



Phase 1/2 data readout of SKY-0515 in Huntington's disease: Month 15 update

October 2026

Developing small-molecule genetic medicines to revolutionize treatment for patients worldwide



Skyhawk's lead drug candidate, SKY-0515, is a small-molecule RNA modulator being developed for Huntington's disease (HD).

Successful Phase 1/2 (Data Sept. 2026)

- Deep target reductions

60-70%
HTT

25%+
PMS1
- Statistically significant results on endpoints cUHDRS, TFC, TMS, SDMT, and SWRT
- Favorable safety profile for once-daily dosing through Month 15

Registrational FALCON-HD Study (ongoing)

- Placebo-controlled study with >600 patients, including >200 enrolled to date
- Enrollment rates 5x peer average signal significant unmet need, interest in once-daily oral pill
- U.S. sites to be activated by Q4 2026

Broad Pipeline for Growth

- Second neuro program clinical entry expected Q2 2027
- Pipeline contains 10 unique assets with additional clinical entries expected in 2028+

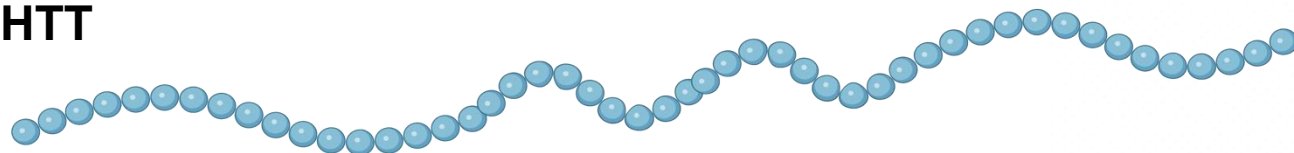
Platform Validation: Skyhawk has received >\$600 million in cash to date from over 10 large pharma collaborations



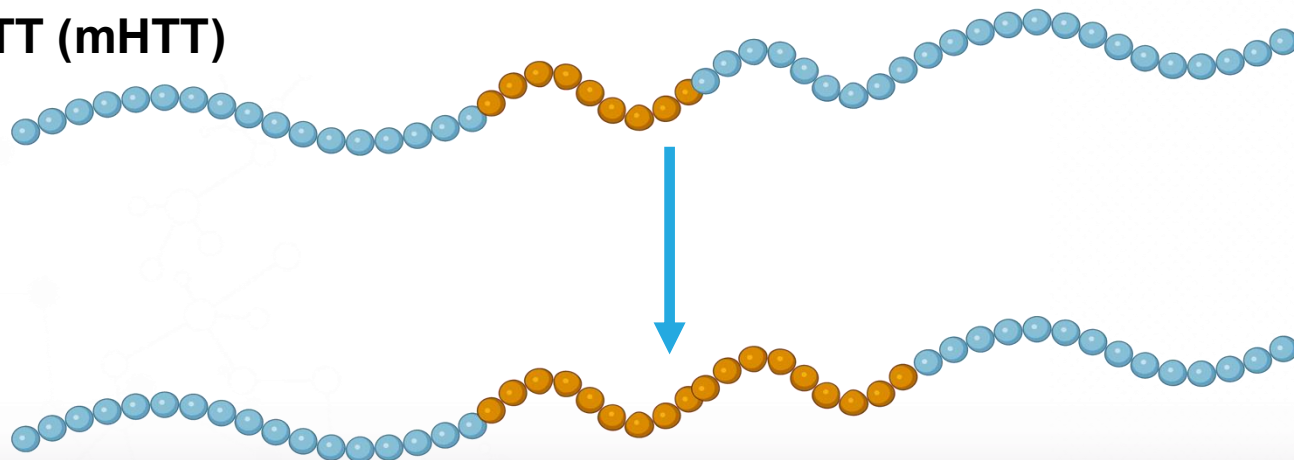
Huntington's disease is a progressive neurodegenerative disease with no approved disease-modifying therapies

Huntington's Disease (HD) is a rare genetic disease caused by repeated "C-A-G" sequences in huntingtin (HTT) mRNA.

