PXL065 (DEUTERIUM-STABILIZED *R*-ENANTIOMER OF PIOGLITAZONE) REDUCES LIVER FAT CONTENT AND IMPROVES LIVER HISTOLOGY WITHOUT PPARγ -MEDIATED SIDE EFFECTS IN PATIENTS WITH NASH: ANALYSIS OF A 36 WEEK PLACEBO-CONTROLLED PHASE 2 TRIAL (DESTINY1)

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Background: Pioglitazone (Pio) is effective as a NASH therapy and recommended by practice guidelines. However, PPARγ-driven side effects - weight gain and edema - limit its use. Pio is a mixture of 2 enantiomers that rapidly interconvert. PXL065, a new chemical entity (NCE), is the deuterium-stabilized R-enantiomer of Pio which lacks PPARγ activity but retains non-genomic target activities (mitochondrial pyruvate carrier and acyl-CoA synthetase 4) and preclinical efficacy in NASH models. DESTINY1, a Phase 2 study, was designed to validate this concept in noncirrhotic NASH patients.

Methods: 117 patients (≥8% liver fat, NAS ≥ 4, F1-F3) were randomized 1:1:1:1 to receive daily oral doses of PXL065 (7.5mg, 15mg, 22.5mg) or placebo for 36 weeks. The primary endpoint was relative % change in liver fat content (LFC) assessed by MRI-PDFF; secondary/exploratory endpoints included histology from paired liver biopsies, liver enzymes, biomarkers of fibrosis, adiponectin, lipids and glycemic parameters as well as safety-tolerability. The study was not powered for histology analysis.

Results: (Table I) All PXL065 groups met the primary endpoint, and up to 40% achieved a relative reduction ≥ 30% in LFC. Improvements in ALT, biomarkers of fibrogenesis and fibrosis risk scores (Pro-C3, PIIINP, ELF, Fib4, NFS) were observed. On histology, 35%-50% of PXL065 treated subjects achieved ≥1 stage fibrosis improvement vs. 17% with placebo and 15%-33% achieved NASH resolution and ≥1 stage fibrosis improvement versus 13% with placebo. Glucose control was improved; placebo-adjusted change in HbA1c reached -0.41% (baseline values 6.07—6.27%) with consistent improvements in insulin, C-peptide and indexes of insulin sensitivity (HOMA-IR, Quicki, Adipo-IR). Adiponectin was modestly increased with PXL065, consistent with some limited PPARγ target engagement. There was no dose dependent effect on body weight (+0.6 kg vs. baseline at 22.5 mg). Incidence of peripheral edema was low and similar across the groups. Overall, PXL065 was safe and well tolerated.

Conclusion: DESTINY1 results support the concept that PXL065 is a novel PPARγ sparing oral NCE which retains an efficacy profile in NASH similar to that reported with Pio without the side effects. PXL065 demonstrated statistically significant reductions in LFC and histology suggests an effect on fibrosis consistent with improvements in the biomarkers. Histological data need to be confirmed in larger, pivotal clinical trials.

Baseline Demographics and Summary of Results				
		PXL065 (Daily Oral Dosing)		
Demographics Parameter (reported as mean unless specified)	**Placebo** **N=30**	**7.5 mg** **N=25**	**15 mg** **N=32**	**22.5 mg** **N=30**
Age (Years)	55	51	54	53
Sex (N, Feale/Male)	21 / 9	14/ 11	18 /14	14 /16
BMI (kg/m^2)	36	34	38	36

% Type 2 Diabetes (T2DM)	43	40	41	40
Liver Fat Content (% via MRI-PDFF)	20	22	20	20
ALT (U/L)	54	72	59	61
NAFLD Activity Score (NAS)	5.4	5.1	4.9	5.5
Fibrosis Stage (% F2-F3)	67	64	66	63
Summary of Results (Non-Invasive)				
Relative Reduction in Liver Fat (%)	+2	-23	-19	-21
LFC % Responder (≥30% reduction)	17	32	34	40
ALT % Responder (≥ 17 U/L decrease)	26	53	38	54
Pro-C3 Change from Baseline (ng/mL)	-1.0	-2.1	-1.8	-2.5
PIIINP Change from Baseline (ng/mL)	-1.1	-2.4	-2.7	-3.4
ELF Score Change from Baseline	-0.1	-0.1	-0.2	-0.4
NAFLD Fibrosis Score Change from Baseline	+0.2	+0.2	0	-0.3
Fib-4 Score Change from Baseline	0	0	-0.1	-0.2
HbA1c (%) Change from Baseline	+0.2	+0.1	-0.1	-0.2
HbA1c (%) Change from Baseline (T2DM)	+0.3	+0.3	0	-0.3
HOMA-IR (C-Peptide) Change from Baseline	+0.1	-0.1	-0.1	-0.2
QUICKI (C-Peptide) Change from Baseline	+7.9	-2.3	-5.8	-0.7
Adipo-IR Change from Baseline	+12.8	-36.2	-17.0	-41.9
Adiponectin (μg/mL) Change from Baseline	-0.1	+1.5	+2.7	+4.7
Summary of Results (Histology – % of Patients Achieving Endpoint)				
Fibrosis improvement by ≥ 1 stage	17	43	50	35
Fibrosis worsening by ≥1 stage	26	10	9	12
≥2-point improvement in NAS with no worsening of fibrosis	30	38	50	50
NASH resolution AND Fibrosis improvement by ≥ 1 stage	13	33	32	15