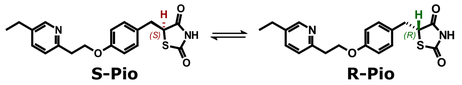
Phase 1 Study of PXL065 Confirms Dose-Proportionality & Stabilization of the Preferred Stereoisomer (R-Pioglitazone) for the Treatment of NASH

Sébastien Bolze[1], Sheila DeWitt[2], Pascale Fouqueray[1], Vincent Jacques[2], and Sandrine Perrimond-Dauchy[1]
[1]Poxel, Lyon, France, [2]DeuteRx, LLC, Andover, MA

Background

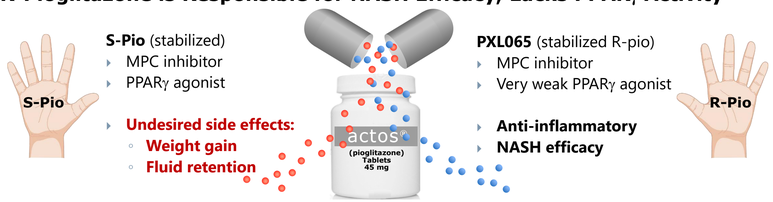
Pioglitazone is Highly Efficacious[1] for NASH but Limited by PPARγ Effects

- 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



S-Pio R-Pio

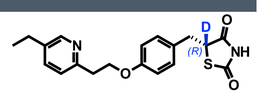
R-Pioglitazone is Responsible for NASH Efficacy, Lacks PPARγ Activity



- 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)

Objectives

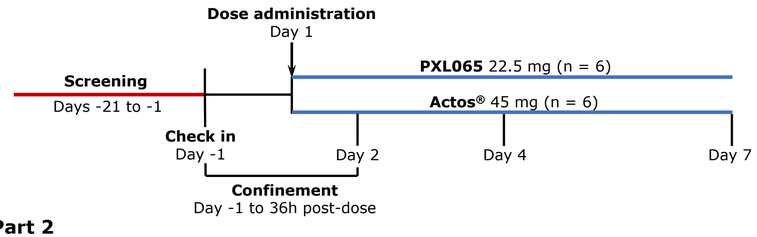
- Safety and Tolerability
- Pharmacokinetic (PK) evaluation
  - Pio R/S ratio
  - Dose proportionality
  - Exposure to major metabolites



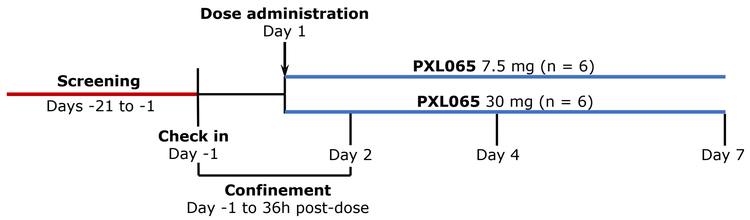
PXL065
deuterium-stabilized R-pio

Methods

Part 1



Part 2



Methods (Cont.)

- Open label study in healthy volunteers (3 males & 3 females per group)
- Actos® 45 mg[9] as reference listed drug
- Endpoints: Safety, tolerability, PK
- PK Analysis
  - GLP LC/MS-MS quantitation of deuterated and protonated R- and S-Pio
  - non-GLP quantitation of deuterated and protonated metabolites M-III, M-IV
  - PK analysis with Phoenix WinNonlin 8.0 or later (Certara L.P.) (non-compartmental extravascular dosing)

