ORIGINAL ARTICLE

Targeting Huntingtin Expression in Patients with Huntington's Disease

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ABSTRACT

BACKGROUND

Huntington's disease is an autosomal-dominant neurodegenerative disease caused by CAG trinucleotide repeat expansion in *HTT*, resulting in a mutant huntingtin protein. IONIS-HTT_{Rx} (hereafter, HTT_{Rx}) is an antisense oligonucleotide designed to inhibit *HTT* messenger RNA and thereby reduce concentrations of mutant huntingtin.

METHODS

We conducted a randomized, double-blind, multiple-ascending-dose, phase 1–2a trial involving adults with early Huntington's disease. Patients were randomly assigned in a 3:1 ratio to receive HTT_{Rx} or placebo as a bolus intrathecal administration every 4 weeks for four doses. Dose selection was guided by a preclinical model in mice and nonhuman primates that related dose level to reduction in the concentration of huntingtin. The primary end point was safety. The secondary end point was HTT_{Rx} pharmacokinetics in cerebrospinal fluid (CSF). Prespecified exploratory end points included the concentration of mutant huntingtin in CSF.

RESULTS

Of the 46 patients who were enrolled in the trial, 34 were randomly assigned to receive HTT_{Rx} (at ascending dose levels of 10 to 120 mg) and 12 were randomly assigned to receive placebo. Each patient received all four doses and completed the trial. Adverse events, all of grade 1 or 2, were reported in 98% of the patients. No serious adverse events were seen in HTT_{Rx}-treated patients. There were no clinically relevant adverse changes in laboratory variables. Predose (trough) concentrations of HTT_{Rx} in CSF showed dose dependence up to doses of 60 mg. HTT_{Rx} treatment resulted in a dose-dependent reduction in the concentration of mutant huntingtin in CSF (mean percentage change from baseline, 10% in the placebo group and –20%, –25%, –28%, –42%, and –38% in the HTT_{Rx} 10-mg, 30-mg, 60-mg, 90-mg, and 120-mg dose groups, respectively).

CONCLUSIONS

Intrathecal administration of HTT_{Rx} to patients with early Huntington's disease was not accompanied by serious adverse events. We observed dose-dependent reductions in concentrations of mutant huntingtin. (Funded by Ionis Pharmaceuticals and F. Hoffmann–La Roche; ClinicalTrials.gov number, NCT02519036.)

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Huntington's disease is a progressive neurodegenerative disorder inherited as an autosomal-dominant trait, with onset typically occurring in mid-adult life and characterized by movement disorder, cognitive decline, and behavioral symptoms.[1] Huntington's disease is caused by CAG trinucleotide repeat expansion in the huntingtin (*HTT*) gene, which encodes huntingtin protein (HTT).[2] The abnormal gene results in the production of gene products, including mutant HTT, containing an expanded polyglutamine tract, which causes neuronal dysfunction and death, putatively by means of toxic gain-of-function mechanisms.[3,4] Current treatments for Huntington's disease are limited to therapies to treat symptoms, because no treatment has been shown to prevent onset or to slow progression. Given the monogenic nature of Huntington's disease, we sought to inhibit *HTT* expression and thus directly target the primary disease mechanism.[5]

IONIS-HTT_{Rx} (also known as ISIS 443139 and RG6042; hereafter referred to as HTT_{Rx}) is a second-generation 2′-O-(2-methoxyethyl) antisense oligonucleotide that was designed to reduce concentrations of *HTT* messenger RNA (mRNA). HTT_{Rx} binds to its cognate mRNA by means of Watson–Crick base-pair interactions, triggering RNase H1-mediated degradation of the target mRNA.[6] Antisense oligonucleotide–mediated selective reduction of *HTT* mRNA leads to lowered HTT concentrations and sustained amelioration of disease-associated phenotypes in multiple transgenic animal models of Huntington's disease.[7] Long-term administration of *HTT*-lowering agents to nonhuman primates without mutations resulted in a reduction in the HTT concentration in central nervous system tissues without adverse effects.[7,8] Experiments with alternative methods that were designed to inhibit *HTT* expression yielded similar effects in animal models of Huntington's disease,[8-10] validating the reduction of the HTT concentration as a potentially viable disease-modifying therapeutic strategy. We report the results of a targeted HTT-lowering agent in this phase 1–2a clinical trial of an *HTT*-targeting antisense oligonucleotide administered intrathecally as a bolus in adults with early Huntington's disease.

