Investigation of SKY-0515 in Patients with Huntington's Disease: Interim Results of a Phase 1/2 Study

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Abstract*

*At the time of presentation, new 12-month data was available. Therefore, this poster presents interim data up to 12 months. Data presented here is subject to change as the study is ongoing.

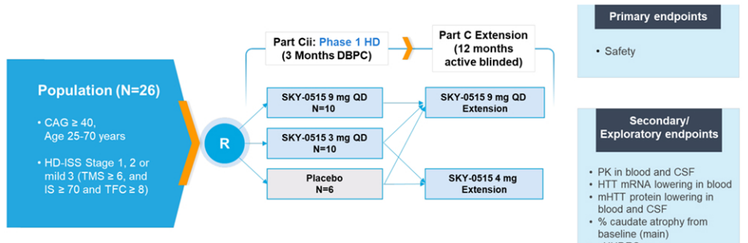
Introduction: Huntington's disease (HD) is a neurodegenerative disorder caused by a trinucleotide (CAG) repeat expansion in the huntingtin (HTT) gene, resulting in a toxic mutant huntingtin (mHTT) protein. Disease onset and progression correlates with the number of inherited CAG repeats and the rate of somatic CAG expansion. SKY-0515 has the potential to provide disease modifying benefits through reduction of disease-linked proteins, mHTT and PMS1, a key driver of somatic expansion. The study aims to evaluate safety, PK/PD and efficacy of SKY-0515, an orally available, brain-penetrant small molecule RNA splicing modulator, in HD patients.

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

Results: 12-month interim results in participants who continuously received SKY-0515 show positive trends in HD efficacy outcomes compared to expected natural history disease progression. In HD participants treated with SKY-0515, early signs of disease stabilization are observed in components of the cUHDRS, including function (TFC=+0.07 points), motor (TMS=-2.00 points), and cognition (Stroop=+3.44 points). SKY-0515 has been well tolerated up to 12 months.

Conclusion: These findings support further clinical evaluation of SKY-0515 as a potential disease-modifying therapy for HD. Confirmatory Phase 2/3 studies (FALCON-HD) are now ongoing.

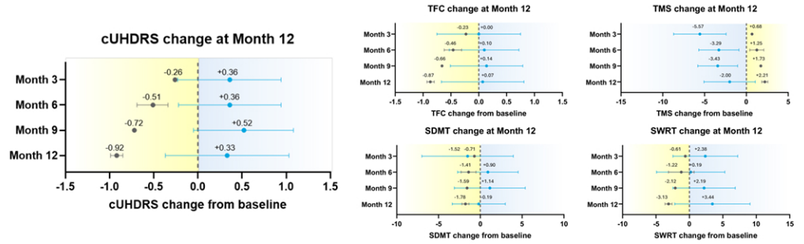
SKY-0515-001 Part C study in HD Patients



Baseline Characteristics Mean ± SD	SKY-0515 4mg (n=7)	SKY-0515 9mg (n=16)
Sex %M/F	57/43	38/62
Age	52.3 ± 8.8	57.8 ± 6.4
CAG repeats	42.4 ± 1.7	42.6 ± 2.1
CAP score	453.5 ± 64.4	510.2 ± 88.1
cUHDRS	12.1 ± 3.1	11.8 ± 2.3
TFC	11.4 ± 1.8	11.8 ± 1.7

- HD Participants were randomized to 3 mg (N=10), 9 mg (N=10) or placebo (N=6) for 84 days, after which participants rolled over onto active drug, receiving either 4 mg or 9 mg (blinded) for an additional 12 months.
- Overall baseline characteristics of the participants in each arm were similar. Based on the CAP scores, the 9 mg cohort was represented by more severe participants compared to 4 mg cohort.

