A Small Molecule Targeting the Cause of Huntington's Disease: Investigation of SKY-0515 in Patients with HD

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Abstract

Huntington's disease (HD) is an inherited, autosomal dominant neurodegenerative disease caused by expansion of a cytosine, adenine, and guanine (CAG) repeat in the first exon of the huntingtin (HTT) gene. The expanded allele leads to the production of a toxic mutant huntingtin (mHTT) protein containing an extended polyglutamine tract, which contributes to mechanisms of neurodegeneration. Currently available treatments focus on symptom management, while there are no approved therapies that have been shown to halt or slow progression of this ultimately fatal disease.

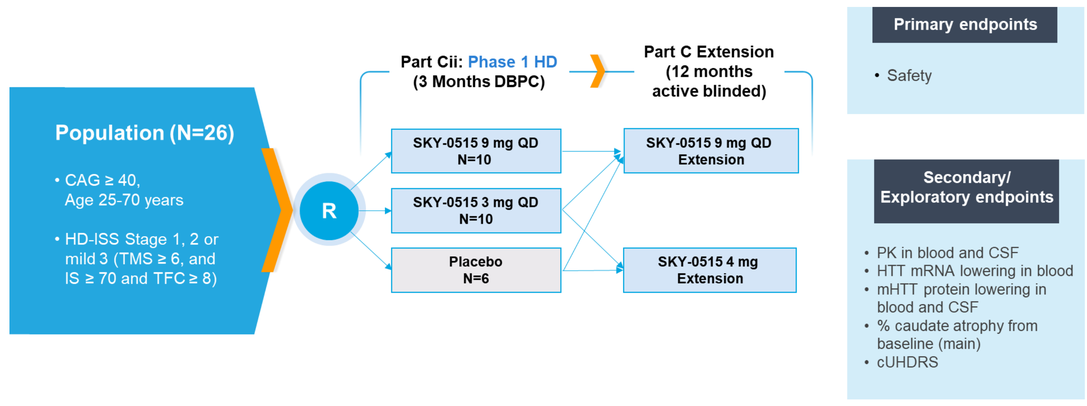
SKY-0515 is an investigational, orally available, brain-penetrant small molecule RNA splicing modulator developed using Skyhawk's novel RNA-splicing platform. SKY-0515 has the potential to provide disease modifying benefits to HD patients through the reduction of mHTT and Postmeiotic Segregation Increased 1 (PMS1) proteins. PMS1 contributes to somatic instability of the CAG repeat expansion, particularly in striatal neurons. Continued expansion of the repeats leads to increased cellular toxicity and is a key driver in time to disease onset and progression.

In a Phase 1 Part C, double-blind, placebo-controlled study investigating SKY-0515, HD patients received 3 mg and 9 mg doses for 84 days. HTT and PMS1 mRNAs in blood were lowered by 62% and 26%, respectively, at the high treatment dose (9mg). Similarly, levels of mHTT protein in blood were lowered by 62% in patients receiving the 9mg dose, and 29% in patients receiving the 3mg dose.

SKY-0515 was well tolerated in a dose range of 3mg to 9mg over a 9-12 month period, and plasma and CSF neurofilament light chain (NfL) levels remained generally stable. The pharmacokinetic properties of SKY-0515 in patients demonstrated a linear and dose proportional PK profile reaching steady state in 5-7 days, and favorable brain penetrance.

Investigation of the safety and efficacy of SKY-0515 is ongoing in an active blinded dose extension of the Phase 1 study and an enrolling Phase 2/3 studies worldwide. Early trends in clinical data from the Phase 1 extension after 9 months of dosing show the potential for disease stabilization.

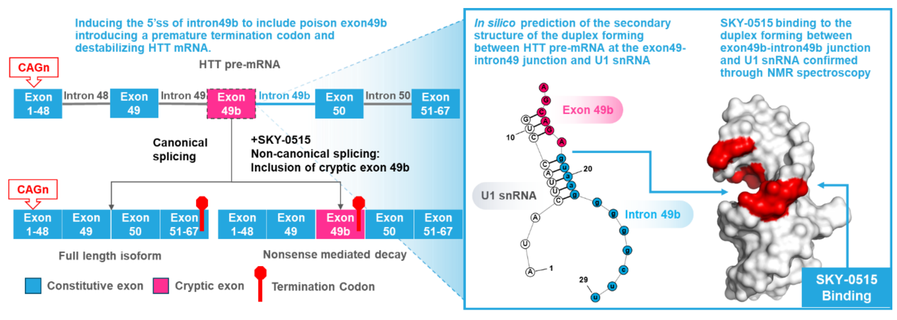
Clinical trial design for SKY-0515-001 Part C Phase 1 study in HD patients