METHODS

TRIAL DRUG

HTT_{Rx} is a chemically modified synthetic oligomer that is perfectly complementary to a 20-nucleotide stretch of *HTT* mRNA. HTT_{Rx} binds to *HTT* mRNA by means of Watson–Crick base pairing, with hybridization resulting in endogenous RNase H1-mediated degradation of the *HTT* mRNA, thus inhibiting translation of the huntingtin protein. The sequence of HTT_{Rx} is (5′ to 3′) $ct_oc_oa_ogTAACATTGACa_oc_oc_oac$, in which capital letters represent 2′-deoxyribose nucleosides, and small letters 2′-(2-methoxyethyl)ribose nucleosides. Nucleoside linkages that are represented with a subscripted "o" are phosphodiester, and all others are phosphorothioate. Letters "a" and "A" represent adenine, "c" and "C" 5-methylcytosine, "g" and "G" guanine, and "t" and "T" thymine nucleobases.

TRIAL OVERSIGHT

The trial was conducted in accordance with the principles of the Declaration of Helsinki. The trial protocol (available with the full text of this article at NEJM.org) and all documentation were approved by the institutional review board or independent ethics committee at each investigational site. All the patients provided written informed consent. The trial was sponsored by Ionis Pharmaceuticals, which provided the trial agents (HTT_{Rx} and placebo). Personnel from Ionis Pharmaceuticals designed the trial in conjunction with collaborators from F. Hoffmann–La Roche, principal academic investigators, and other disease experts. An independent data and safety monitoring board authorized each dose escalation after unblinded review of safety data and consultation with the sponsor, Ionis Pharmaceuticals. The investigators collected the data, which were held and maintained by the sponsor. Data were analyzed by personnel from the sponsor and were interpreted by all the authors. The investigators vouch for the fidelity of the trial to the protocol and protocol amendments. The authors vouch for the completeness and accuracy of the data. The authors and sponsor made the decision to submit the manuscript for publication.

PATIENTS

Eligible participants were between 25 and 65 years of age and had early Huntington's disease, defined as 36 or more CAG repeats in *HTT* and clinical stage 1 disease (Unified Huntington's Disease Rating Scale total functional capacity score of 11 to 13, on a scale from 0 to 13, with higher scores indicating less functional impairment; a score of 11 to 13 indicates little to no functional impairment across the items assessed [occupation, finances, domestic chores, activities of daily living, and care level]).[11] Further details of the inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

TRIAL DESIGN AND END POINTS

HTT_{Rx}-CS1 was a randomized, double-blind, placebo-controlled, multicenter, phase 1–2a trial. The trial was performed at nine centers in the United Kingdom, Germany, and Canada from August 2015 through November 2017. A centralized automated randomization system was used to assign patients in a 3:1 ratio to receive HTT_{Rx} or placebo within each of five dose cohorts in an ascending-dose design (10 mg, 30 mg, 60 mg, 90 mg, or 120 mg).

Each patient received four bolus intrathecal injections of HTT_{Rx} or placebo (artificial cerebrospinal fluid) at 4-week intervals; subsequently, there was a 4-month follow-up period during which no trial agent was administered. A cerebrospinal fluid (CSF) sample was obtained before each administration of HTT_{Rx} or placebo and either 4 or 8 weeks after the last dose was administered (Fig. 1). Investigators, patients, the sponsor (Ionis Pharmaceuticals), and its collaborator (F. Hoffmann–La Roche) were unaware of the trial-group assignments for the duration of the trial.

The primary end point was the safety of HTT_{Rx} treatment. Safety evaluations included physical examination, neurologic examination, the Columbia Suicide Severity Rating Scale, laboratory assessments, vital signs, electrocardiograms, and safety neuroimaging sequences. At each trial visit, patients were queried for other changes in health status in an open-ended fashion.

The secondary end point was the characterization of the pharmacokinetics of HTT_{Rx} in CSF. Exploratory end points were the characterization of the pharmacokinetics of HTT_{Rx} in plasma and exploration of the effects of HTT_{Rx} on pharmacodynamic biomarkers and clinical end points relevant in Huntington's disease, including the concentrations of mutant HTT and neurofilament light protein in the CSF, ventricular volume, and the composite cognitive score on the Huntington's Disease Cognitive Assessment Battery. After the completion of the trial, participants were offered the opportunity to enroll in a 15-month, open-label extension study (ClinicalTrials.gov number, NCT03342053) evaluating the effects of intrathecal administration of 120 mg of HTT_{Rx} either monthly or every other month.