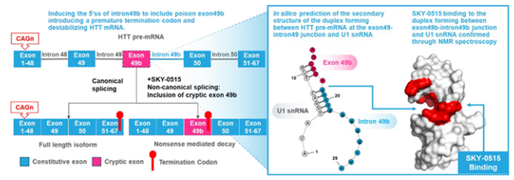
Interim Clinical Results from Phase 1/2 in HD Patients



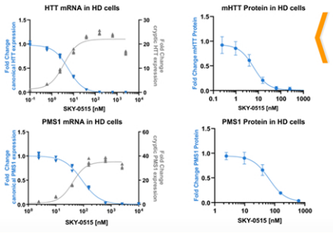
- SKY-0515-001-treated participants maintained cUHDRS scores over 12 months, diverging from the decline predicted by matched natural history controls at every assessed timepoint. The observed separation between the treated arm and the propensity score weighting (PSW) natural history reference — reaching a Δ=+1.25 at the primary 12-month endpoint — is suggestive of a disease-modifying effect that stabilizes multiple disease domains in manifest Huntington's disease.
- The cUHDRS subcategories Total Motor Score (TMS), Total Functional Capacity (TFC), and Stroop Word Reading Test (SWRT) individually showed disease stabilization relative to baseline across all timepoints, with statistically significant separation from estimated natural history at various timepoints up to Month 12.

cUHDRS and subcategory scores at 3, 6, 9 and 12 months, for participants receiving SKY-0515 once-daily. Data show change from baseline (mean ± 95% CI) for pooled 4 mg and 9 mg treatment groups and includes additional participants who received placebo for three months prior to switching to active treatment (Day 1 to Month 9: n=21, Month 12: n=15). Propensity score weighting was performed using ENROLL-HD, CREST-E and CARE2 datasets. Months 3 and 9 estimates for propensity score (PS) methods are extrapolated. Month 6 used the CREST-E and CARE2 clinical trials to construct the external control arm (ECA) for the PS methods. Month 12 used ENROLL-HD natural history study to construct the ECA for the PS methods. Two participants with significant non-HD-related comorbidities and/or receipt of prohibited medications were excluded based on investigator assessment. Based on interim analysis of May 7th, 2026. Data is based on interim analysis and is subject to change.

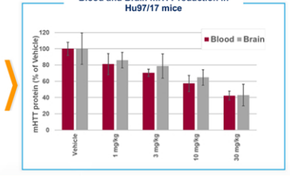
SKY-0515 is a brain-penetrant small molecule RNA splicing modulator, identified using the SKYSTAR® platform



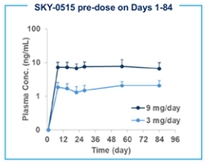
SKY-0515 is a selective modulator of HTT and PMS1 mRNA and protein in human cells



- In vitro pharmacology studies demonstrated that SKY-0515 promotes HTT and PMS1 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

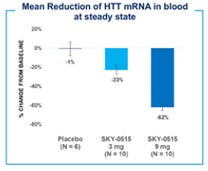


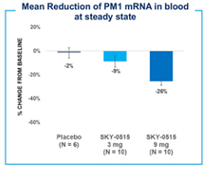
PK/PD Results



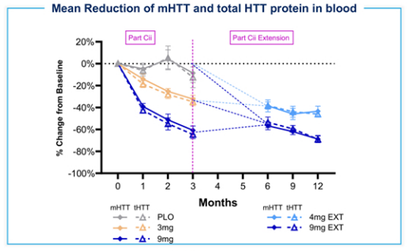
SKY-0515 exposure in HD patients CSF	Kp,uu
3 mg (N = 10)	0.84
9 mg (N = 7)	0.73

- Twenty HD participants 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 were 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 participants demonstrated excellent brain penetration based on the ratio between free plasma and CSF drug concentration (Kp,uu).





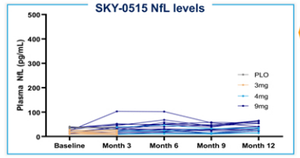
- After daily administration of SKY-0515 to participants with HD at doses of up to 9 mg/day for 3 months, mean HTT and PMS1 mRNA reductions of up to approximately 62%, and 26%, respectively, were observed.



