Press Release

Skyhawk Therapeutics Announces Final Fifteen-Month Results from Phase 1/2 Clinical Trial of SKY-0515 in Huntington's Disease Patients

- *The fifteen-month dataset represents the final analysis from the Phase 1/2 study*
- *At the Month 15 primary timepoint, SKY-0515-treated patients (n=15) showed a +1.59-point difference in Composite Unified Huntington's Disease Rating Scale (cUHDRS) change from baseline versus overlap-weighted external natural history control*
- *Differences favoring SKY-0515 were statistically significant across all four cUHDRS components – Total Functional Capacity, Total Motor Score, Symbol Digit Modalities Test and Stroop Word Reading Test – and cUHDRS differences favored SKY-0515 at every prespecified timepoint in the study*
- *SKY-0515 has shown consistent average reductions in mutant huntingtin protein (mHTT) throughout the study of more than 60%*
- *SKY-0515 has shown consistent average reductions in PMS1 mRNA of more than 25%*
- *The Company's Phase 1/2 program and global Phase 2/3 FALCON-HD 004-ANZ + 004-WW pivotal program for Huntington's disease now have enrolled over 200 patients across twenty trial sites in ten countries.*

BOSTON, Mass., September 15, 2026 - Skyhawk Therapeutics, Inc., a clinical-stage biotechnology company developing novel small molecule therapies designed to modulate RNA targets, today announced final fifteen-month results from its Phase 1/2 clinical trial evaluating SKY-0515, an investigational oral treatment for Huntington's disease (HD).

The Phase 1/2 patient study is a randomized, double-blind, placebo-controlled parallel-group study evaluating two dose levels of SKY-0515 in patients over twelve weeks, followed by a twelve-month blinded Extension period during which all participants receive active treatment at either a low or high dose (4mg or 9mg), with the majority of patients on the 9 mg dose.

At Month 15, the primary timepoint, patients treated with SKY-0515 improved on the cUHDRS by an average of 0.94 points from where they started, while a comparison group of untreated patients from the Enroll-HD natural history database — statistically weighted to resemble the treated group on key baseline characteristics — declined by an average of 0.65 points. The gap between the two groups was 1.59 points (95% CI: 1.09, 2.09; p<0.001).

SKY-0515 patients also did better than the comparison group on each of the four measures that make up the cUHDRS: daily function (Total Functional Capacity, +0.98 points), movement (Total Motor Score, −9.38 points, where a lower score is better), processing speed (Symbol Digit Modalities Test, +4.15 points) and reading speed (Stroop Word Reading Test, +4.18 points). All differences were statistically significant.

Table 1. Change from baseline at Month 15 in cUHDRS and its components, SKY-0515 versus overlap-weighted external control

Endpoint	Treated LS Mean (SE), M15 (n=15)	External Control LS Mean (SE), M15	Treatment Difference	95% CI	p-value
cUHDRS	+0.94 (0.42)	-0.65 (0.27)	+1.59	1.09, 2.09	**<0.001**
TFC	+0.38 (0.43)	-0.60 (0.26)	+0.98	0.34, 1.61	**0.003**
TMS	-6.85 (1.02)	+2.53 (0.59)	-9.38	-11.58, -7.19	**<0.001**
SDMT	+4.63 (1.60)	+0.48 (0.98)	+4.15	1.04, 7.25	**0.009**
SWRT	+3.55 (1.62)	-0.63 (0.98)	+4.18	0.55, 7.80	**0.024**

CI = confidence interval; SE = standard error.

The same pattern held throughout the study. At every scheduled checkpoint, SKY-0515 patients were doing better on the cUHDRS than the comparison group: 0.66 points at Month 3, 0.78 points at Month 6, 1.04 points at Month 9, 0.79 points at Month 12 and 1.59 points at Month 15. The difference was statistically significant from Month 9 onward.

On average, SKY-0515-treated patients' cUHDRS scores held at or above their baseline level at every assessment through Month 15, while the external comparison group's average score declined from Month 6 onward.

