CORRESPONDENCE

Tominersen in Adults with Manifest Huntington's Disease

TO THE EDITOR: The antisense oligonucleotide tominersen was designed to slow the progression of Huntington's disease by lowering levels of huntingtin gene (*HTT*) products, including mutant huntingtin protein (HTT). A phase 1–2a study of tominersen showed a dose-dependent reduction in cerebrospinal fluid (CSF) levels of mutant HTT in participants with Huntington's disease.[1] We conducted a phase 3 trial (GENERATION HD1; ClinicalTrials.gov number, NCT03761849), in which 791 participants with manifest Huntington's disease were randomly assigned in a 1:1:1 ratio to receive intrathecal tominersen, at a dose of 120 mg every 8 weeks or every 16 weeks, or placebo (see the protocol and Fig. S1 and Tables S1, S2, and S3 in the Supplementary Appendix; both the protocol and the Supplementary Appendix are available with the full text of this letter at NEJM.org). After an initial 4-week screening period, the participants who were assigned to one of the tominersen dose groups received tominersen at the time of randomization, 4 weeks after randomization, and then every 8 or 16 weeks, depending on their trial-group assignment.

The primary end point was the change from baseline in the score on the composite Unified Huntington's Disease Rating Scale (cUHDRS) or Total Functional Capacity (TFC) scale at week 101. Scores on the cUHDRS range from −8 to 25, with higher scores indicating improvement (a change in score of 1.2 points is considered to be clinically meaningful), and scores on the TFC scale range from 0 to 13, with higher scores indicating improvement (a change in score of 1 point is considered to be clinically meaningful). Biomarker end points included levels of mutant HTT in CSF, levels of neurofilament light protein (NfL) in CSF, and ventricular volume.

On the basis of an overall benefit–risk assessment by an independent data monitoring committee, treatment was stopped in March 2021; therefore, an ad hoc analysis of the results at week 69 was carried out (post-treatment analyses are provided in Fig. S5). In the every-8-week tominersen group, the mean change from baseline in the score on the cUHDRS at week 69 was significantly worse than that in the placebo group (−0.54 points, adjusted P=0.001), but the mean change from baseline in the score on the TFC scale did not differ significantly (−0.40 points, adjusted P=0.09). In the every-16-week tominersen group, the mean changes from baseline in the scores on the cUHDRS and the TFC scale did not differ significantly from those in the placebo group (−0.16 points, adjusted P=0.84; and −0.04, adjusted P=1.00, respectively) (Fig. 1). The P values and widths of the confidence intervals were adjusted to account for the testing of two primary end points. Nonetheless, these results must be interpreted with caution, given the ad hoc nature of the analysis.

The changes in mutant HTT levels in CSF were consistent with dose regimen–dependent decreases and concomitant increases in ventricular volume (Fig. 1), a finding that was perhaps due to the reduced absorption of CSF, which in

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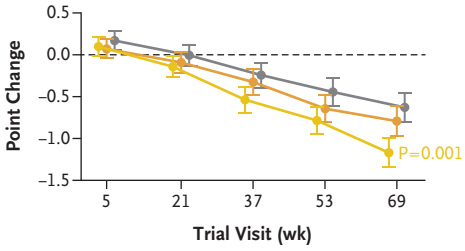
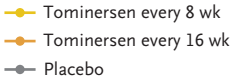
A Change from Baseline in cUHDRS Score

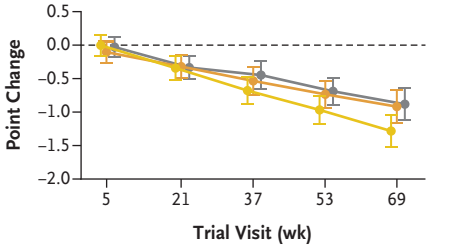




No. of Patients

Tominersen every 8 wk	252	250	223	223	199
Tominersen every 16 wk	251	244	219	229	193
Placebo	252	256	217	233	202

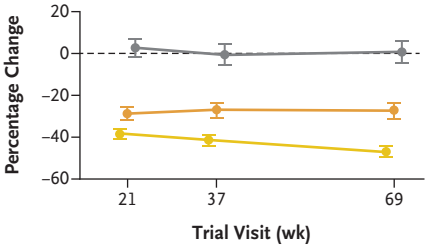
B Change from Baseline in TFC Scale Score



No. of Patients

Tominersen every 8 wk	255	252	239	240	203
Tominersen every 16 wk	253	246	228	233	199
Placebo	253	256	233	239	206

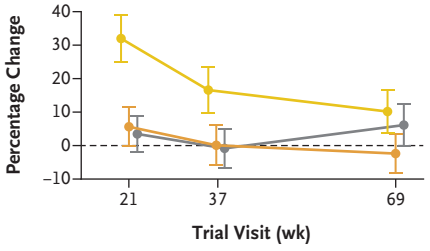
C Change from Baseline in CSF Mutant HTT Level



No. of Patients

Tominersen every 8 wk	204	181	163
Tominersen every 16 wk	202	185	162
Placebo	206	184	163

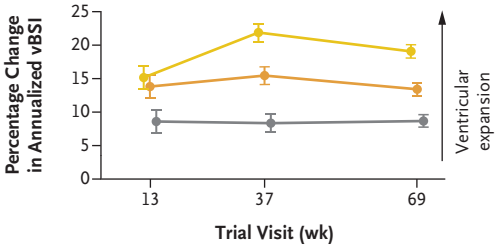
D Change from Baseline in CSF NfL Level



No. of Patients

Tominersen every 8 wk	224	190	172
Tominersen every 16 wk	209	188	163
Placebo	225	195	169

