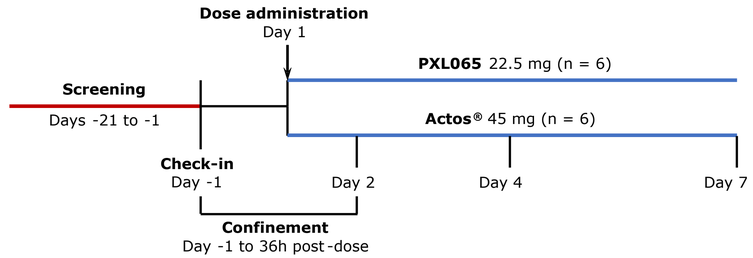


IC_{50}
PXL065: 6.5 μM
Pioglitazone: 6.8 μM



EC_{50}
PXL065: >100 μM
Pioglitazone: 4.6 μM

Methods (Phase 1a, Part 1)



- 45 mg Actos® (branded, racemic pio) or 22.5 mg PXL065[9]
- 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)

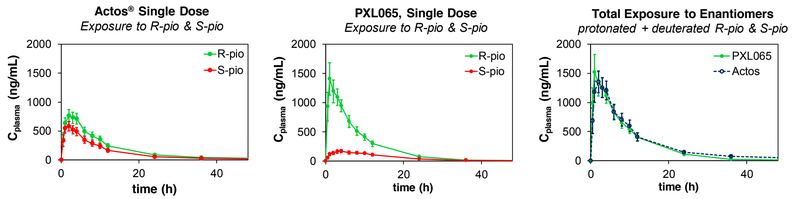
Note: Part 2 ongoing with additional dose(s) for dose proportionality evaluation

Safety, Tolerability & PK

Safety & Tolerability
- PXL065 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 PXL065 (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 limited S-pio
- 2x increase in C_{max} of R-pio
- Same overall exposure to "Total racemic pio" at ½ the dose

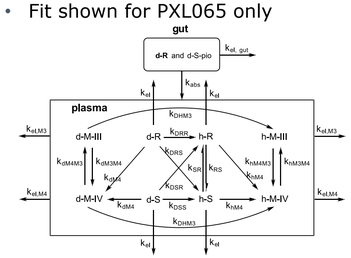


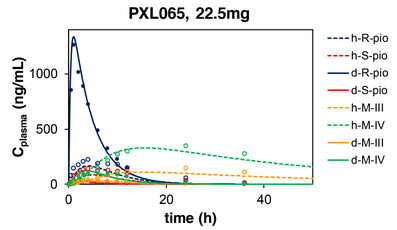
Data presented as sum of concentrations of protonated and deuterated enantiomers for PXL065

PK Parameter	R-pio/S-pio Ratio After Dosing:	
	Actos® (45 mg)	PXL065 (22.5 mg)
AUC_{last}	1.5	4.2
C_{max}	1.4	8.5

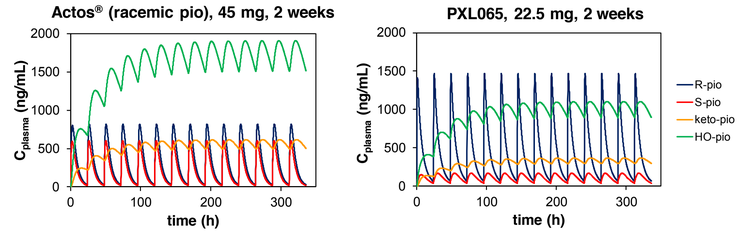
PK Model

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[10].
- Fitted rate constants used to predict
  - Time to steady state
  - Dose of PXL065 for same exposure to R-pio as 45 mg Actos®
- Fit shown for PXL065 only





PK Model Predicts 15 mg PXL065 Efficacious Without Weight Gain
- No accumulation of R-pio or S-pio with daily dosing
  - Results consistent with published data with racemic pio[11]
- 15 mg PXL065: Predicted same R-pio exposure as 45 mg Actos®
- 15 mg PXL065: 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[12])
- Supporting experimental data with PXL065
  - In mouse, no weight gain but excellent NASH efficacy[7,8]
  - In human, relative exposure to R-pio vs S-pio similar to mouse[7,8]



Conclusions

- Deuterium stabilizes pio enantiomers & enables characterization[6,7]
  - PXL065 is deuterium-stabilized R-pio
- R-pio responsible for NASH efficacy, lacks PPARγ activity[6,7] (preclinical)
- PXL065 human PK: Relative exposure to R-pio increased >3x
- PK model predicts 15 mg PXL065 efficacious for NASH, no weight gain
  - R-pio exposure similar to 45 mg racemic pio (efficacious for NASH[2])
  - S-pio exposure similar to 7.5 mg racemic pio (no weight gain[12])

Notes & References

* Formerly known as DRX-065. Poxel has acquired DRX-065 (now known as PXL065) as well as a portfolio of additional deuterated drug candidates from DeuteRx for metabolic, specialty and rare diseases.

1. Hardy, et al., Curr Opin Gastroenterol. 2015, 31(3),175–183.
2. Cusi, et al., Ann Intern Med. 2016, 165(5), 305-315.
3. Chang et al., Hepatology 2012, 55(5), 1462-1472; Lin et al., J Clin Pharm Ther. 2014, 39, 354-360.
4. EASL, EASD, EASO J Hepatol. 2016, 64(6), 1388-1402; Chalasani et al., Hepatology 2018, 67, 328-357
5. Rinella, et al., Therap Adv Gastroenterol. 2016, 9(1), 4-12
6. DeWitt, et al., Hepatology. 2015, 62(1), 281A-282A (AASLD Abstract 143).
7. Prosecution history for DeuteRx International Appl. WO 2015/109037.
8. Jacques, et al., Hepatology. 2016, 64(6), 1137A-1138A (AASLD Abstract LB-32).
9. Actos®, racemic pio, is a 1:1 mixture of R-pio & S-pio. Therefore, PXL065 is dosed at 1/2 the dose.
10. Model used non GLP experimental data for 2 major active human metabolites of pio, M-III and M-IV.
11. Budde, et al., Br J Clin Pharmacol. 2003, 55(4), 368-374.
12. Rajagopalan, et al., Diabetes Res Clin Pract. 2015, 109(3), e32-e35.