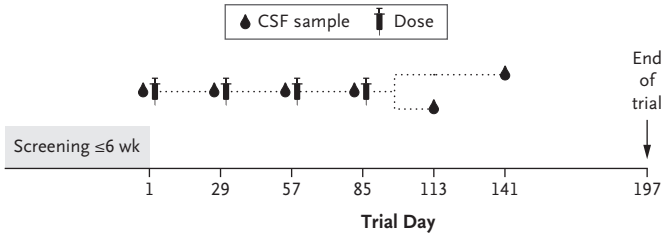


Figure 1. Trial Design.

At the conclusion of the screening period, eligible patients were randomly assigned in a 3:1 ratio to receive the antisense oligonucleotide drug HTT_{Rx} or placebo. Cerebrospinal fluid (CSF) samples were obtained before the administration of the trial agent on days 1, 29, 57, and 85. The CSF sample on day 1 served as the baseline sample, and the CSF samples on days 29, 57, and 85 served as 28-day post-dose trough samples. One sample was obtained from each patient after the completion of the regimen, either on day 113 or day 141 according to randomized assignment. The CSF sample that was obtained on day 113 served as a 28-day post–last dose sample; the sample obtained on day 141 served as a 56-day post–last dose sample. Dotted lines indicate the relationship between each dose and the subsequent CSF sample.

MEASUREMENT OF CEREBRAL VOLUME

We obtained 3-T T_1-weighted structural magnetic resonance imaging (MRI) scans of the head and transferred these data to an independent image-analysis provider that performed quality-control, processing, and volumetric analyses, blinded to trial-group status, according to established methods.[12] Whole-brain and regional volume changes were calculated with the use of the boundary shift integral, a semiautomated

method that determines volume change from three-dimensional shift between paired images of a regional boundary.

STATISTICAL ANALYSIS

The primary objective of the trial was the evaluation of the safety of HTT_{Rx} treatment (primary end point). Adverse events and serious adverse events during the trial, laboratory tests (in blood and CSF), vital signs, electrocardiographic measures, and observations from the Columbia Suicide Severity Rating Scale were summarized according to trial group. Where possible, pharmacokinetic variables were assessed for HTT_{Rx} in CSF (secondary end point) and plasma (exploratory end point). Analyses of pharmacodynamic biomarkers and clinical end points were summarized according to trial group, and the HTT_{Rx}-treated groups were compared with the placebo group.

The treatment differences and 95% confidence intervals for changes in the mutant HTT concentration in CSF were Hodges–Lehmann estimations that were based on the Wilcoxon rank-sum test or were obtained with the use of analysis of variance, depending on the normality of the data. Relationships between reductions in the concentration of mutant HTT in CSF and clinical outcomes were explored in a post hoc analysis with the use of Spearman's correlation coefficient, and the 95% confidence interval of the correlation coefficient was based on Fisher's z transformation. Because of the exploratory nature of this trial, adjustments for multiplicity of testing were not used. Interpretation of HTT_{Rx} effects on mutant HTT in tissue was based on the extent of reduction of the mutant HTT concentration in CSF and a linked pharmacokinetic and pharmacodynamic clearance model that was based on data collected in human mutant HTT–transgenic mice and nonhuman primates (see the Supplementary Appendix).

RESULTS

PATIENTS

From August 2015 through April 2017, a total of 52 patients were screened for eligibility, and 46 patients underwent randomization according to the protocol. All the patients received all scheduled doses of the assigned trial agent (HTT_{Rx} or placebo), and all the patients who had undergone randomization completed the trial according to the protocol. (A diagram of the flow of patients through the trial is provided in Fig. S3 in the Supplementary Appendix.) The characteristics of the patients at baseline were representative of early-stage Huntington's disease and were similar across the trial groups (Table 1).