Wildtype HTT



Mutant HTT (mHTT)



Accumulation of >35 repeats leads to symptomatic disease

~135K

Global, symptomatic
HD patients

~650K

Individuals worldwide with
50% risk of developing HD

15-20

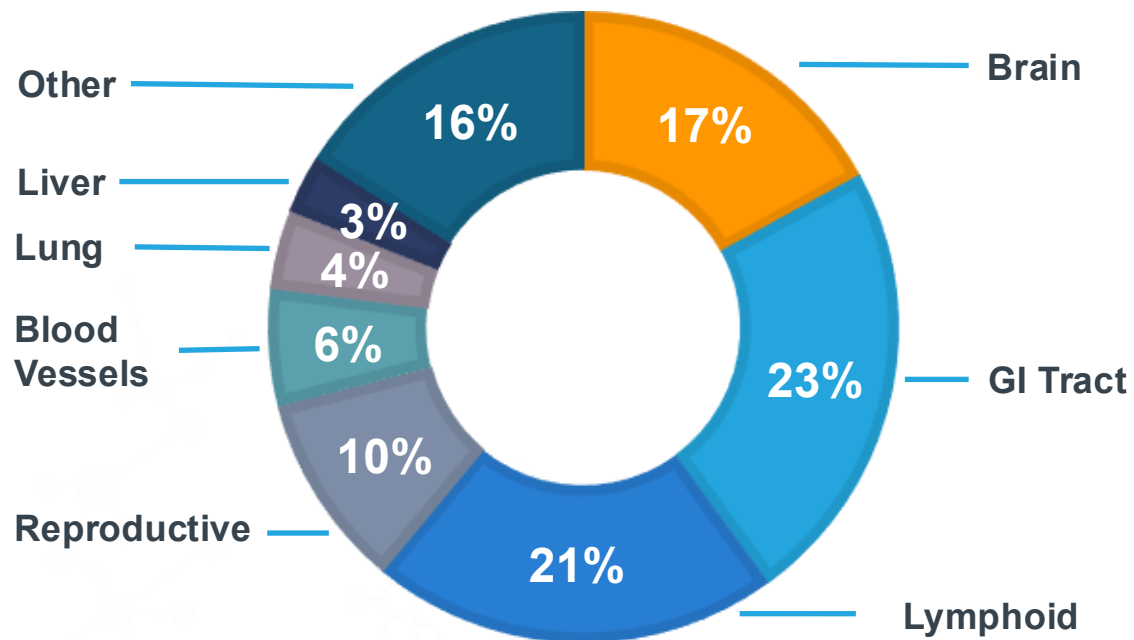
years life expectancy
after diagnosis

0

approved disease-modifying
treatments

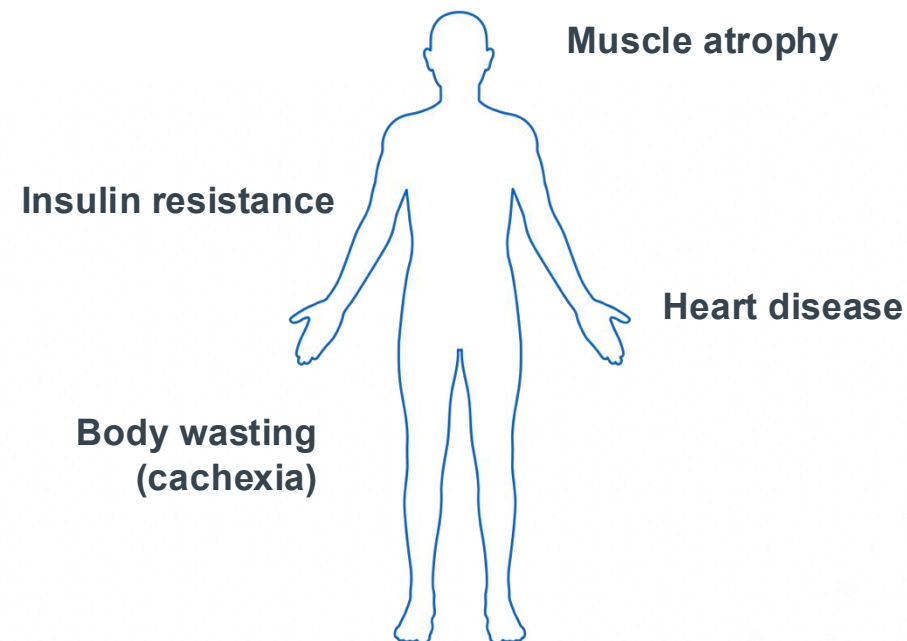
Neurological symptoms are accompanied by whole-body ailments, reflecting systemic distribution of HTT

Only 17% of HTT expression occurs in brain tissues



Source: Human Protein Atlas.

