Neurofilament light chain level change in plasma of ALS patients following IPL344 treatment in phase 1/2a clinical trial (NCT03652805, NCT03755167)

Ilana Cohen PhD,[1] Yossef Lerner MD,[2] Eran Ovadia MBA,[1] Marc Gotkine MBBS[2]

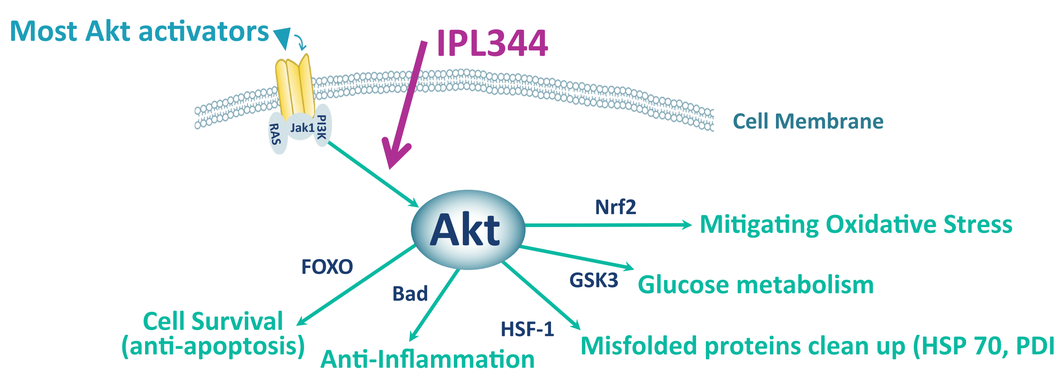
[1]Immunity Pharma Ltd., Mevasseret Zion, Israel; [2]Hadassah Medical Center, Jerusalem, Israel

Objective

Evaluate the change in plasma Neurofilament light (NfL) levels in patients with amyotrophic lateral sclerosis (ALS) following IPL344 treatment.

Background

- The Akt pathway is an intracellular signal transduction pathway that promotes cell survival and prevents neurodegeneration. Dysfunction of the PI3K (phosphoinositide 3-Kinases)-Akt signaling pathway is common to many age-related neurodegenerative diseases, including 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 cell membrane receptors) in *in vitro* models (see figure) and extend survival in the SOD1 mouse model of ALS.[6,7]



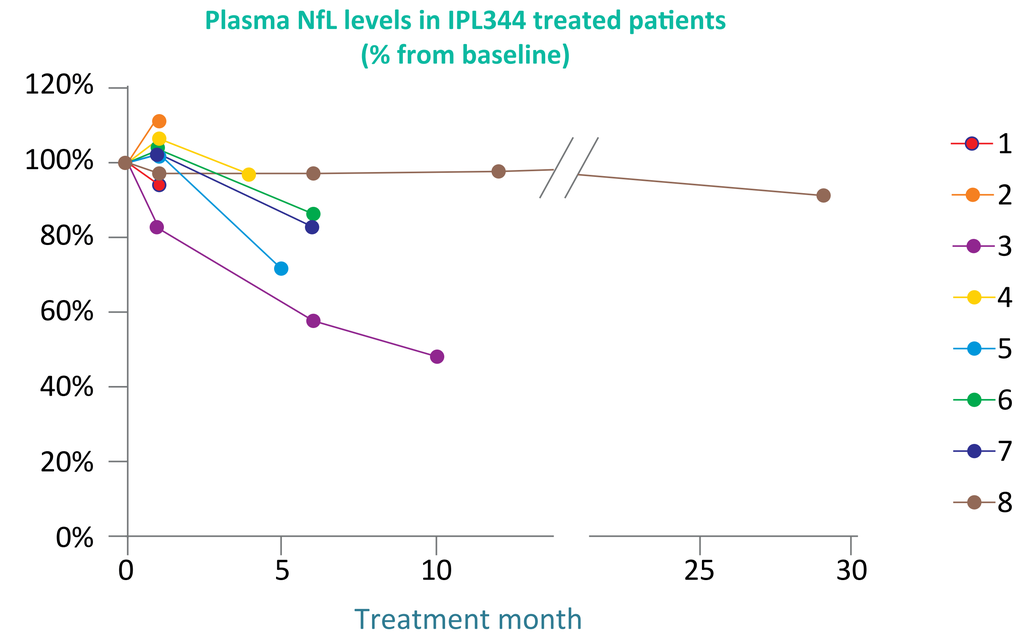
- We have previously reported key safety and efficacy results from this small (N=9) phase 1/2a clinical trial plus an additional participant who was treated under a compassionate protocol. Results indicated that IPL344 treatment is safe with signals of efficacy indicating a significantly reduced progression by 48-64% in ALS functional rating scale (ALSFRS-R) rate compared to historical controls.[8] Patients also had an increased (rather than reduced) body weight. Trends also indicated reduced SVC deterioration (44% reduction)[8] and a reduced risk of death (Hazard Ratio of 0.35) following treatment.
- Neurofilament light (NfL) levels are a biomarker for ALS progression (reflecting neuronal injury), and blood NfL levels correlate with the rate of disease progression and shorter lifespan.[9,12,13] In established disease, NfL levels remain relatively stable[9] or slightly increase (7-20%).[10,11] Decreases in blood NfL levels could indicate efficacy of potential therapeutic agents.

