First in human phase 1/2a open label study evaluating the safety and efficacy of the Akt activator, IPL344 in amyotrophic lateral sclerosis

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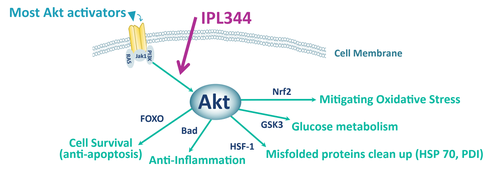
Background

- The PI3K (Phosphoinositide 3-Kinases)-Akt pathway is an intracellular signal transduction pathway that promotes cell survival and growth by preventing neurodegeneration and apoptosis, and regulating glycogen metabolism as well as reducing inflammation and protein misfolding and aggregation.
- Dysfunction of the Akt signaling pathway is common to many age-related neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) where it is downregulated in motor neurons and skeletal muscles.[1-3]
- Studies have shown that higher Akt levels and/or activation in humans and certain cell types provide some protection from ALS[4] as well as a slower progression rate of the disease and better overall survival in ALS patients.[5]
- IPL344 is a short peptide which has been shown to activate Akt (independently of Pi3K) in *in vitro* models and extend survival in the SOD1 mouse model of ALS.

Akt Activation targets the key pathologies that drive ALS



Objective

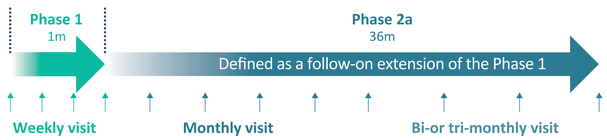
Evaluate the safety and tolerability and preliminary efficacy of IPL344 in 9 participants with ALS treated up to 36 months

Methods

IPL344 study design

- This open-label Phase 1/2a study was divided into a 28-day dose escalation phase and a voluntary long-term phase 2a extension.
- Participants with rapidly progressing ALS (reduction of >0.55 points/month on the ALS functional rating scale [ALSFRS-R] as detected prior to enrolment), were enrolled at a single site.
- IPL344 was administered intravenously on a daily basis via a central venous catheter as home treatment.
- Participants were followed up to 36 months (average IPL344 treatment 11 months) for safety, functional assessment (ALSFRS-R), lung function (SVC), weight, and ALS-related events. Those discontinuing treatment were still followed for survival/tracheostomy. An additional participant was treated under a compassionate protocol.
- Data analysis used methods suitable for small clinical trials sample size.[6,7]

Study design. Patients were treated for an average of 14.0 months



Natural history comparison

- Study results were compared against the natural history of ALS as captured by the PRO-ACT database, including the pooled placebo groups from 16 studies (selected for long duration) included in the PRO-ACT database[6, 8] and by the ceftriaxone study (for endpoints where the PRO-ACT database was incomplete).[9]
- When comparing to PRO-ACT, analysis was against all patients included in the database with available data for the analyzed end point.
- ALSFRS-R was also assessed vis-à-vis each participant's rate during the lead-in period.

Results

Baseline demographics. Before treatment, the PRO-ACT population showed less severe disease and a slower rate from onset (ΔFRS) compared to the IPL344 test population

	IPL344 (N=9)	PRO-ACT Placebos (N=10,723)	P value
Age (years); mean (SD)	58.5 (12.6)	n=7702 56.3 (11.7)	0.311
Sex, (female); n (%)	4 (44%)	n=10,717 4,253 (40%)	
Months from onset Mean (SD)	23.2 (13.2)	n=6,877 21.8 (16.0)	0.380
Diagnostic delay (months); mean (SD)	7.3 (4.8)	n=4,447 10.9 (8.2)	0.066
ALSFRS-R total score	30.1 (7.6)	n=2,531 37.7 (5.5)	0.022
ΔFRS (points/ month);	-0.98 (0.57)	n=2,380 -0.71 (0.53)	0.212
FVC%	72% (18%)	n=3,148 76% (27%)	0.510
SVC%	74% (20%)	n=459 91% (16%)	0.041
Bulbar onset	22.2%	23.7%	0.1797
Using riluzole	89%	NR	-

NR. Not reported

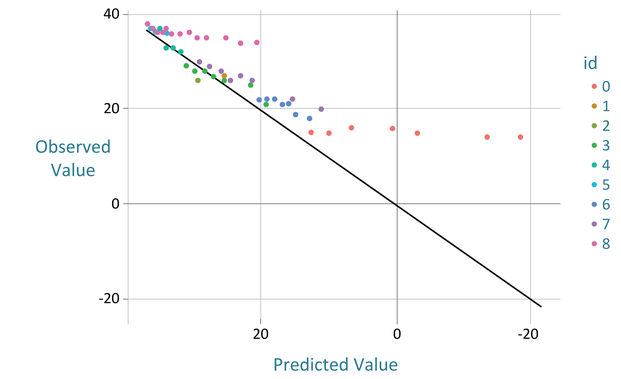
IPL344 was well tolerated with no major safety concerns

Treatment emergent adverse events	(N=9)
Pneumonia complication*	n=2
Fall	n=1
Catheter related AE	n=2
Drug related hypersensitivity**	n=1

**One patient had tracheostomy and one patient died, neither SAE was considered related to treatment. **Occurred in patient enrolled for compassionate treatment after 12 months, TEAE resolved with reduced infusion rate*

IPL344 treated patients had a 67% slower ALSFRS-R progression rate compared to the participants' pre-treatment lead-in rate*

