Ifezuntrigene Inilparvovec (AMT-130) for Huntington's Disease

Draft Background and Scope

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Background

Huntington's disease (HD) is a hereditary, fatal neurodegenerative disorder that causes progressive motor, cognitive, and psychiatric symptoms affecting around 40,000 people in the United States (US).[1] It is caused by a mutation in the huntingtin (HTT) gene, which results in an expansion of a repeating sequence of three base-pairs ("triplet repeat"); people who inherit 40 or more repeats will develop HD during their lifetimes unless they die at an early age.[2] The disease is inherited in an autosomal dominant manner, meaning that 50% of offspring will be affected. Symptom onset is typically between age 30 and 50 years; however, there is also a juvenile form, as well as later-onset forms.[3] Life expectancy is around 15-20 years after symptom onset but can be longer, depending on age of onset.[4] Because of the long course of the disease, healthcare utilization and costs are higher for HD patients than non-HD patients,[5] with caregiver costs among the largest financial burden, especially in later stages of the disease.[6]

Diagnosis of HD can be difficult, especially in those people who do not have a family history, as initial symptoms can be subtle and are more likely to be related to mental health (e.g., mood disorders, depression, apathy, irritability and aggression) and cognitive symptoms (e.g., difficulty multitasking, forgetfulness).[2] Motor symptoms tend to appear later and include chorea (involuntary brief, random dance-like movements), problems with balance and falls, and difficulty speaking and swallowing. Confirmation of diagnosis is through genetic testing examining the number of triplet repeats. In asymptomatic family members of those with HD, predictive genetic testing can be done, as presence of the gene mutation can affect planning for the future, including family planning.[7] The symptoms of HD also affect a person's ability to work, and the majority of people living with HD stop working within four years of diagnosis.[8]

There are currently no approved disease-modifying therapies for HD. Current treatment is symptomatic – vesicular monoamine transporter type 2 (VMAT2) inhibitors such as tetrabenazine and valbenazine to treat chorea are the only HD-specific medications; neuroleptic medications,

antidepressants, and mood stabilizers are commonly prescribed to manage psychiatric and behavioral symptoms. There are no current treatments for the cognitive symptoms of HD. Along with medications, symptoms can be treated with physical therapy, occupational therapy, and speech and swallow therapy. Clinical practice guidelines recommend that education and family support be offered along with current treatments.[2] This may be accomplished by a multidisciplinary team including neurologists, psychiatrists, physical and occupational therapists, speech language pathologists, dieticians, genetic counselors, and social workers.

Ifezuntrigene inilparvovec ("AMT-130", uniQure N.V.) is one of the first gene therapies developed for HD. AMT-130 uses a viral vector to deliver microRNA directly into the brain via a one-time, magnetic resonance imaging (MRI)-guided surgical procedure. The microRNA targets and silences HTT gene RNA, lowering production of mutant proteins to slow progression of disease. The treatment was tested in a randomized Phase I/II study, which included low and high dosage treatment, and also a sham surgery arm. However, due to the lengthy follow-up necessary to assess outcomes in HD, the manufacturer, in consultation with the US Food and Drug Administration (FDA), shifted to comparison with a natural history control group in December 2024 as part of a plan to pursue accelerated approval of the treatment.[9] In November 2025, the FDA let the company know that comparison with natural history data would not be sufficient for a Biologics License Application (BLA).[10] Following FDA leadership changes and additional meetings, the manufacturer announced in June 2026 that the FDA had agreed that three-year follow-up data from the Phase I/II study could be used to support a BLA for accelerated approval; uniQure stated a plan to file the application in the third quarter of 2026.[11] AMT-130 has been granted Orphan Drug, Fast Track, Regenerative Medicine Advanced Therapy (RMAT), and Breakthrough Therapy designations from the FDA.[12]

Stakeholder Input

To develop this draft scoping document, ICER sought input from diverse stakeholders, including patient advocacy organizations, clinicians, researchers, and the manufacturer of the agent of focus in this review. To date, the manufacturer uniQure has been unwilling to speak with ICER and asks ICER to note, "that uniQure did not participate in the process and did not review or approve the methodology, findings, or conclusions."

This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public, as well as publicly available patient testimonials, including an FDA "Voice of the Patient" report, and reports in the scientific literature.[13] A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of treatments.

Huntington's disease has a tremendous impact on daily life, including family, friendships, and work. During an FDA panel on the patient experience of HD, people living with HD and caregivers described the impact that the psychiatric symptoms of HD had on their lives.[13] Anger, apathy, aggression, and lack of impulse control resulted in inappropriate behavior and sometimes violence. One family member stated, "These symptoms have ripped my family apart, causing endless heartache and suffering." Depression and anxiety also affect many people living with HD. Caregivers of people living with HD described how cognitive impairment left their loved ones unable to accomplish activities of daily living such as reading a newspaper, grocery shopping, doing schoolwork, or even carrying on conversations. Impairment in executive function can be an early symptom of HD and can cause difficulty at work or an inability to work.[14] Motor symptoms are also a prominent feature of the disease and affect individuals' ability to walk, talk, eat, and sleep. Finally, some caregivers described the neuropathy that can occur with HD, which can cause pain and/or itching, as a very bothersome symptom that is difficult to manage.