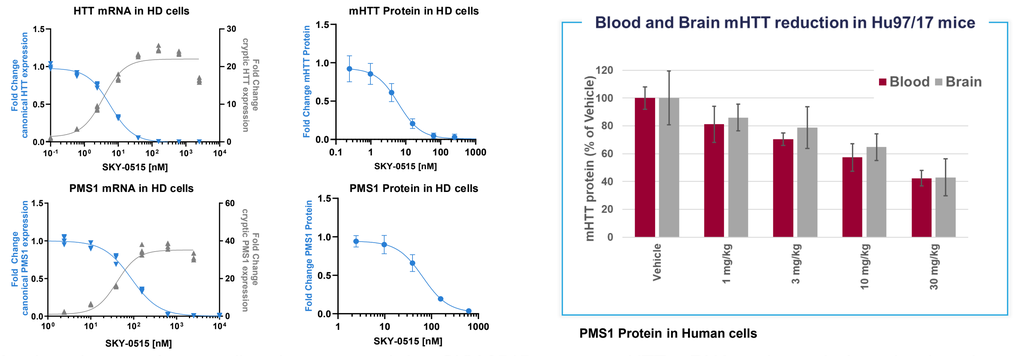
Baseline characteristics Mean ± SD	Placebo (n= 6)	SKY-0515 3mg (n=10)	SKY-0515 9mg (n=10)
Sex %M/F	50/50	60/40	40/60
Age	58.3 ± 9.3	55.9 ± 7.2	55.9 ± 6.3
CAG repeats	41.7 ± 0.8	42.1 ± 1.9	42.9 ± 2.4
cUHDRS	11.5 ± 1.0	12.8 ± 3.0	11.3 ± 2.8
TFC	12.3 ± 8.2	12.0 ± 1.6	12.1 ± 1.9

SKY-0515-001-C is an ongoing 15-month Phase 1 study in HD. Patients were randomized to 3 mg (N=10), 9 mg (N=10) or placebo (N=6) for 84 days, after which patients rolled over onto active drug, receiving either 4 mg or 9 mg (blinded) for an additional 12 months. Key enrollment criteria include genetic diagnosis of HD (CAG≥40), age 25-70 years and clinical baseline of TFC≥8, IS≥70, and TMS≥6, reflecting an HD-ISS disease stage 2 or mild stage 3.

SKY-0515 is a brain-penetrant small molecule splicing modulator, identified using the SKYSTAR® platform

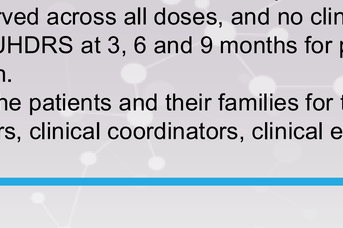


SKY-0515 is a selective modulator of HTT and PMS1 mRNA and protein in human cells



- In vitro pharmacology studies demonstrated that SKY-0515 promotes HTT mRNA and protein lowering in cultured human lymphocytes, with a limited number of off-target genes
- In Hu97/18 mice treated with SKY-0515 at 1, 3, 10 and 30 mg/kg once daily (QD) for 30 days, a concurrent and comparable dose-dependent decrease of mHTT protein compared to vehicle controls occurred in brain and peripheral blood

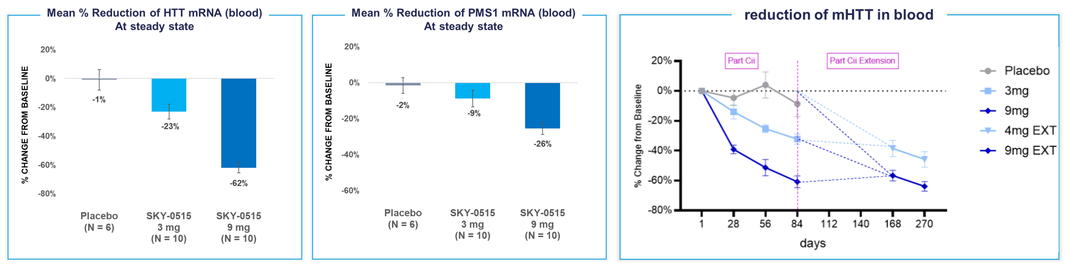
SKY-0515 demonstrates dose-proportional PK properties and is brain-penetrant in HD patients



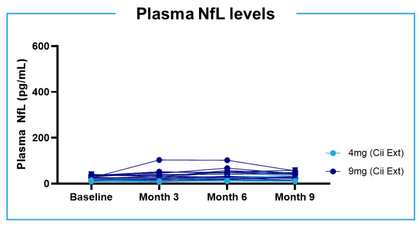
SKY-0515 exposure in HD patients CSF	Kp,uu
3 mg (N = 10)	0.84
9 mg (N = 7)	0.73

- Twenty HD patients were exposed to daily dosing of 3 mg (n=10) or 9 mg (n=10) SKY-0515 for 84 days. Plasma concentrations of SKY-0515 pre-dose on each of the days 1, 8, 15, 22, 28, 56 and 84 we analyzed. SKY-0515 shows an approximate 3-fold increase in exposure between 3 mg and 9 mg doses and reaches a plateau by day 8, showing stable concentration at all subsequent time points.
- SKY-0515 concentrations in CSF from HD patients demonstrated excellent brain penetration based on the ratio between free plasma and CSF drug concentration (Kp,uu).