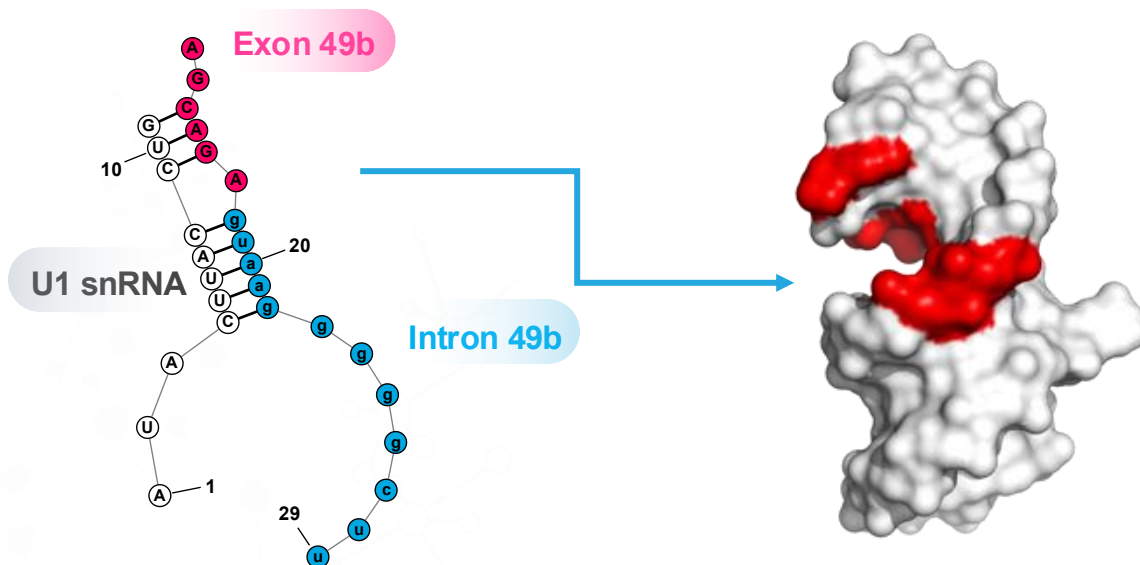
Whole-body symptoms of HD include:



An ideal treatment is a small molecule delivered broadly and systemically, to address mHTT expressed throughout the body.

SKY-0515 is a small-molecule genetic medicine designed to overcome limitations of gene therapy, nucleic acid approaches

SKY-0515 is a systemically-delivered, brain-penetrant small molecule designed to interact directly with HTT mRNA.



A profile with best-in-disease potential:

- **Efficacy:** SKY-0515 drove **72% mHTT reduction at RP3D**, supporting hypothesis for selective and systemically-delivered small molecule
- **Convenience:** Oral daily therapy provides **noninvasive treatment** option, drives faster study enrollment
- **Global access:** Lower manufacturing and logistics costs vs. biologics or genetic medicines make small molecules **global options**