PRIMARY END POINT OF SAFETY

The incidence of adverse events was similar among patients receiving HTT_{Rx} and those receiving placebo (Table 2). Adverse events were reported in 98% of the patients; all events were mild (83%) or moderate (17%) in severity. The most commonly reported adverse events in patients who received HTT_{Rx} were procedural pain and post–dural-puncture headache, which occurred after approximately 10% of lumbar punctures and had no apparent relationship to trial duration or dose. There was no evidence of an increased risk of post–dural-puncture headache with successive lumbar punctures. All post–dural-puncture headaches resolved (median duration, 2 days), and no blood patches were used. Very few adverse events (6%) were considered by the investigators (who were unaware of the trial-group assignment) to be related to HTT_{Rx} or placebo, and most of the related events (83%) were also considered to be related to a trial procedure. There were no deaths, dose-limiting adverse events, discontinuations of regimens, or delays in trial-agent administration during the trial.

The only serious adverse event was an inpatient admission of a patient in the placebo group for observation of a mild post–dural-puncture headache. Neither suicidal behavior nor serious suicidal ideation emerged in any patient during the trial. One case of a mildly increased CSF leukocyte count (20 to 23 cells per cubic millimeter, measured in triplicate) without associated symptoms was observed 8 weeks after the last 60-mg dose of HTT_{Rx} was administered; the clinical safety MRI and electroencephalographic results were normal. The asymptomatic elevation persisted throughout the post-treatment period and resolved before the patient's initiation of treatment in the extension study, 64 weeks after the last dose in this trial.

SECONDARY END POINT

HTT_{Rx} was measurable in the CSF of most patients who received doses of 30 mg or more.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=12)	HTT_{Rx}					
		All (N=34)	10 mg (N=3)	30 mg (N=6)	60 mg (N=6)	90 mg (N=9)	120 mg (N=10)
Age — yr	49±10	46±10	44±17	53±7	43±11	46±10	45±10
Female sex — no. (%)	4 (33)	14 (41)	1 (33)	1 (17)	3 (50)	3 (33)	6 (60)
White race — no. (%)†	11 (92)	32 (94)	3 (100)	5 (83)	6 (100)	9 (100)	9 (90)
No. of CAG repeats	44±2	44±3	46±6	43±2	45±2	44±3	45±4
Montreal Cognitive Assessment score‡	25±2	26±3	26±4	27±2	26±3	26±3	26±3
Total functional capacity score — no. (%)§							
11	6 (50)	9 (26)	0	2 (33)	2 (33)	2 (22)	3 (30)
12	4 (33)	15 (44)	1 (33)	4 (67)	3 (50)	4 (44)	3 (30)
13	2 (17)	10 (29)	2 (67)	0	1 (17)	3 (33)	4 (40)
Total motor score¶	24±7	22±10	21±7	20±13	25±13	22±10	21±9
Independence scale score‖	89±8	90±8	93±6	88±11	86±8	93±8	90±6
Disease-burden score**	398.4±50.1	383.7±66.0	385.2±109.1	366.7±50.8	383.8±34.3	364.5±68.7	410.8±75.1
Concentration of mutant HTT in CSF — fmol/liter	109±43	110±46	144±50	120±45	117±30	105±65	96±35

* Plus–minus values are means ±SD. Patients were assigned to receive either placebo or ascending doses of the antisense oligonucleotide drug HTT_{Rx}. Percentages may not total 100 because of rounding. CSF denotes cerebrospinal fluid, and HTT huntingtin protein.
† Race was reported by the patient.
‡ Scores on the Montreal Cognitive Assessment range from 0 to 30, with higher scores indicating better cognitive function.
§ Total functional capacity scores on the Unified Huntington's Disease Rating Scale range from 0 to 13, with higher scores indicating less functional impairment. A score of 11 to 13 indicates little to no functional impairment across the items assessed (occupation, finances, domestic chores, activities of daily living, and care level).
¶ Total motor scores range from 0 to 124, with lower scores indicating less impairment.
‖ Independence scale scores range from 0 to 100, with higher scores indicating higher levels of independence.
** The disease-burden score is calculated as follows: (CAG repeat length − 35.5) × age in years.[13] Larger numbers represent a higher burden of disease.

Trough concentrations increased with increasing dose, from below the limit of quantification at the 10-mg dose through the 60-mg dose, with a plateau in the concentration in CSF beyond the 60-mg dose (Fig. 2A). No accumulation of HTT_{Rx} in CSF was observed over time.

EXPLORATORY END POINTS

Plasma Concentrations of HTT_{Rx}

The median peak plasma concentrations of HTT_{Rx} were reached within 4 hours after the bolus intrathecal administration and declined to less than 30% of the peak concentration by 24 hours after administration. The concentration of HTT_{Rx} in plasma increased approximately proportionally to the dose over the explored dose range (Fig. 2B). There was no evidence of accumulation of concentration in plasma 24 hours after dose administration over the course of the trial, and there was a minor increase (<20%) in the peak concentration at the 120-mg dose level.