Topline interim results from a Phase 1 Part C study in HD patients

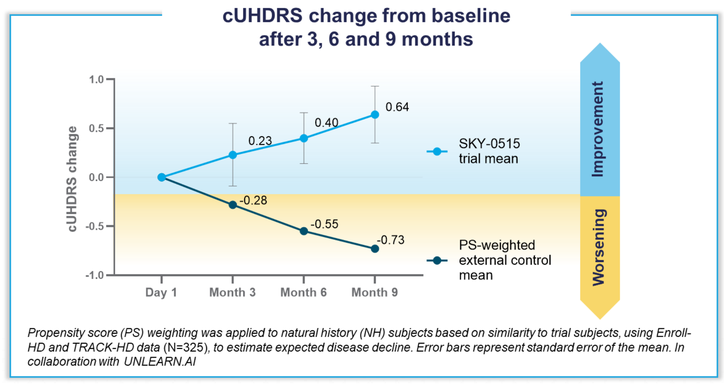


- After daily administration of SKY-0515 to participants with HD at doses of up to 9 mg/day for 84 days, mean HTT and PMS1 mRNA reductions of up to approximately 62%, and 26%, respectively, were observed.
- In Part Cii, increasing reductions in blood mHTT and total HTT proteins were observed at 15, 28, 56, and 84 days, reaching mean reductions of up to approximately 62% and 65% for mHTT and total HTT, respectively, at the 9 mg dose by Day 84. This further supports that approximately 35% of WT HTT protein remains.
- Moving into the Part Cii Extension, participants treated with 9 mg maintained similar suppression from Day 28 through Day 270 (Month 9). Participants switching from 3 mg to 4 mg showed incrementally an ~10% decrease, as expected.



- Across all arms, NfL levels remained generally stable from baseline through Day 270 (Month 9), with no consistent dose-related increases observed. While some inter-individual variability is present, including isolated higher values, there was no overall trend toward persistent increases in NfL with continued dosing. There have been no TEAEs suggestive of peripheral neuropathy in participants with HD during the 9 months treatment period.

- In Part Cii and Part Cii Extension, the majority of TEAEs were Grade 1 (mild) or Grade 2 (moderate) in intensity and the incidence rate was similarly distributed across all arms. There have been no clinically significant changes in labs, ECG, vitals.
- Severe/Serious adverse events included a prolonged headache (possibly drug related), an episode of psychosis (unlikely related to drug), a case of pneumonia and pleural effusion (unrelated to drug), and a case of abdominal pain and tooth infection (unrelated to drug). All events were resolved.



Propensity score (PS) weighting was applied to natural history (NH) subjects based on similarity to trial subjects, using Enroll-HD and TRACK-HD data (N=325), to estimate expected disease decline. Error bars represent standard error of the mean. In collaboration with UNLEARN.AI

- Patients receiving SKY-0515 continuously in the Part C of the Phase 1 clinical trial (n=17, placebo patients excluded), showed early trends toward improvement in the cUHDRS relative to baseline. At nine months, in a pooled analysis, this improvement is +0.64 points compared to an expected worsening at nine months in the cUHDRS in symptomatic patients of -0.73 points, based on natural history propensity score weighting methods using ENROLL-HD and TRACK-HD data. One patient was excluded due to significant intercurrent events affecting her HUHDRS assessments.

Conclusion

- SKY-0515 aims to be a disease-modifying therapy for the treatment of Huntington's disease, by lowering the amount of mHTT and PMS1 proteins that are linked to the cause of the disease. SYK-0515, is a daily pill that is taken by mouth and works by lowering the amount of total HTT and PMS1 mRNA, leading to the reduction of mHTT and PMS1 proteins.
- Preclinical and clinical data demonstrate that SKY-0515 is dose-proportionally distributed in the body and has excellent brain CNS penetration. In HD patients, SKY-0515 reaches stable levels in about a week.
- In the Phase 1 Part C study in HD patients, SKY-0515 has demonstrated target engagement through the lowering of HTT mRNA and protein by up to approximately 62% at the 9 mg dose, and PMS1 mRNA by up to approximately 26% at the 9 mg dose.
- SKY-0515 has been well-tolerated in patients receiving treatment up to 9 months. No significant safety signal have been identified across all explored doses to date. Furthermore, no consistent increases in NfL have been observed across all doses, and no clinical signs of nerve damage have been identified.
- Average cUHDRS at 3, 6 and 9 months for patients who received SKY-0515 once a day continuously for at least 9 months compared to a matched natural history cohort show encouraging trends towards disease stabilization.
- We thank the patients and their families for their participation in these trials and the individuals who were instrumental in the conduct and the collection of data, particularly the principal investigators, supporting investigators, clinical coordinators, clinical evaluators and study coordinators.