Phase 1b Study of PXL065 (Deuterium-Stabilized R-Pioglitazone), a Novel NASH Candidate, Predicts 15mg Equivalent to 45 mg Actos®

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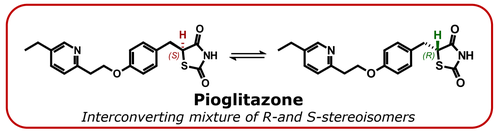
Background

Pioglitazone (Pio) Efficacious for NASH but Limited by PPARγ Effects

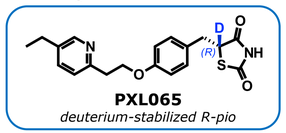
- Achieved "Resolution of NASH without worsening of fibrosis" (Phase 4 trial[1])
- Only drug recommended for NASH by AASLD & EASL Practice Guidelines[2]
- Currently prescribed by ~14% of physicians for biopsy-proven NASH[3]
- Limited use due to PPARγ effects: weight gain, fluid retention, bone fracture

PXL065: NCE with Benefits of Pio, Reduced PPARγ, New IP, 505(b)(2)

- Pio known safety profile, used in T2D for >20 yrs:
  - >30 Mil patient-years of exposure[4]
  - Established CV outcomes benefit[5]
- Pio exhibits both genomic (PPAR) and nongenomic mechanisms of action (including inhibition of mitochondrial pyruvate carrier (MPC)
- Pio complicated as a mixture of 2 interconverting stereoisomers
- PXL065 is stabilized, preferred R-stereoisomer of pio for NASH
- Deuterium stabilizes the chiral center but does not change metabolism



Pioglitazone
Interconverting mixture of R-and S-stereoisomers



PXL065
deuterium-stabilized R-pio

Preclinical studies showed dramatic differences between S- vs R-pio

S-Pio (stabilized)
- MPC inhibitor
- Strong PPARγ agonism
- **Undesired side effects:**
  - **Weight gain**
  - **Fluid retention**

PXL065 (stabilized R-pio)
- MPC inhibitor
- Very weak PPARγ agonism
- Little / no PPARγ-related side effects
- **Anti-inflammatory**
- **Activity in NASH**

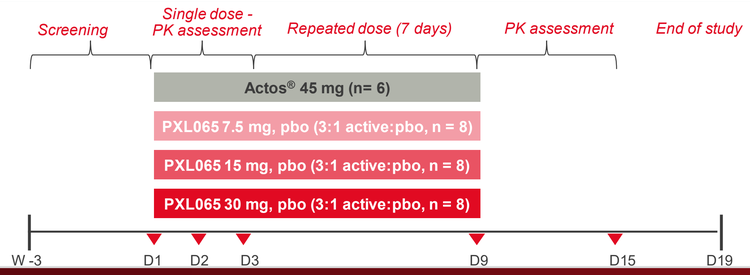
Phase 1a PXL065 (7.5, 22.5, 30 mg) vs Actos (pio, 45 mg) met goals[6,7]

- Demonstrated good safety & tolerability
- Relative exposure to R-pio increased >3x
- Dose proportional up to 22.5 mg and ½ exposure to metabolites

Objectives of Phase 1b Study

- Assess safety and tolerability
- Pharmacokinetic (PK) evaluation
  - Assess and compare relative exposures to R- and S-pio
  - Evaluate dose proportionality up to 30 mg
  - Assess intra-individual variability & food effect
  - Assess and compare exposure to major metabolites, M-III and M-IV

Methods



Methods (Cont.)

- Double-blind, randomized, placebo-controlled study in healthy subjects
  - 7 days of repeated dosing to achieve steady state
  - PXL065 dosed as 7.5, 15, or 30 mg tablets
  - Actos 45 mg[7] as reference listed drug
  - Food effect (high fat, high calorie breakfast) assessed for PXL065 15 mg
- Endpoints: safety, tolerability, PK
- PK Analysis
  - Quantitation of R- and S-pio used validated LC/MS-MS method
  - Quantitation of M-III and M-IV used qualified LC/MS-MS method
  - PK analysis with Phoenix WinNonlin 8.0 or later (Certara L.P.) (non-compartmental extravascular dosing)