Concentrations of Mutant HTT in CSF

In patients who received HTT_{Rx}, there were dose-dependent decreases in the concentration of mutant HTT in CSF at the last available 28-day post-dose sampling point (mean percentage change from baseline of –20%, –25%, –28%, –42%, and –38% in the HTT_{Rx} 10-mg, 30-mg, 60-mg, 90-mg, and 120-mg dose groups, respectively), with a maximum reduction of 63% in an individual patient (in the 120-mg cohort). In patients who received placebo, the mean percentage change from baseline was an increase of 10% in the concentration of mutant HTT in CSF (Fig. 3A and 3B, and Table S1 in the Supplementary Appendix). Steady-state maximal reduction of the concentration of mutant HTT in CSF did

Table 2. Adverse Events Reported in at Least Three Patients Receiving HTT_{Rx}, According to Grade.*

Event	Grade 1		Grade 2		Grade 3 or 4	
	HTT_{Rx} Groups (N=34)	Placebo Group (N=12)	HTT_{Rx} Groups (N=34)	Placebo Group (N=12)	HTT_{Rx} Groups (N=34)	Placebo Group (N=12)
	number of patients with event (percent)					
Any adverse event	20 (59)	7 (58)	13 (38)	5 (42)	0	0
Any serious adverse event	0	1 (8)	0	0	0	0
Event according to system organ class or preferred term						
Injury, poisoning, or procedural complication	19 (56)	7 (58)	7 (21)	4 (33)	0	0
Procedural pain	17 (50)	4 (33)	2 (6)	2 (17)	0	0
Post–lumbar-puncture syndrome	8 (24)	4 (33)	4 (12)	1 (8)	0	0
Fall	7 (21)	2 (17)	0	1 (8)	0	0
Skin abrasion	5 (15)	1 (8)	0	0	0	0
Infection or infestation	21 (62)	4 (33)	2 (6)	2 (17)	0	0
Nasopharyngitis	7 (21)	0	0	2 (17)	0	0
Upper respiratory tract infection	3 (9)	1 (8)	1 (3)	0	0	0
Bronchitis	2 (6)	0	1 (3)	0	0	0
Influenza	2 (6)	0	1 (3)	0	0	0
Rhinovirus infection	3 (9)	0	0	0	0	0
Nervous system disorder	9 (26)	4 (33)	3 (9)	3 (25)	0	0
Headache	4 (12)	3 (25)	2 (6)	3 (25)	0	0
Hypoesthesia	3 (9)	0	0	0	0	0
Musculoskeletal or connective-tissue disorder	9 (26)	4 (33)	1 (3)	1 (8)	0	0
Arthralgia	4 (12)	2 (17)	0	0	0	0
Back pain	3 (9)	1 (8)	1 (3)	0	0	0
General disorder or administration-site condition	5 (15)	2 (17)	1 (3)	0	0	0
Fatigue	4 (12)	0	1 (3)	0	0	0
Gastrointestinal disorder	5 (15)	1 (8)	1 (3)	0	0	0
Toothache	2 (6)	0	1 (3)	0	0	0
Vascular disorder	3 (9)	0	0	0	0	0
Hematoma	3 (9)	0	0	0	0	0

* Shown are adverse events that occurred from the first dose of trial agent through the end of the trial. Each adverse event was rated as mild, moderate, or severe, corresponding to grades of 1, 2, and 3, respectively. In addition, serious adverse events were rated as life-threatening (grade 4) or not life-threatening. At each level of summation (overall and according to system organ class or preferred term), patients for whom more than one adverse event was reported were counted only once according to the most severe category of event.

not appear to have been reached during the 3-month trial period (Fig. 3A and 3C).

Additional Exploratory Outcomes

Functional, cognitive, psychiatric, and neurologic clinical outcomes were generally unchanged at the dose-group level during the trial, and no meaningful differences were observed between patients who received placebo and patients who received HTT_{Rx}, regardless of the dose level (Table S2 in the Supplementary Appendix). The ventricular volume showed dose-dependent and time-dependent increases at day 113 and at day 197, without adverse consequences, in the 90-mg and 120-mg dose groups that were greater than those in the placebo group (boundary shift integrals at days 113 and 197 were 2.6 ml and 5.0 ml, respectively, in the 90-mg group and 2.3 ml and 5.3 ml, respectively, in the 120-mg group).