Table 2. Change from baseline in cUHDRS by timepoint, SKY-0515 versus overlap-weighted external control

Timepoint	Treated LS Mean (SE)	Treated Patients	External Control LS Mean (SE)	Treatment Difference	95% CI	p-value
Month 3	+0.70 (0.30)	n=24	+0.05 (0.47)	+0.66	-0.33, 1.64	0.191
Month 6	+0.47 (0.39)	n=20	-0.31 (0.21)	+0.78	-0.00, 1.56	0.051
Month 9	+0.70 (0.38)	n=20	-0.34 (0.23)	+1.04	0.39, 1.70	**0.002**
Month 12	+0.29 (0.44)	n=18	-0.50 (0.26)	+0.79	0.11, 1.48	**0.023**
Month 15	+0.94 (0.42)	n=15	-0.65 (0.27)	+1.59	1.09, 2.09	**<0.001**

CI = confidence interval; SE = standard error. See footnote[1] for data analysis discussion.

SKY-0515 has shown consistent average reductions of more than 60% mutant huntingtin protein (mHTT) and 25% PMS1 mRNA in patients throughout the study. Mutant huntingtin is the primary protein responsible for HD pathology, while PMS1 is a key driver of somatic CAG repeat expansion associated with disease progression.

SKY-0515 has demonstrated excellent central nervous system exposure and has been generally well tolerated across all dose levels studied through fifteen months of treatment, with no treatment-related SAE.

“Skyhawk’s Phase 1/2 results are extremely encouraging clinical data. A 1.59-point cUHDRS difference versus a rigorously weighted natural history control at fifteen months is exactly the type of signal the field looks for in early studies of a potentially effective therapeutic agent. The consistent effects on function, motor and cognitive measures need to be further studied in ongoing placebo-controlled studies but it is an exciting step forward for HD and the program,” said Dr. Samuel Frank, Director of the Huntington’s Disease Society of America Center of Excellence at Beth Israel Deaconess Medical Center. “SKY-0515’s dual reduction of mHTT and PMS1 addresses two core pathogenic mechanisms of Huntington’s disease. If these findings are confirmed in the ongoing Phase 2/3 FALCON-HD pivotal program, the impact on people living with HD across the world could be profound.”

“For almost two decades, I have fought as an advocate for Huntington’s disease patients, bearing witness to countless heartbreaking trial setbacks that have let our families down. To finally see results like these—patients experiencing improvements in function, movement, and cognition — is what we have been hoping for and waiting for,” said Katie Jackson, Chief Executive Officer of Help 4 HD International. “What makes SKY-0515 especially exciting is that it is a pill, taken once a day at home.

[1] Skyhawk Therapeutics, Inc. 'Phase 1 cUHDRS LS mean change from baseline vs. external control at 3, 6, 9, 12 and 15 months, estimated via ANCOVA, for patients receiving SKY-0515 once-daily. Nominal timepoints are anchored to each participant's first dose of SKY-0515 (Day 1 to Month 3: n=24, Month 6: n=20, Month 9: n=20, Month 12: n=18, Month 15: n=15). Participants received placebo, 3 mg or 9 mg during the first 3 months; afterwards, all participants received 4 mg or 9 mg following Extension-phase randomization. Overlap-weighted propensity score weighting was performed using Enroll-HD, 2CARE and CREST-E datasets (Month 3: n=21, Month 6: n=180, Month 9: n=588, Month 12: n=3569, Month 15: n=1337),' September 2026.

Note: The Month 15 decline in participants partly reflects study design, as the 12-month Extension period caps SKY-0515 exposure at 12 months for the participants who initially received 3 months of placebo. The primary analysis includes all eligible participants with an available Month 15 cUHDRS assessment. Per the study's statistical analysis plan, a small number of participant-timepoints were excluded following a qualifying intercurrent event — onset of an unrelated medical condition, initiation of a medication that could confound assessment of treatment effect, or a change in background Huntington's disease therapeutic intervention.

Every step forward in HD matters and we celebrate all of them, but a therapy that is noninvasive and does not require care in a specialized center has the potential to reach so many more patients – in rural communities, in families who can't travel, and across the world where care is hard to come by.

My husband didn't get a treatment in time. I am hopeful that my children and the children of thousands of families like ours will. We are the generation of change, and Skyhawk's drug, if these promising results are fully confirmed in future trials, is what change looks like."