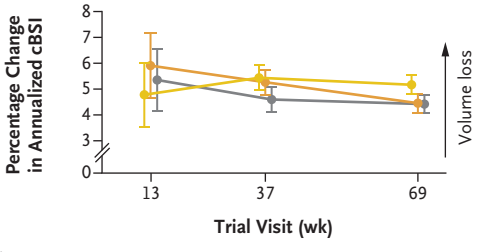
E Rate of Change from Baseline in Ventricular Volume



No. of Patients

Tominersen every 8 wk	231	194	141
Tominersen every 16 wk	228	201	169
Placebo	241	215	198

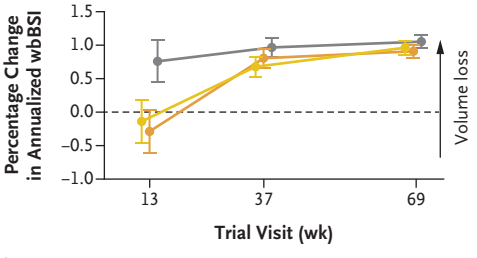
F Rate of Change from Baseline in Caudate Volume



No. of Patients

Tominersen every 8 wk	194	207	173
Tominersen every 16 wk	181	198	175
Placebo	202	196	182

G Rate of Change from Baseline in Whole-Brain Volume



No. of Patients

Tominersen every 8 wk	198	171	155
Tominersen every 16 wk	192	184	169
Placebo	206	180	178

Figure 1 (facing page). Clinical and Biomarker End Points.

Panels A and B show the least-squares mean values, Panels C and D the least-squares mean of the percentage change in the geometric mean, and Panels E, F, and G the least-squares mean of the percentage change in the annualized boundary shift integral (BSI) values, as determined in the analysis of the mixed model for repeated measures. I bars indicate the 95% confidence intervals. Data that were collected before March 22, 2021, and from visits up to week 69 were included in the ad hoc analysis. Scores on the composite Unified Huntington's Disease Rating Scale (cUHDRS) range from –8 to 25, with higher scores indicating improvement (a change in score of 1.2 points is considered to be clinically meaningful). Scores on the Total Functional Capacity (TFC) scale range from 0 to 13, with higher scores indicating improvement (a change in score of 1 point is considered to be clinically meaningful). CSF denotes cerebrospinal fluid, HTT huntingtin protein, NfL neurofilament light protein, vBSI ventricular boundary shift integral, and wbBSI whole-brain boundary shift integral.

turn could be due to an increased white-cell count and protein levels in CSF. The absence of whole-brain volume loss in the context of ventricular expansion and the absence of a correlation between the change in CSF NfL levels and change in ventricular volume suggest that increases in ventricular volume do not reflect increased atrophy (Fig. S6). The absence of whole-brain volume loss in the context of ventricular expansion contrasts with the natural history of Huntington's disease, which shows that ventricular volume changes occur in the context of progressive neurodegeneration and atrophy.[2]

A transient increase was seen in CSF NfL levels in the every-8-week tominersen group at week 21; although neuroaxonal damage may be implicated, increased levels of leukocytes and total protein in CSF in some participants suggest an inflammatory component (additional preclinical data are provided in Fig. S7). CSF NfL levels in the every-16-week tominersen group and the placebo group were similar at all time points. No linear relationship between CSF NfL levels and clinical outcome was shown. More adverse events occurred in the participants in the every-8-week tominersen group than in those in the placebo group and the every-16-week tominersen group (Tables S7 through S12).

The role of antisense oligonucleotide–related toxic effects (possibly inflammatory in nature), as compared with total HTT lowering, on the outcomes observed in GENERATION HD1 cannot be distinguished, given the close relationship between drug exposure and HTT lowering. The results of post hoc analyses support the hypothesis that younger participants (who have less disease burden) may benefit from tominersen therapy (Fig. S8); this hypothesis is currently being tested in a phase 2 dose-finding trial (GENERATION HD2; NCT05686551).

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A list of the GENERATION HD1 investigators is provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

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

A data sharing statement provided by the authors is available in the Supplementary Appendix.

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Tight Blood-Glucose Control without Early Parenteral Nutrition in the ICU

TO THE EDITOR: Tight glucose control was not shown to improve outcomes in critically ill patients in the TGC-Fast trial conducted by Gunst et al. (Sep. 28 issue).[1] However, assessment of glycemic variability (rather than glycemic control alone) might be useful. Critically ill patients are often exposed to high glycemic variation, regardless of whether initial stress hyperglycemia has been corrected; stress hyperglycemia constitutes an adaptive response to acute illness.[2]

Various definitions exist for glycemic variability, measured according to either the glycemic variation coefficient or the standard deviation to the mean glucose level. In the current trial, a tight-control protocol led to a substantial reduction in glycemia on day 1.

Multiple observational studies have shown statistical correlations between high glycemic variability and increased mortality in the intensive care unit (ICU), regardless of hypoglycemia or diabetes status.[3,4] A pathophysiological explanation could be increased oxidative stress induced by strong glycemic variation, especially in patients with diabetes.[5]

It is difficult to define general rules regarding the glycemic target, and an individualized approach should be considered. The use of a computer algorithm in the current trial may have reduced glycemic variation, but a post hoc analysis could be interesting, despite its limitations.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Insulin is a powerful drug with pleomorphic metabolic effects.[1] The history of its effect on enhancing survival in persons with and without diabetes spans several decades, beginning with the GIK (glucose–insulin–potassium) polarizing solution in the 1960s,[2] followed by Van den Berghe's pioneering work showing how insulin reduces mortality despite a high incidence