Elevations of the concentration of neurofila-

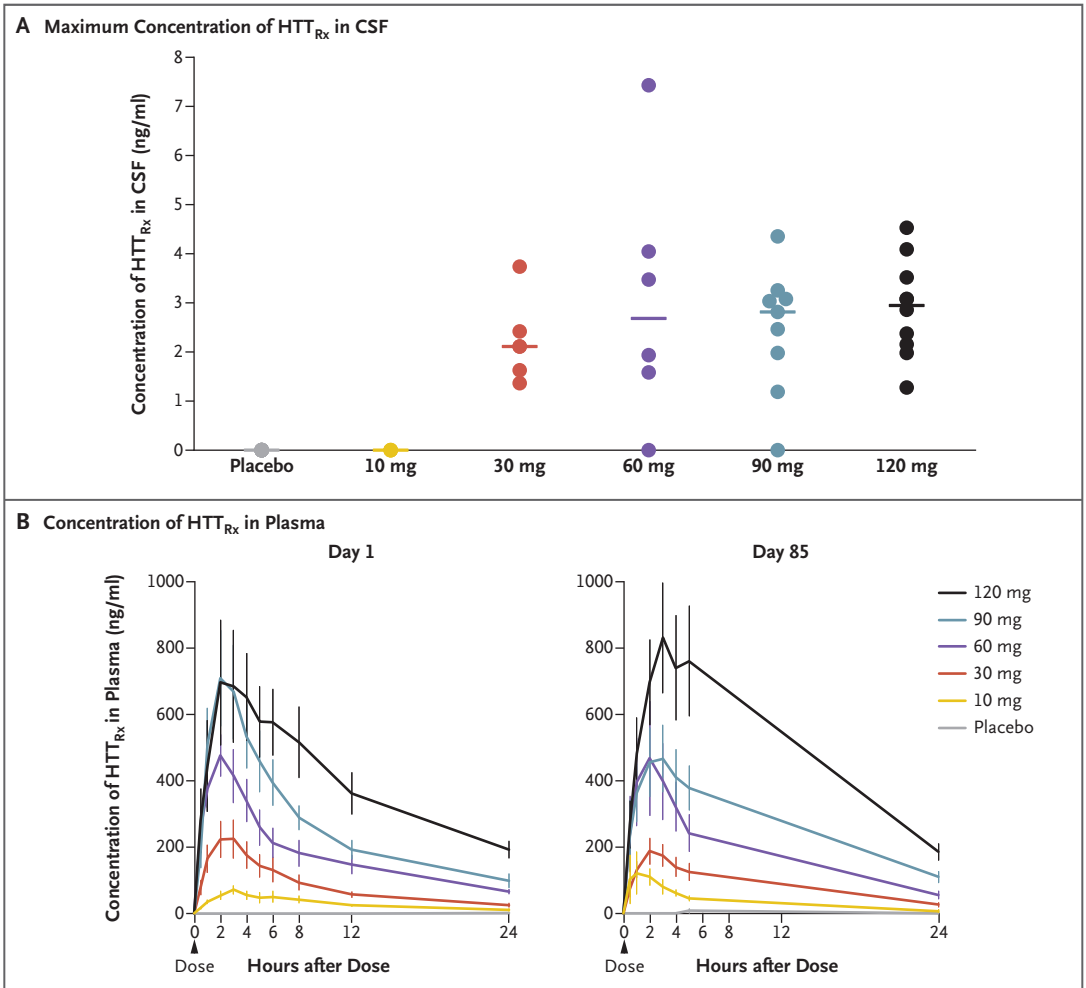


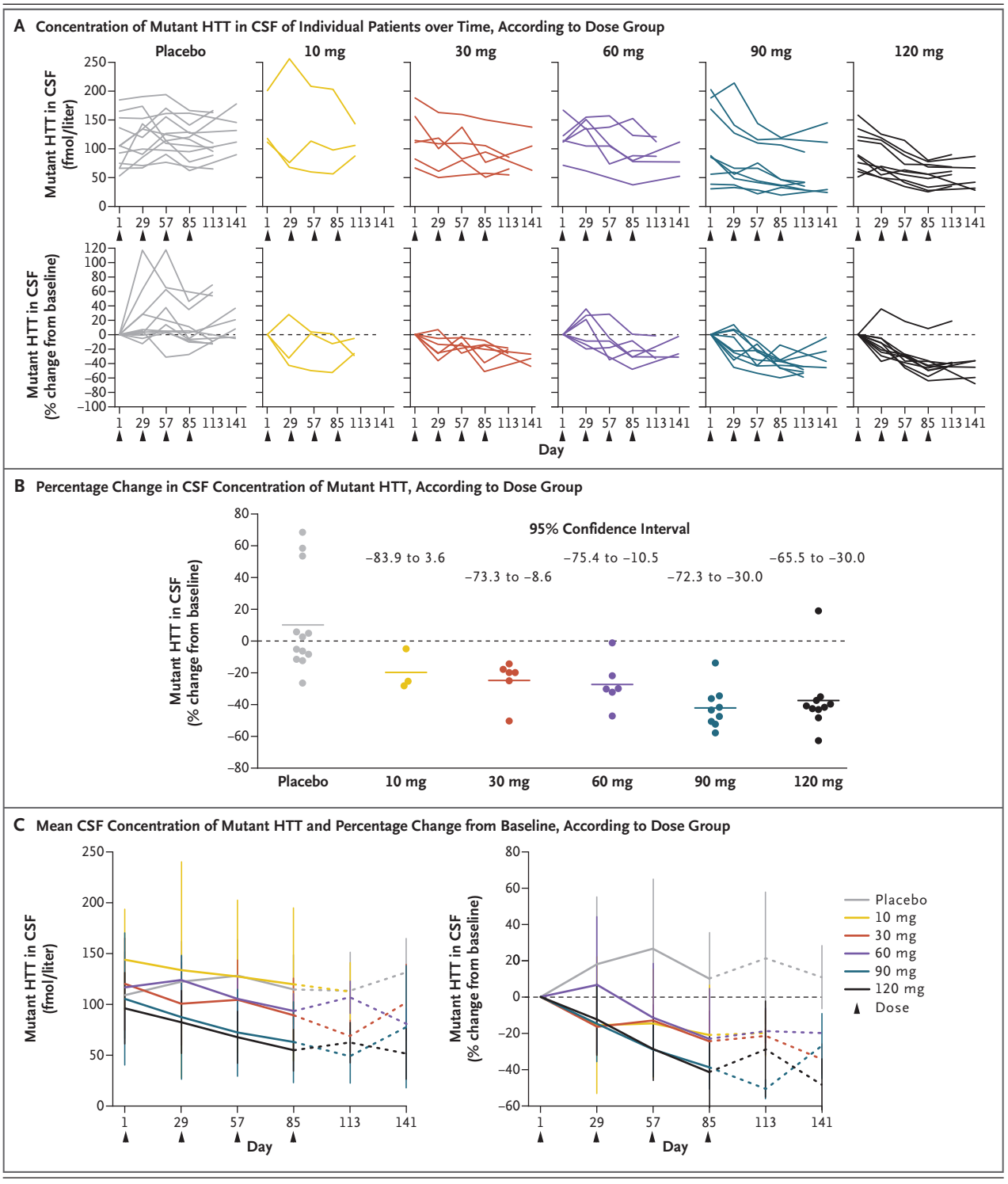
Figure 2. HTT_{Rx} Exposure.

Panel A shows the maximum predose (i.e., 28-day trough) concentration of the antisense oligonucleotide drug HTT_{Rx} in CSF according to dose group (placebo or the various HTT_{Rx} dose groups). Panel B shows the mean concentration of HTT_{Rx} in plasma, according to dose group, over the 24-hour periods after the administration of the first dose (left side; day 1) and fourth dose (right side; day 85). Error bars indicate the standard error. Further discussion of the observed concentrations of HTT_{Rx} is provided in the Supplementary Appendix.

ment light protein in CSF occurred in some patients in the 90-mg and 120-mg cohorts at day 113 or day 141 (i.e., 1 or 2 months after cessation of the regimen, respectively), but there were no associated adverse events or safety changes on MRI (Fig. S4 in the Supplementary Appendix). By the start of the extension study (7 to 27 months after the final doses were administered in this trial), the concentrations of neurofilament light protein in the CSF had generally returned to pretrial concentrations. During the extension study, the concentrations rose with a time course and magnitude that were similar to those observed in this trial and then decreased at later time points despite continued treatment (unpublished data).