HD has been described as a "family disease and experience," since the disease permeates the family, both in terms of its inheritance and caregiving impact.[15] Caregiver impact increases as the disease progresses and individuals become more dependent on others, with 24/7 care eventually needed, particularly during the last five years of life. Many people with HD require care in a long-term care facility because of the heavy caregiving needs, and caregivers often need to change their career or work less to accommodate the needs of the individual with HD.[16] Navigating the financial burden of HD also takes a toll on families, particularly the need to navigate insurance issues and the application for disability.[17]

Children of people with HD not only need to cope with the challenges of an ill parent, often resulting in mental health issues of their own, but also the possibility that they may develop the disease themselves.[18] With regard to testing, children experienced ambivalence, uncertainty, and psychological stress when thinking about whether or not to get tested.[7]

Clinical experts relayed that only about 30% of patients with HD get specialty care with a movement disorders neurologist, and only half of those patients get care at a HD Center of Excellence. This difficulty in accessing specialized neurology care results both in a long journey to diagnosis and concerns about patients' ability to access new treatments that may only be offered at specialty centers. In addition, clinicians emphasized the importance of multidisciplinary care, including neurologists, psychiatrists, therapists, social workers, and geneticists, as families need assistance not only with medical issues but also with financial issues such as long-term care and life insurance, and testing for family members. Finally, clinical experts spoke about the need for new treatments that slow progression of the disease, as current treatments are only symptomatic.

Report Aim

This project will evaluate the health and economic outcomes of AMT-130 for Huntington's disease. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Applicable Framework Adaptations

We propose to assess AMT-130 under an adaptation of the ICER Value Framework for treatments of high-impact "single and short-term therapies" (SSTs), because we believe it may meet the following criteria defined as:

- The therapy is delivered through a single intervention or a short-term course (less than one year) of treatment that offers a significant potential for substantial and sustained health benefits extending throughout patients' lifetimes.
- The therapy can eradicate a disease or condition or produce sustained major health gains that can halt the progression of significant illnesses.

Following formal public comment and discussions with stakeholders, ICER will make a final decision on whether the therapy meets these criteria and will be assessed using an adapted approach.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is adults with early symptomatic Huntington's disease.

Interventions

The full list of interventions is as follows:

- ifezuntrigene inilparvovec ("AMT-130," uniQure N.V.)

Comparators

- Usual symptomatic care (treatment for movement disorders [e.g., chorea], psychiatric and mood symptoms, physical therapy, etc.)

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Disease progression
        - Motor function and chorea severity
        - Functional capacity and activities of daily living
        - Cognitive function and executive functioning
        - Psychological and behavioral symptoms
        - Swallowing function and dysphagia
    - Health-related quality of life
    - Caregiver and family impact
    - Mortality
    - Need for long-term care
    - Hospitalizations
    - Adverse events including:
        - Falls and mobility-related safety
        - Mental health outcomes (e.g., anxiety, suicide risk)
        - Headache
        - Procedure-related adverse events (e.g., headache, complications, pain)
        - Post lumbar puncture syndrome
        - Serious adverse events
        - Other adverse events (e.g., constipation, insomnia, back pain)

- Other Outcomes
    - Biomarkers such as Neurofilament light chain (NfL) and mutant huntingtin protein levels (mHTT)

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least six months duration.

Settings

All relevant settings will be considered.

Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There are particular obligations to people with this condition because of disease severity and/or unmet need with currently available therapies.
There are particular obligations to people with this condition because it disproportionately affects those from a racial/ethnic group that have not been equitably served by the health care system.
Apart from issues around disease severity/unmet need and race/ethnicity, there are other particular obligations to people with this condition.
The treatments are likely to improve caregivers' quality of life and/or ability to pursue their own education, work, and family life.
If payment/cost were not an issue, the treatments are likely to improve access to treatment because of its method of delivery and/or treatment setting.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on November 16, 2026. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of AMT-130 relative to usual symptomatic care. The model structure will be based in part on a literature review of prior published models of HD. Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Societal impacts (e.g., patient and caregiver productivity, interactions with the criminal justice system) and other indirect costs will be considered in a separate modified societal perspective analysis. This analysis will be considered as a co-base case when relevant direct data on societal effects and/or costs are available, and at least one of these two conditions is met: (1) the impact of treatment on available societal effects/costs is judged to be substantial; (2) the contribution of societal effects/costs to the total effects/costs associated with the condition is judged to be substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per equal value of life years gained (evLY) or quality-adjusted life years (QALY) gained, or when the result crosses the threshold of $100,000 or $150,000 per evLY or QALY gained. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of AMT-130 on productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).

The target population will consist of adults with early symptomatic HD. The model will consist of health states capturing distinct levels of clinical progression, based on Total Functional Capacity (TFC) scores. A cohort of patients will transition between states during predetermined cycles of one year over a lifetime time horizon, modeling patients from treatment initiation until death.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using relevant clinical trials.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of years of independent living gained, life-years gained, QALYs gained, and evLYs. Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect

costs will be included in a separate analysis, as available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLY gained, cost per life-year gained, and cost per year of independent living gained.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its report's information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by AMT-130 (e.g., premature transition to full-time specialized care), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of Huntington's disease beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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