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Deuterium-Stabilized (R)-Pioglitazone, PXL065, for Treatment of X-Linked Adrenoleukodystrophy (ALD)

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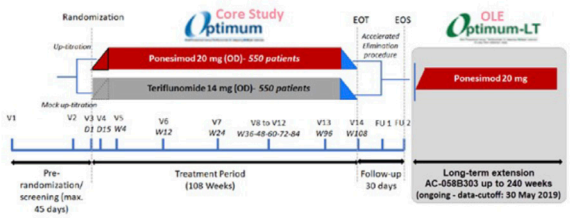

D: day; EOS: End of study; EOT: end of treatment; FU: Follow-up; M: Month; V: visit; W: week

Fig 1. Study Design

Overview of treatment-emergent adverse events, by frequency and per subject-year in the combined analysis period, Safety Set

Characteristic		Ponesimod 20 mg / Ponesimod 20 mg N=565	
Cumulative observation time (subject-years)		1419.0	
Subjects with at least one	n (%)	Number of events	(rate)
AE	522 (92.4)	3519	(2.48)
Severe AE	54 (9.6)	83	(0.06)
Drug-related AE	311 (55.0)	959	(0.68)
AE leading to study drug discontinuation	57 (10.1)	69	(0.05)
Serious AE	60 (10.6)	77	(0.05)
Drug-related serious AE	19 (3.4)	24	(0.02)
Fatal AE	0	0	

Ongoing study interim analysis data cut-off: 30 May 2019

AE = adverse event
Cumulative number subject-years = cumulative observation time in the treatment-emergent period of the Analysis Period over all subjects. Total number of events = number of qualifying events in this period (multiple events per subject may be counted in each category).
Rate = events per subject-years of exposure.

Fig 2. TEAEs - combined analysis period

Extension Analysis Period

Overview of treatment-emergent adverse events in the extension analysis period, Extension Set

Characteristic	Ponesimod 20 mg / Ponesimod 20 mg N=439	Teriflunomide 14 mg / Ponesimod 20 mg N=438		Total N=877	
Cumulative observation time (subject-years)				697.0	
Subjects with at least one	n (%)	n (%)	n (%)	Number of events	(rate)
AE	263 (59.9)	289 (66.0)	552 (62.9)	1610	(2.31)
Severe AE	19 (4.3)	15 (3.4)	34 (3.9)	49	(0.07)
Drug-related AE	117 (26.7)	139 (31.7)	256 (29.2)	512	(0.73)
AE leading to study drug discontinuation	9 (2.1)	24 (5.5)	33 (3.8)	41	(0.06)
Serious AE	14 (3.2)	17 (3.9)	31 (3.5)	44	(0.06)
Drug-related serious AE	8 (1.8)	5 (1.1)	13 (1.5)	18	(0.03)
Fatal AE	0	0	0	0	

Ongoing study interim analysis data cut-off: 30 May 2019

AE = adverse event
Cumulative number subject-years = cumulative observation time in the treatment-emergent period of the Analysis Period over all subjects. Total number of events = number of qualifying events in this period (multiple events per subject may be counted in each category).
Rate = events per subject-years of exposure.

Fig 3. TEAEs - extension analysis period

Disclosure: MR-B, AW, AL, MA-T, AV and TS are or were employees of Janssen and may own stock or stock options in Johnson & Johnson. XM received speaker honoraria from Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, Genzyme, Immunic, Medday.

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Deuterium-Stabilized (R)-Pioglitazone, PXL065, for Treatment of X-Linked Adrenoleukodystrophy (ALD)

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Background and aims: X-linked Adrenoleukodystrophy (ALD) is a rare neurometabolic disorder caused by ABCD1-gene mutations, leading to Very-Long-Chain Fatty Acids (VLCFA; in particular C26:0) accumulation, inflammation, mitochondrial impairment and demyelination. PXL065, a clinical-stage deuterium-stabilized(R)-stereoisomer of pioglitazone, retains pioglitazone non-genomic actions but lacks PPARγ activity. As pioglitazone exhibits beneficial effects in ALD models and PXL065 may avoid PPARγ-related side effects, we investigated PXL065 effects of in preclinical models.
Methods: Patient-derived fibroblasts and lymphocytes and Abcd1-KO mouse glial cells were exposed to PXL065 (5-10µM) and pioglitazone (10µM) for 7 days. VLCFA content was measured by mass spectrometry, selected gene expression by RT-qPCR, and mitochondrial function using a Seahorse Analyzer (after 72hr). PXL065 or pioglitazone (15mg/kg QD) were administered to 6-8-week or 13-month old Abcd1-KO mice for 8 and 12 weeks, respectively. VLCFA content (mass spectrometry), sciatic nerve axonal morphology (electronic microscopy), and locomotor function (open field test) were measured.
Results: In patient and mouse glial cells, PXL065 and pioglitazone corrected C26:0, improved mitochondrial function, increased compensatory Abcd2-3 transporter gene expression, and decreased inflammatory gene expression.
In Abcd1-KO mice, C26:0 levels were normalized in plasma and decreased in spinal cord (-55%, $p<0.01$) and brain (-49%, $p<0.0001$). Pioglitazone had no effect in spinal cord. Following PXL065 and pioglitazone treatment, abnormal axonal morphology (stellate-shaped cells) was improved but only PXL065 showed significantly improved locomotor test results.
Conclusion: Despite reduced PPARγ activity, PXL065 showed substantial signs of efficacy and superior therapeutic potential vs. pioglitazone (in vivo) supporting clinical development for ALD. A Phase 2a study is planned in 2022.
Disclosure: Studies funded by Poxel SA.