POST HOC ANALYSES

In parallel with this trial, the composite Unified Huntington Disease Rating Scale (cUHDRS) was developed to serve as a measure of clinical progression in early Huntington's disease.[14] We examined the relationships between the degree of lowering of the CSF concentration of mutant HTT and changes in the cUHDRS score and its four components and observed correlations be-



tween reduction in the CSF concentration of mutant HTT and improvements in the cUHDRS score and two of its components (Fig. S5 in the Supplementary Appendix). These correlations should be interpreted with caution, because the tests were not prespecified and the coefficients of correlation were not adjusted for multiple testing.

Figure 3 (facing page). Effect of HTT_{Rx} on CSF Concentrations of Mutant Huntingtin Protein (HTT).

Panel A shows the concentrations of mutant HTT in CSF over time for individual patients in each dose group; absolute values, measured in femtomoles per liter, are shown in the top graphs, and the percentage changes from baseline (dotted line) are shown in the bottom graphs. Arrowheads indicate the 4 days on which HTT_{Rx} or placebo was administered. A discussion of the individual patient data that were observed in the 120-mg dose group is provided in the Supplementary Appendix. Panel B shows the percentage change in the concentration of mutant HTT in CSF from baseline (dotted line) to the last available time point 28 days after the previous dose (i.e., either day 113 for the patients who underwent CSF sampling at day 113 or day 85 for the other patients). Circles indicate individual patients, and horizontal lines indicate group means; 95% confidence intervals are also shown for the active-agent dose groups. Panel C shows the mean concentration of mutant HTT in CSF (left) and the mean percentage change from baseline (right) over time according to dose group. Error bars indicate the standard deviation. Samples from days 113 and 141 were each obtained in a randomized subgroup of patients (dotted lines).

DISCUSSION

A regimen of four repeated monthly bolus intrathecal administrations of HTT_{Rx}, an *HTT* mRNA-targeting antisense oligonucleotide, to adults with early Huntington's disease was not accompanied by any serious adverse events. The intervention resulted in a dose-dependent reduction in the concentration of mutant HTT, the protein that putatively causes Huntington's disease, in the CSF. Given the results of only this trial, we do not know whether this reduction reflects a reduction in the concentration of mutant HTT in the central nervous system, although preclinical studies support the hypothesis that concentrations of mutant HTT in the CSF reflect the concentrations of mutant HTT in central nervous system tissue (see the Supplementary Appendix, as well as Southwell et al.[15]). Although the positive effects of sustained lowering of the concentration of mutant HTT on motor function and survival in mouse models of Huntington's disease[7,8] provided a rationale for the development of an HTT-targeting antisense oligonucleotide, larger studies of greater duration will be needed to determine whether HTT_{Rx}-mediated reduction of the concentration of mutant HTT in CSF is associated with a treatment effect on the disease course, which is typically slow, with changes on standard outcomes generally occurring over a period of years.

The ventricular volume showed apparent dose-dependent and time-dependent increases during the trial with no corresponding changes in whole-brain volume. Slow, progressive whole-brain atrophy (i.e., irreversible loss of brain tissue) and ventricular expansion are characteristic features of Huntington's disease,[16] and neuroinflammation is a known phenomenon in patients with the disease.[17,18] Although pseudoatrophy (i.e., ventricular expansion due to resolution of inflammatory edema and gliosis) has been described in clinical studies of multiple sclerosis and Alzheimer's disease, it has been a challenge to differentiate between treatment-induced pseudoatrophy and disease-related atrophy,[19-24] and we have not assessed the effect of HTT_{Rx} treatment on inflammation or gliosis in humans or animal models.

The putative neuronal injury marker, the concentration of neurofilament light protein in the CSF,[25] showed apparent dose-dependent and time-dependent increases during the trial and reversed after the cessation of the trial regimen and also after transient increases during the extension study. To our knowledge, there are no published longitudinal studies of neurofilament light protein in the CSF of persons with Huntington's disease, and so the magnitude of increase that corresponds with an adverse outcome is unknown. The values that we observed in this trial are within the range of values observed in a cross-sectional study involving patients with Huntington's disease.[26]

In conclusion, we found that the antisense oligonucleotide drug HTT_{Rx} reduced the concentration of mutant HTT in the CSF of persons with Huntington's disease. More generally, we found antisense-mediated protein suppression in the central nervous system of patients with a neurodegenerative disease.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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