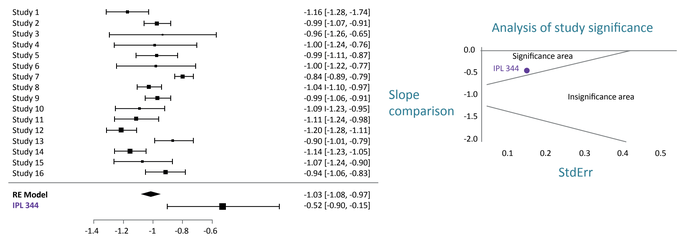
Observed ALSFRS-R compared to prediction from pretreatment values



**Model assumes that ALSFRS-R during a lead-in period has a linear trajectory that varies with patients, and it has a different linear trajectory during treatment that also varies with patients. The magnitude of treatment benefit is represented by the extent that the patient ALSFRS-R values were above the 'without treatment' reference line.*

Compared to historical placebo, patients treated with IPL344 showed 49% slower progression of ALSFRS-R (p= 0.027)*

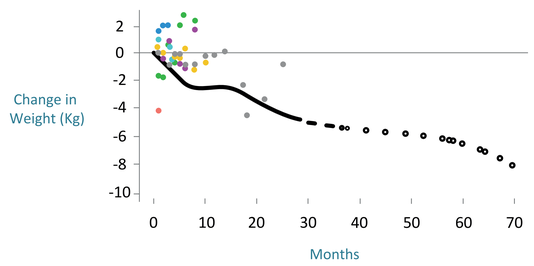
Analysis of slope of ALSFRS-R compared to historical controls
IPL344 treatment effect (without correction)



**16 studies were analyzed to determine the average rate of change in ALSFRS-R and the variation in the average rate of change from study to study.[6] This analysis was used to generate 95% tolerance limits for a new study as a function of the standard error of the treatment effect for that study. A slope above these tolerance limits implies superiority versus historical controls accounting for study variability in the mean slope of ALSFRS-R.*

Patients treated with IPL344 gained weight, while those in the historical placebo control lost weight (p=0.026)

Comparison of weight loss/gain to historical data

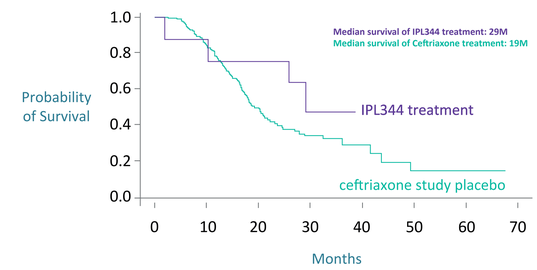


Mortality analysis compared to ceftriaxone study

Change in weight of the two treatments over time. Individual IPL344-treated patients (N=9) are distinguished by colors, while the black line represents smoothed PRO-ACT placebo values (data is smoothed using a spine with five knots).

Comparison with the ceftriaxone study[9] placebo showed 70% lower risk of death (p=0.13)

Mortality analysis compared to ceftriaxone study



Cox model incorporating covariates measured in both studies. The robust variance is used which is reported to be accurate for small samples.[7]

Summary of the Statistical Analysis Report

Clinical endpoints	Type of control	Control value	IPL344 value	Estimated reduction	P value
ALSFRS-R slope (points change/month)	Slope during treatment compared to slope before treatment, interception point derived by trajectories[1]	-1.14	-0.37	67%	NA
	16 studies in PRO-ACT[2]	-1.03	-0.52	49%	0.027
	PRO-ACT database, slopes corrected for covariates[3]	-1.09	-0.39	64%	0.034
Median survival (months), risk of death	Ceftriaxone study placebo	19.1	29.0	70%	0.13
SVC slope (% change/month)	PRO-ACT database, slopes corrected for the covariates[4]	-2.8%	-1.6%	44%	0.16
Weight Loss/Gain (Kg change/month)	PRO-ACT database, corrected for the covariates[4]	-0.39	+0.47	-122%	0.026

1. Estimated linear trajectories for the population. In similar two randomized studies with no treatment lead in phases Gordon et. al.(2007) and Miller(2007), the drop in ALSFRS-R was 20% greater after treatment started in their placebo group, making a placebo effect less likely.
2. Mean slopes for control studies and IPL344 treated patients without trajectories/corrections for covariates
3. Covariates used for correction: ALSFRS-R rate from onset (ΔFRS), ALSFRS-R at baseline and bulbar onset.
4. Covariates used for correction: ALSFRS-R rate from onset (ΔFRS), and bulbar onset

Conclusions

- IPL344 treatment was generally safe, with signals of efficacy indicating 49–67% slower progression in several outcome parameters.
- These results warrant further evaluation in randomized placebo-controlled study, currently being planned.
- Initial (ongoing) pilot studies measuring Akt activation in leucocytes from IPL344-treated participants as a biomarker suggested successful target engagement.

References

1. Wu et al. *Proc Natl Acad Sci U S A.* 2006;103(32):12132-12137. 2. Dewil et al. *Neuropathology and Applied Neurobiology.* 2007;33(5):499-509. 3. Léger et al. *Faseb j.* 2006;20(3):583-585. 4. Allodi et al. *Stem Cell Reports.* 2019;12(6):1329-1341. 5. Yin et al. *Muscle Nerve.* 2012;46(6):861-870. 6. Schoenfeld et al. *Clin Trials.* 2019;16(5):531-538. 7. Lin & Wei. 1989;84(408):1074-1078. 8. Atassi et al. *Neurology.* 2014;83(19):1719-1725. 9. Cudkowicz et al. *Lancet Neurol.* 2014;13(11):1083-1091. 10. Gordon et al. *Lancet Neurol.* 2007;6(12):1045-1053. 11. Miller et al. *Neurology.* 2007;69(8):776-784.

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