- In Part Cii, increasing reductions in blood mHTT and total HTT (tHTT) proteins were observed at months 1, 2 and 3, reaching mean reductions of up to ~62% and ~65%, respectively, at the 9 mg dose at month 3. Over the following 9 months in Part Cii Extension, the reduction of mHTT and tHTT stabilized, with a maximum mean reduction at the 9mg dose of ~69% for both mHTT and tHTT, supporting the preservation of ~30% of WT HTT protein.

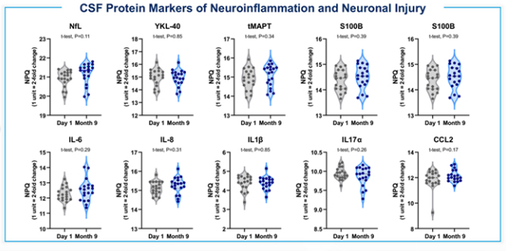
Safety

- SKY-0515 has been well tolerated. In healthy participants (SKY-0515-001 Parts A and B), no severe or serious adverse events were observed at single doses up to 16 mg and multiple doses up to 9 mg/day over 14 days; all treatment-emergent adverse events were mild or moderate, the most common being headache.
- In HD participants, 12 months of daily dosing at up to 9 mg has been well tolerated with no new safety signal emerging. In SKY-0515-001 Part Cii and its Extension, the most common related treatment-emergent adverse events in HD participants (reported by two or more participants) were headache, diarrhea, and nausea, with the majority of events mild or moderate in severity.



- Plasma NfL (up to 12 months) and CSF NfL (up to 9 month) has been generally stable.
- No serious adverse events were assessed as related to SKY-0515. In SKY-0515-001 Part Cii and its Extension, three participants experienced at least one serious adverse event (Grade 3 mania; Grade 3 tooth infection; and Grade 3 pneumonia and pleural effusion in one participant), none considered related to study drug

- Ten CSF protein markers of neuroinflammation and neuronal injury were measured at Day 1 and Month 9 by NULISA (NULISA Protein Quantification; NPQ = log2-normalised NGS counts). All 10 markers remained stable, including: YKL-40/CHI3L1 (astrocyte activation; p=0.85), CSF NfL/NEFL (axonal injury; p=0.11), S100B (glial injury; p=0.39), MAPT (neurodegeneration; p=0.53), CCL2/MCP-1 (monocyte recruitment; p=0.17), and five pro-inflammatory cytokines (IL-6, IL-8, IL-1B, IL-17A, TNF; all p>0.23).



Conclusions

- 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 linked to the cause of the disease. SYK-0515 is a once daily oral small molecule RNA splicing modulator that lowers the amount of HTT and PMS1 mRNA leading to the reduction of HTT, including mutant HTT, and PMS1 proteins.
- Preclinical and clinical data demonstrate that SKY-0515 is dose-proportionally distributed in the body, including the brain. In HD patients, SKY-0515 reaches stable levels in about a week and is eliminated in ~1 week after discontinuing drug (data not shown).
- In the Phase 1/2 study in HD patients, SKY-0515 has demonstrated remarkable dose-dependent target engagement with mean reductions of up to 69% for mutant HTT protein, and 26% for PMS1 mRNA at the 9 mg dose.
- SKY-0515 has been well-tolerated in participants receiving treatment up to 12 months. No significant safety signals have been identified across all explored doses to date. No consistent increases in NfL have been observed across all doses. A panel of neuroinflammation and neuronal injury markers shows no significant increases at 9 months in CSF.
- In a pooled analysis of HD participants compared to propensity score weighted natural history controls, average cUHDRS and its subcategories show trends towards disease stabilization up to 12 months.

Skyhawk Therapeutics is deeply thankful to all of the patients and their families for their participation in SKY-0515 trials, and the individuals who are instrumental in the conduct and the collection of data, particularly the principal investigators, supporting investigators, study coordinators, clinical evaluators, and supporting CROs.