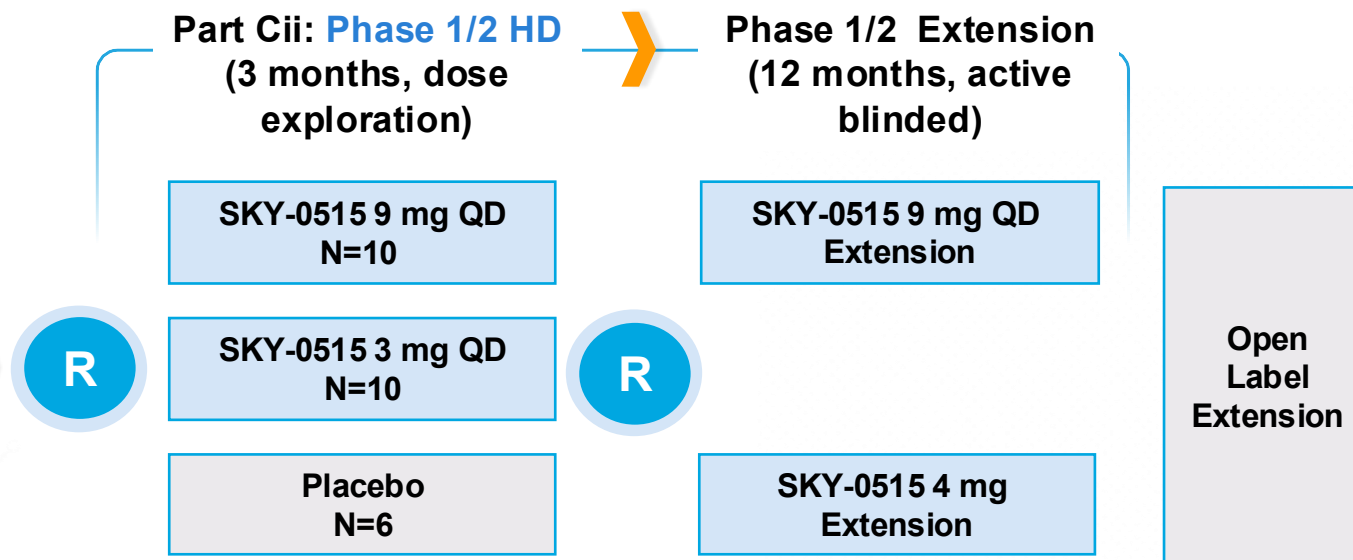
Phase 1/2 Study of SKY-0515 in Huntington's disease (HD)

Biomarker Data

SKY-0515's Phase 1/2 study is designed to evaluate safety, determine RP3D, and provide early efficacy data to Month 15

Population (N=26)

- CAG > 40,
Age >25-70 years
- HD-ISS Stage 1, 2 or
mild 3 (TMS > 6, and IS
≥ 70 and TFC ≥ 8)