"The completion of this Phase 1/2 study with SKY-0515, showing statistically significant clinical benefit across every cUHDRS component, is a powerful demonstration of what Skyhawk's SKYSTAR® platform can achieve: a daily pill, taken at home, that modifies RNA splicing to lower disease-causing proteins in the CNS and systemically throughout the body," said Sergey Pauskin, Co-founder and Head of R&D at Skyhawk. "We are applying the same platform to a series of challenging neurological diseases now advancing toward human trials, and the data from SKY-0515 confirms that the possibilities of extraordinary novel drugs generated by Skyhawk's SKYSTAR platform are very exciting."

Huntington's disease is a rare, hereditary, and ultimately fatal neurodegenerative disorder affecting more than 40,000 symptomatic individuals in the United States, with hundreds of thousands impacted worldwide. There are currently no approved therapies shown to slow or halt disease progression.

SKY-0515 is an orally administered investigational small molecule RNA splicing modifier developed using the company's proprietary SKYSTAR platform. SKY-0515 is designed to reduce both mHTT and PMS1 proteins.

The worldwide Phase 2/3 FALCON-HD-004-WW pivotal study is now active across more than ten countries and twenty clinical sites. SKY-0515's Phase 1/2 and FALCON-HD pivotal studies have now enrolled more than 200 patients.

Skyhawk expects to advance additional novel therapies targeting rare neurological diseases with no approved disease-modifying treatment into clinical development by the end of 2027.

About the Fifteen-Month Analysis

Phase 1/2 cUHDRS LS mean change from baseline versus external control at 3, 6, 9, 12 and 15 months, and cUHDRS subcomponents LS mean change from baseline versus external control at 15 months, were estimated via overlap-weighted ANCOVA for patients receiving SKY-0515 once daily. Nominal timepoints are anchored to a participant's first dose of SKY-0515 (Day 1 to Month 3: n=24, Month 6: n=20, Month 9: n=20, Month 12: n=18, Month 15: n=15). Overlap-weighted propensity score weighting was performed using Enroll-HD, 2CARE and CREST-E datasets (Month 3: n=21, Month 6: n=180, Month 9: n=588, Month 12: n=3569, Month 15: n=1337).

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About SKY-0515's Phase 1/2 Clinical Program

SKY-0515's Phase 1/2 clinical trial is a first-in-human study designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of SKY-0515 in healthy volunteers and patients with early-stage Huntington's disease (HD).

The trial consists of three parts. Parts A and B evaluated SKY-0515 in Healthy Volunteers. Part C is a randomized, double-blind, placebo-controlled parallel-group study evaluating two dose levels of SKY-0515 in patients with early-stage HD (HD-ISS Stage 1, Stage 2, or mild Stage 3) over 84 days, followed by a twelve-month blinded Extension period during which all participants receive active treatment at either a low or high dose.

Study assessments include measurements of mutant HTT protein, PMS1 mRNA, and cUHDRS. Enrollment and treatment in the Phase 1/2 study are complete, and the fifteen-month analysis represents the final clinical dataset from the study.

About SKY-0515's Phase 2/3 FALCON-HD (004-ANZ and 004-WW) Pivotal Program

The FALCON-HD pivotal program (NCT06873334 and NCT07378644) is a randomized, double-blind, placebo-controlled, dose-ranging study evaluating the pharmacodynamics, safety and efficacy of SKY-0515.

Eligible patients receive once-daily oral SKY-0515 at one of three dose levels or placebo.

FALCON-HD 004-ANZ enrolled 144 participants with Stage 2 and Stage 3 HD across sites in Australia and New Zealand. Enrollment is complete.

FALCON-HD 004-WW plans to enroll approximately 600 participants with Stage 2 and Stage 3 HD across more than 40 sites worldwide and is actively recruiting.

Additional information regarding FALCON-HD, including participating sites and eligibility criteria, is available at ClinicalTrials.gov and www.FALCON-HD.com.

About Skyhawk Therapeutics

Skyhawk Therapeutics is a clinical-stage biotechnology company leveraging its proprietary SKYSTAR® platform to discover and develop small molecule RNA-modulating therapies for the world's most intractable diseases. For more information, visit www.skyhawktx.com.

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