Methods

- In this open-label phase 1/2a study, 8 participants with rapidly progressing ALS (reduction of >0.55 points/month on the ALSFRS-R as detected prior to enrolment) were enrolled at the Hadassah Medical Center, Jerusalem, Israel. IPL344 was administered intravenously on a daily basis via a central venous catheter as home treatment and participants were followed up to 36 months (average IPL344 treatment 9.2 months).
- Functional assessments were performed using the ALSFRS-R at dose escalation, monthly until Month 6, and then bi- or tri-monthly thereafter. Individual ALSFRS-R slopes for each participant were compared against ΔFRS.
- For the 8 enrolled participants, blood sampling was performed prior to the study and during IPL344 treatment. Plasma NfL levels were quantified using the Simoa NF-light® assay (Quanterix).
- Associations between the percent reduction in plasma NfL levels and the reduction of ALSFRS-R slope following IPL344 treatment were evaluated using linear regression.

Results

Overall, NfL levels were either reduced or maintained across follow-up



** Patient 2 died shortly after enrolment*

NfL levels were reduced by a mean of 20% in patients treated more than 1 month* (P=0.02).

Patient	Time of last plasma sample (month)	ΔFRS	ALSFRS-R change/ month from initiation to last plasma sample	ALSFRS-R slope reduction after treatment vs. ΔFRS (points/month)	NfL compared to baseline (%)/% change
1	1	0.68	0.00	0.68	94.45 / -5.55
2	1	1.32	5.45	-4.14	112.26 / 12.26
3	10	2.11	1.01	1.10	48.08 / -51.92
4	4	0.97	0.90	0.07	97.4 / -2.6
5	5	0.34	0.20	0.14	72.16 / -27.84
6	6	0.54	0.48	0.06	86.66 / -13.34
7	6	1.28	1.09	0.18	82.87 / -17.13
8	29	0.36	0.17	0.19	91.55 / -8.45

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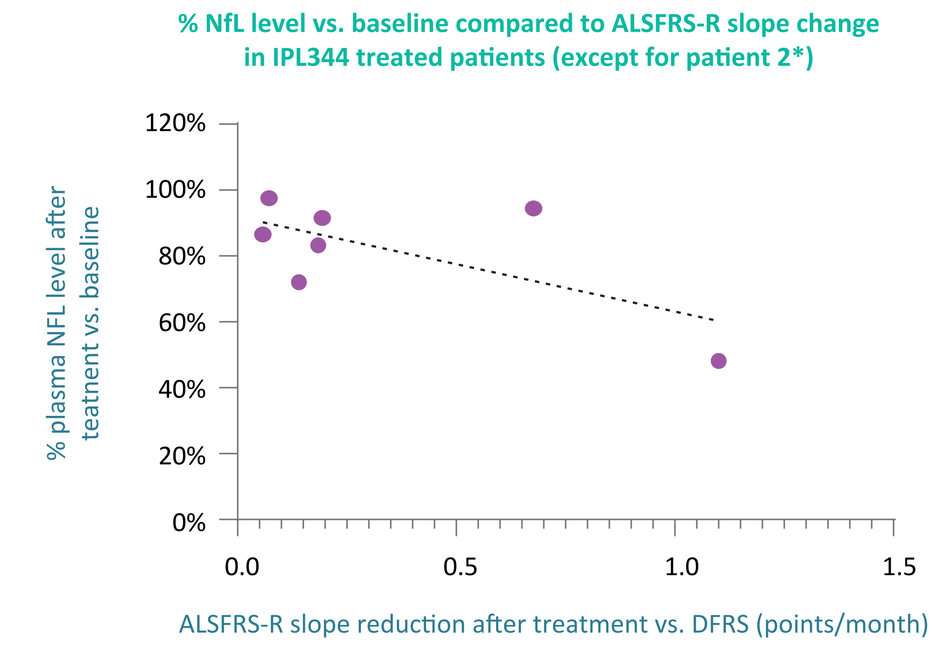
Correlation analyses indicated a linear relationship between the percent reduction in plasma NfL and the reduction in ALSFRS-R slope following IPL344 treatment (P= 0.02 for patients monitored >1M)



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Conclusions

- We have previously reported ALSFRS-R slope reductions of 48-64% in this small, first-in-human study compared to historical controls and 67% compared to individual pretreatment slope, a slope steeper than ΔFRS used in this analysis.[8]
- The reduction of NfL following IPL344 treatment and the correlation between NfL reduction and ALSFRS-R slope reduction, support the clinical data indicating that IPL344 merits further exploration as a potential disease modifying treatment.
- We hypothesize that NfL levels will be a useful biomarker to investigate efficacy in a planned controlled trial of IPL344.

References

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