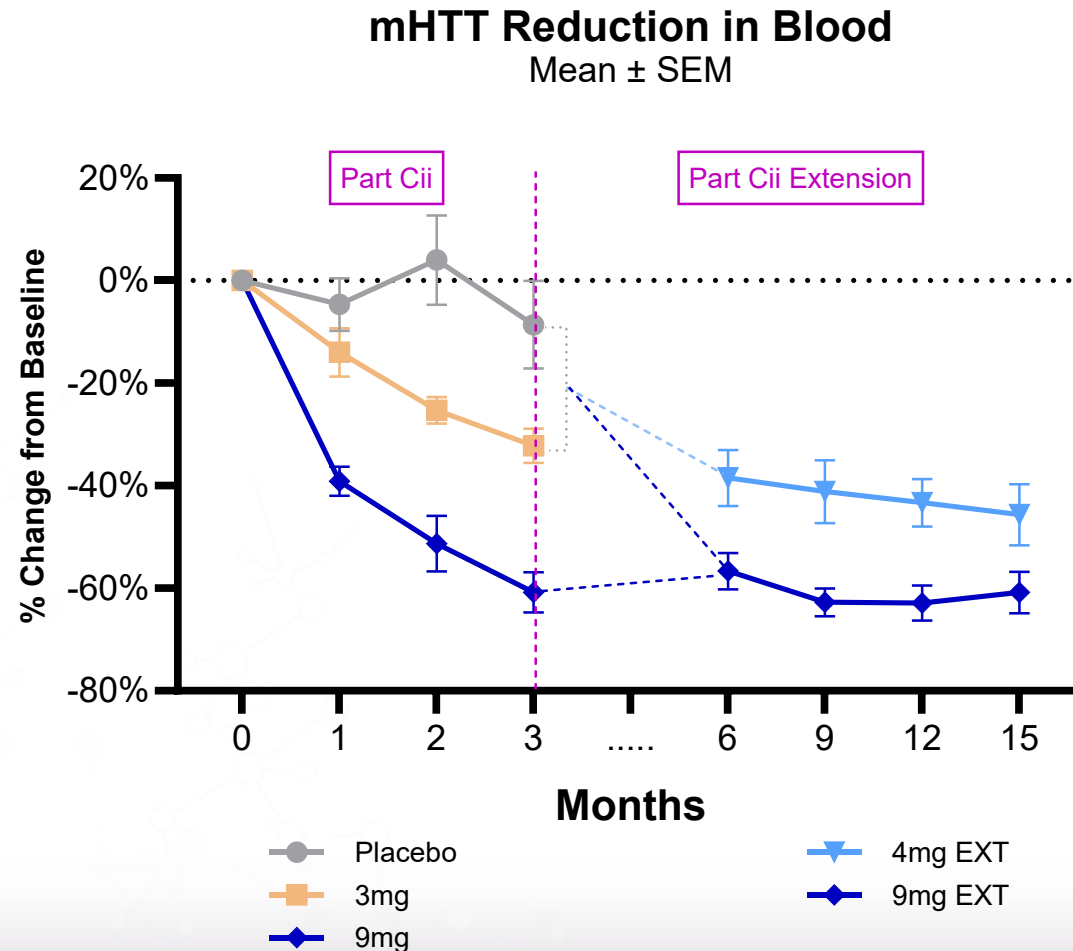
Primary endpoints

- Safety

Secondary / Exploratory endpoints

- PK in blood and CSF
- HTT mRNA lowering in blood
- mHTT protein lowering in blood and CSF
- % caudate atrophy from baseline (main)
- cUHDRS

SKY-0515 achieved deep reductions in serum mHTT protein and HTT mRNA at RP3D dose levels, with deepening responses at 4mg and 9mg