Results

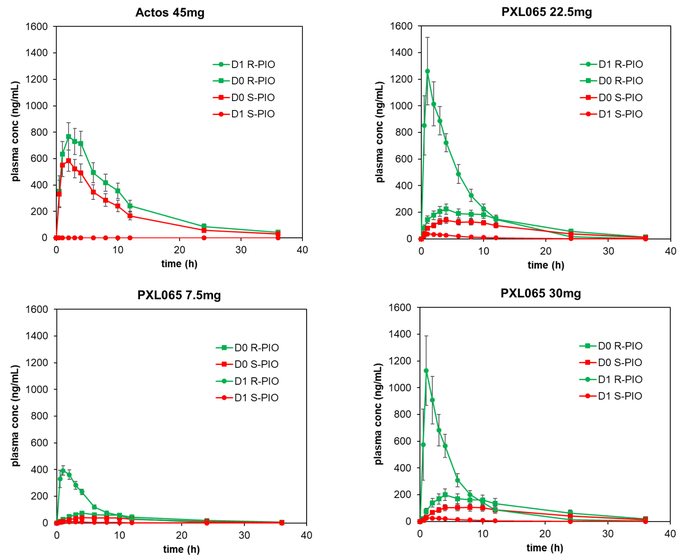
Safety & Tolerability

- PXL065 safe and well-tolerated at all tested doses
- No serious adverse events

PK Results

- Single Dose of Actos (45 mg)
  - Higher exposure (AUC) to R-pio (59%) vs S-pio (41%)
- Single Dose PXL065 vs. Actos
  - Dose-dependent increase in C_{max} and AUC (R-Pio and total Pio) from 7.5 to 22.5 mg
  - Similar C_{max} and AUC (R-Pio and total Pio) at 30 mg vs. 22.5 mg
  - Increased relative exposure (AUC) to R-pio (R/S ratio) ~3x compared to Actos, irrespective of dose
  - Some deuterium loss (D/H exchange) and formation of limited S-pio
  - Same exposure to "total pio" at ½ the dose (22.5 mg vs. Actos 45 mg)
  - ½ exposure to metabolites M-III & M-IV for PXL065 22.5 mg vs Actos 45 mg

Protonated and Deuterated R- and S-Pio Plasma Concentration-Time Plots

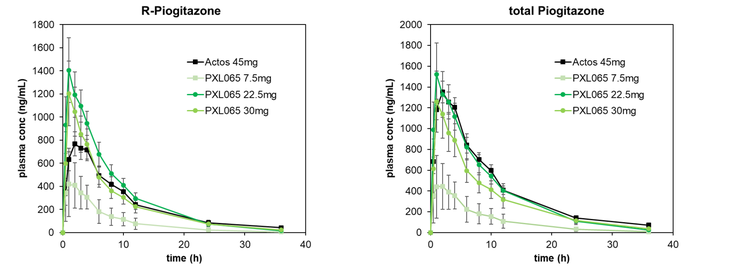


Data presented as mean (n=6) ± SD of protonated (D0) and deuterated (D1) enantiomers of Pio (S-Pio in red and R-pio in green; deuterated as circles and protonated as squares)

PK Parameter	R-pio/S-pio Ratio After Dosing:			
	Actos® (45 mg)	PXL065 (22.5 mg)	PXL065 (7.5 mg)	PXL065 (30 mg)
$AUC_{0-\infty}$	1.4	4.2	4.4	4.1
C_{max}	1.4	8.5	9.9	9.6

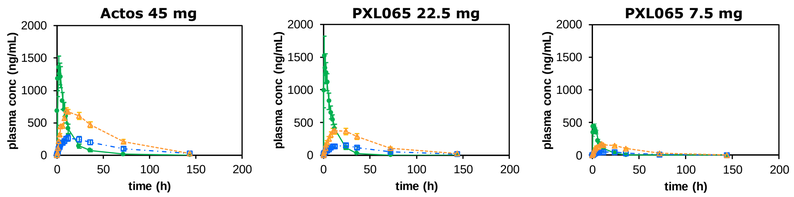
Results (Cont.)

R-Pio and "total Pio" Plasma Concentration-Time Plots



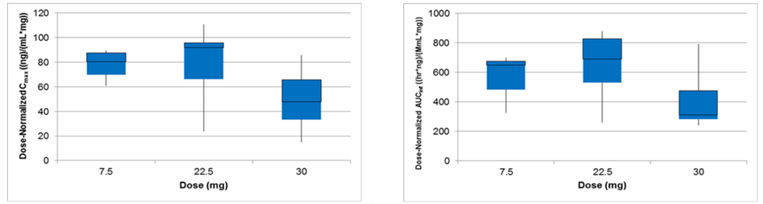
Data as mean (n=6) ± SEM for R-Pio (left, sum of protonated and deuterated R-Pio) and total Pio (right, sum of protonated and deuterated R-Pio and S-Pio)

"Total Pio", Metabolites M-III and M-IV Concentration-Time Plots



Data as mean (n=6) ± SEM for "total Pio" (green, sum of protonated and deuterated R-Pio and S-Pio), metabolites (sum of protonated and deuterated) M-III (blue) and M-IV (orange)

Dose-Normalized C_{max} and AUC_{0-last} (total Pio) as Function of PXL065 Dose



Data presented as box (1st to 3rd quartile) and whiskers (min to max)

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 predicted similar to 45 mg racemic pio (efficacious for NASH[2])
  - S-pio exposure predicted 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.

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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. Budde, et al., Br J Clin Pharmacol. 2003, 55(4), 368-374.
11. Rajagopalan, et al., Diabetes Res Clin Pract. 2015, 109(3), e32-e35.