Results

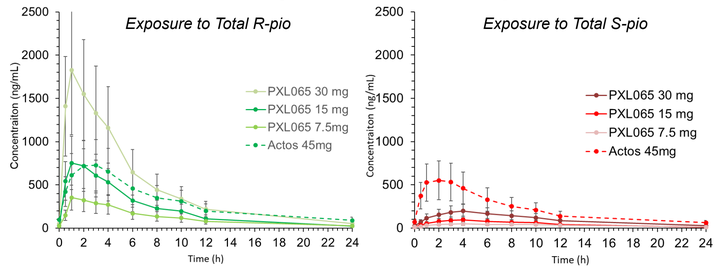
Safety & Tolerability

- PXL065 was safe and well-tolerated at all doses

PK Results

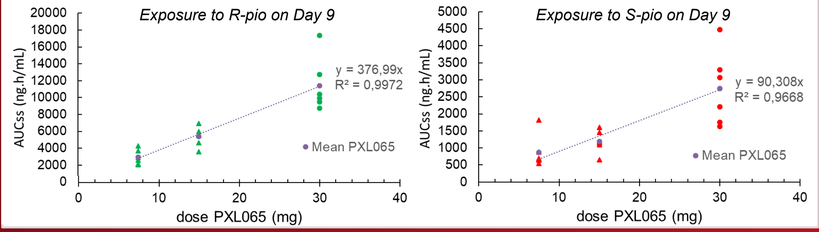
- Exposure to total R- and S-pio (deuterated + protonated)
  - Stabilization confirmed with R/S ratio of ~80/20 at all doses of PXL065
  - R-pio exposure similar at 3x lower dose of PXL065 vs Actos (15 vs 45 mg)
  - S-pio exposure 5x lower after dosing PXL065 vs Actos (15 vs 45 mg)
  - 55% - 75% higher relative bioavailability to total pio after PXL065 vs Actos
  - Elimination $t_{1/2}$ of R- or S-pio unchanged with PXL065 vs Actos
- Dose proportionality in exposure observed from 7.5mg to 30mg of PXL065
- Intra-individual variability with PXL065 ~22% for C_{max} and 16% for AUC_{0-24}
  - Similar variability observed with Actos
- No clinically meaningful food effect (~15% reduction of C_{max} and AUC_{0-24})
- Exposure to major metabolites, M-III and M-IV
  - No change in metabolism with deuterium at chiral center compared to pio (no new major metabolites)
  - Same relative exposure to M-III and M-IV as Actos
- Tablet formulation reduced PK variability vs capsule (used in Phase 1a)

15 mg PXL065 Dose Yields Similar R-Pio Exposure as 45 mg Actos while S-Pio Exposure Decreased by ~5-fold



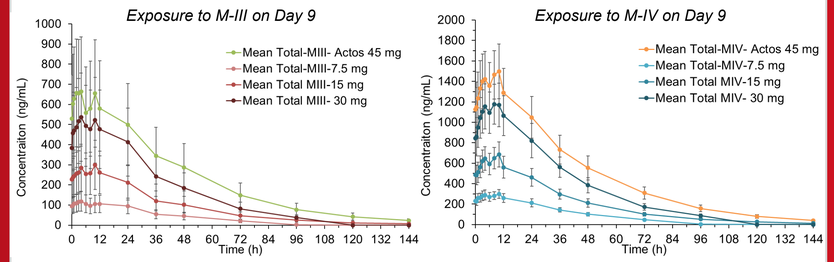
Data presented as mean (n=6) ± SD of total R- or S-pio (protonated and deuterated) following dosing of PXL065 or Actos. Formation of protonated S-pio due to some limited deuterium / hydrogen exchange in vivo

PXL065 Exhibits Dose Proportionality at All Doses (7.5 to 30 mg)



Results (Cont.)

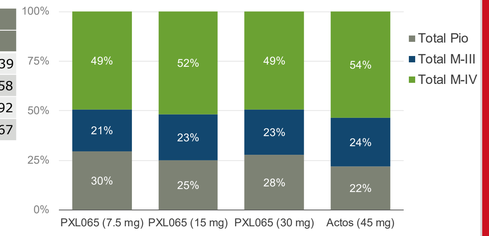
Major Metabolites Reduced with PXL065 vs Equivalent Dose of Actos
Reduction of 57% with PXL065 15 mg vs Actos 45 mg
(expected because 2-fold difference between equivalent doses of PXL065 and Actos[7])



Data as mean (n=6) ± SEM for M-III (left, sum of protonated and deuterated M-III) and M-IV (right, sum of protonated and deuterated M-IV) following dosing of PXL065 or Actos

Same Relative Exposure to Total Pio, M-III, and M-IV after Dosing PXL065 vs Actos

Agent dosed	AUC (ng.h/mL)		
	Total Pio	M-III	M-IV
PXL065 - 7.5 mg	3,678	2,626	6,139
PXL065 - 15 mg	6,505	6,034	13,458
PXL065 - 30 mg	13,802	11,286	24,492
Actos - 45 mg	12,567	13,861	30,567



Conclusions

1. Deuterium stabilizes the chiral center of R-pio resulting in reproducible enrichment of the preferred stereoisomer (R-pio>>S-pio) at steady state
2. Deuterium at the chiral center does not change the metabolism of pio.
3. Based on preclinical and Phase 1 human PK results, ~15 mg PXL065 is predicted to yield similar chronic exposure to R-pio - and NASH efficacy - as 45 mg Actos with little or no PPARγ-related side effects (e.g. weight gain).
4. Phase 2 trial (Destiny I) in biopsy-proven NASH patients (NCT04321343) started Sep 2020

Notes & References

* PXL065 was formerly known as DRX-065. Poxel acquired DRX-065 and a portfolio of additional deuterated drug candidates from DeuteRx in 2018.

1. Cusi, et al., Ann Intern Med. 2016, 165(5), 305
2. EASL, EASD, EASO, J Hepatol. 2016, 64(6), 1388; Chalasani, et al., Hepatology 2018, 67, 328
3. Rinella, et al., Therap Adv Gastroenterol. 2016, 9(1), 4
4. Takeda 2014. https://www.takeda.com/newsroom/newsreleases/2014
5. DeFronzo, et al., Diab Vasc Dis Res. 2019, 16(2), 133
6. Bolze, et al., Hepatology. 2019, 70(S1), 1264A (AASLD Abstract 2135)
7. Actos® is a 1:1 mixture of R-pio & S-pio. The highest approved Actos dose is 45 mg. Equivalent dosing of R-pio with PXL065 is 1/2 dose of Actos (e.g. 22.5 vs 45 mg).