Decrease in HTT mRNA in patient blood

3mg

-39%

4mg

-45%

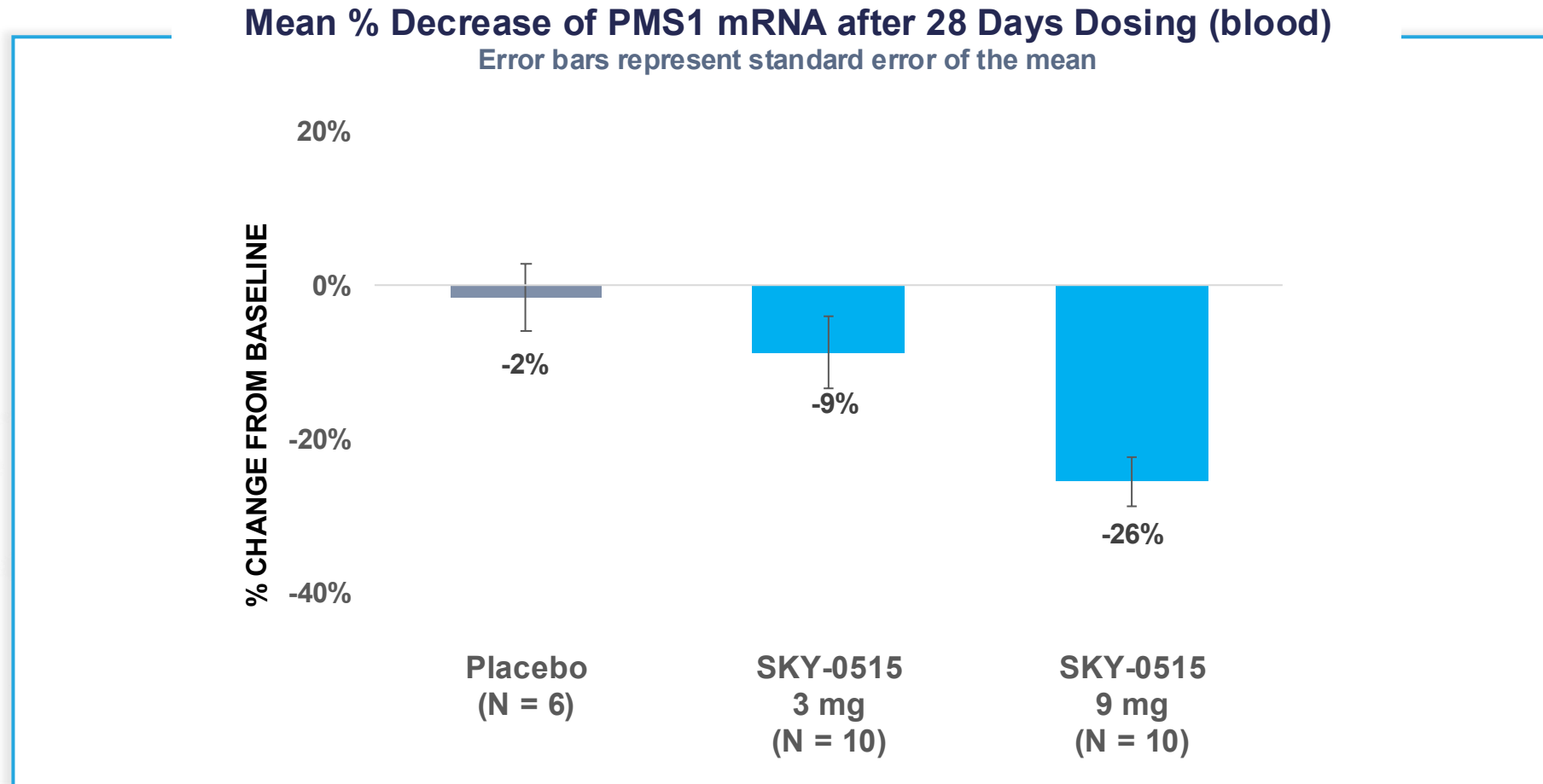
9mg

-62%

~1:1

mRNA and Protein Lowering

SKY-0515 also drives reductions in serum PMS1, a documented somatic mutation driver of HD, within weeks of beginning treatment; other HD treatments do not



A recent Genome-Wide Association Study (GWAS) study shows HD patients naturally born with loss-of-function in one of their two PMS1 copies developed Huntington's motor symptoms roughly 6.7 years later than expected.¹

1 Gelfman et al 2026



Phase 1/2 Study of SKY-0515 in Huntington's disease (HD)

Month 15 Safety and Efficacy

In final Month 15 Phase 1/2 clinical trial results of SKY-0515 for HD, patients did better than the comparison group on each of the four sub-components that make up the cUHDRS

- SKY-0515 patients 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

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 (composite)	+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.

At every scheduled checkpoint, SKY-0515 patients did better on the cUHDRS endpoint, than the comparison group

- 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
- As expected, the treatment difference increased over time
- The difference was statistically significant from Month 9 onward

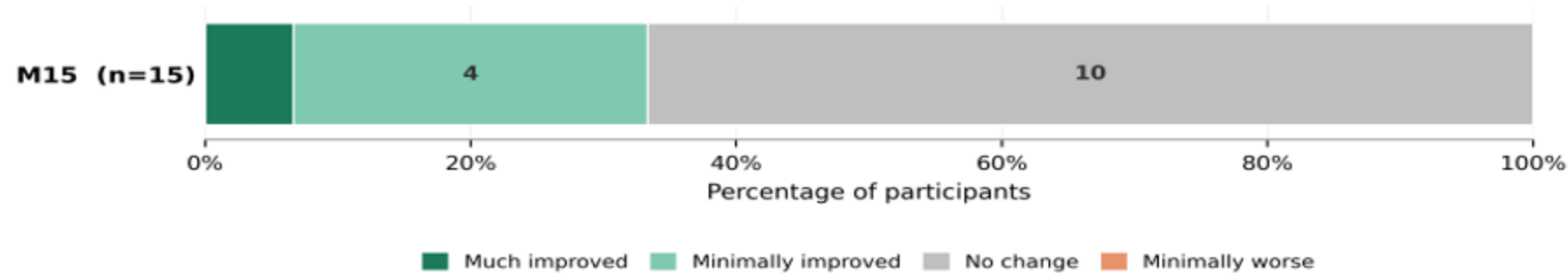
Change from baseline in cUHDRS by timepoint, SKY-0515 versus overlap-weighted external control

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

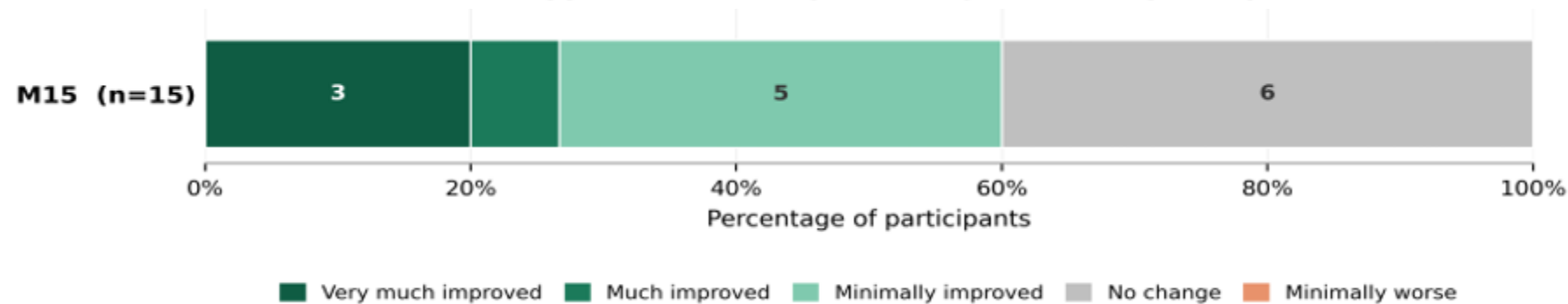
Phase 1/2 cUHDRS LS mean change from baseline vs. external control at 3, 6, 9, 12 and 15 months, estimated via overlap-weighted ANCOVA, for patients receiving SKY-0515 once-daily. Nominal timepoints are anchored to each participant's first dose of SKY-0515 (Day 1 to Month 3: n=24, Month 6: n=20, Month 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). 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.

Global impression-Improvement of disease as assessed by patients (PGI-C) or their clinician (CGI-I) at Month 15 also shows encouraging benefits from the use of SKY-0515

CGI-I: supportive summary including crossover participants



PGI-C: supportive summary including crossover participants



SKY-0515 has been well tolerated thus far, and our safety database keeps deepening with >220 patients randomized as of Q4 2026

>220

Total Patients Randomized

26

Study -001

144

FALCON Study -004-ANZ

>50

FALCON Study -004-WW

>50 patients rolled over into Open Label Study -008 currently receiving 9mg

Small molecule RNA modulators have potential commercial advantages over gene therapy and nucleic acid modalities

Modality	Administration	Safety	Logistics	Scalability
SKY-0515 target product profile	Once-daily oral pill, broadly distributed in the deep brain and peripheral tissues	Generally well-tolerated, easily reversible as it washes out after a few days	Room temperature storage (20°C to 25°C), easy to distribute worldwide	Synthesized via accessible and traditional synthetic and organic chemistry processes
AAV gene therapy	Invasive 8- to 10-hour brain surgery (intrastriatal)	Neuroinflammation, AAV immune responses, irreversible	Requires ultracold storage (-80°C)	Manufacturing viral vectors requires expensive, risky, and complex process
RNA interference (RNAi)	Invasive intracranial injection	Generally well-tolerated, increased NfL* possible, reversible over months	Requires refrigeration (2°C to 8°C)	Synthesis via phosphoramidite chemistry has low yields, toxic wastes, and requires explosion-proof facilities
Antisense oligos (ASOs)	Invasive intrathecal injection	Generally well-tolerated, increased NfL* possible, reversible over months	Requires refrigeration (2°C to 8°C)	Synthesis via phosphoramidite chemistry has low yields, toxic wastes, and requires explosion-proof facilities

*NfL=neurofilament light protein is a biomarker for neuroinflammation and cell damage

Skyhawk Therapeutics is well-positioned to advance SKY-0515, a wholly-owned asset



- SKY-0515 is our first wholly-owned asset to enter clinical trials
- Preliminary Phase 1/2 data readouts demonstrate encouraging effect of SKY-0515 across multiple clinical metrics, including cUHRS and TFC, as well as strong physician and patient impressions
- Global Phase 2/3 FALCON-HD study evaluating SKY-0515 in Huntington's disease is enrolling faster than expected, suggesting strong unmet need and interest in patient-friendly oral treatment option
- \$600 million in upfront cash milestones since inception



>10 Collaborations large pharma focused on small molecule RNA modulators have generated \$600 million in upfronts that power Skyhawk's platform and SKY-0515 commercialization





END