uniQure Announces Update on Phase I/II Clinical Trials of AMT-130 Gene Therapy for the Treatment of Huntington's Disease

December 19, 2023

~ Patients treated with AMT-130 continue to show evidence of preserved neurological function with potential dose-dependent clinical benefits relative to an inclusion criteria-matched natural history of the disease ~

~ Mean CSF NfL continue to demonstrate favorable trends with low-dose patients below baseline at 30 months and high-dose patients near baseline at 18 months ~

~ AMT-130 continues to be generally well-tolerated across both doses ~

~ Data support continuing clinical development of AMT-130 and pursuing regulatory interactions to discuss potential strategies for ongoing development ~

~ Investor conference call and webcast today at 8:30 a.m. ET ~

LEXINGTON, Mass. and AMSTERDAM, Dec. 19, 2023 (GLOBE NEWSWIRE) -- uniQure N.V. (NASDAQ: QURE), a leading gene therapy company advancing transformative therapies for patients with severe medical needs, today announced updated interim data including up to 30 months of follow-up from 39 patients enrolled in the ongoing U.S. and European Phase I/II clinical trials of AMT-130 for the treatment of Huntington's disease.

"The clinical assessment trends in the ongoing studies of AMT-130 look very promising and continue to show disease stability in Huntington's disease patients treated with this one-time administered gene therapy, several of whom have now been followed more than two years," stated Walid Abi-Saab, M.D., chief medical officer of uniQure. "We are observing favorable trends in evaluation of motor skills, functional independence, and composite rating scores as compared to a non-concurrent criteria-matched natural history cohort."

"We also are pleased to observe further declines in levels of NfL, a measurement of neuronal degradation and disease progression, with low-dose patients below baseline at 30 months of follow-up and high-dose patients near baseline at 18 months," he continued. "Importantly, AMT-130 continues to be generally well-tolerated with a manageable safety profile at both its low and high doses. We will continue to follow these patients and look forward to initiating regulatory interactions next year."

"The results from these Phase I/II trials continue to be very encouraging as they show positive-trending, potentially dose-dependent signals across multiple key clinical and functional measures, in conjunction with further declines in NfL," stated Edward Wild, Ph.D., FRCP, professor of neurology at University College London (UCL) Queen Square Institute of Neurology, consultant neurologist at National Hospital for Neurology & Neurosurgery, and associate director of UCL Huntington's Disease Centre. "While there are well-known complexities associated with analyzing and interpreting other biomarkers in Huntington's disease, these NfL data are consistent with the clinical data suggesting possible disease stability and support the continued development of AMT-130. The Huntington's disease community has endured a prolonged and challenging wait for disease-modifying treatment options, and we enthusiastically embrace this potentially important advancement for this devastating disease."

Ongoing Phase I/II Trials of AMT-130 in Huntington's Disease

In the multi-center, Phase I/II clinical trial of AMT-130 being conducted in the U.S., a total of 26 patients with early-manifest Huntington's disease have been enrolled, including an initial 10-patient low-dose cohort (6 treated, 4 control) with up to 30 months of follow-up and a subsequent 16-patient high-dose cohort (10 treated, 6 control) with up to 18 months of follow-up. Patients were randomized to treatment with AMT-130 or an imitation (sham) surgery. The U.S. study consists of a blinded 12-month core study period followed by unblinded long-term follow-up of five years for treated patients. Four of the six control patients in the high-dose cohort were crossed over to treatment and the remaining two patients failed to meet the study's inclusion criteria.

The multi-center, open-label, Phase I/II clinical trial of AMT-130 being conducted in Europe and the UK enrolled a total of 13 patients with the same early manifest criteria for Huntington's disease as the U.S. study. Six patients were treated with AMT-130 in the initial low-dose cohort and seven patients were treated in the subsequent high-dose cohort.

The combined U.S. and European data presented in this release are subject to a September 30, 2023 cut-off date and do not include efficacy and biomarker data from the control patients who crossed over to treatment.

Updated Interim Data

Exploratory Efficacy Data

Clinical and functional measurements for treated patients in each dose cohort were compared to baseline measurements, as well as to control patients (up to 12 months) and a non-concurrent criteria-matched natural history cohort. The natural history cohort was developed by uniQure in collaboration with the Cure Huntington's Disease Initiative (CHDI) using the TRACK-HD natural history study of patients with early Huntington's disease. The cohort includes 31 patients that met the uniQure clinical trial inclusion criteria of Total Functional Capacity, Diagnostic Classification Level and minimum striatal volumes.

- Updated clinical data through 30 months for the low-dose cohort and 18 months for the high-dose show ongoing evidence of potential dose-dependent clinical benefit relative to the non-concurrent criteria-matched natural history.

- For patients receiving the high dose, neurological function as measured by cUHDRS and each of its individual components was preserved or improved at 18 months compared to pre-treatment baseline measurements.
- For patients receiving the low dose, neurological function as measured by Total Motor Score (TMS) and Total Functional Capacity (TFC) was preserved at 30 months compared to pre-treatment baseline measurements.
- When compared to the expected rate of decline from the natural history cohort, AMT-130 showed favorable trends in cUHDRS, TFC and TMS.
    - *composite Unified Huntington's Disease Rating Scale (cUHDRS)* : AMT-130 showed a favorable difference in cUHDRS of 0.39 points at 30 months and 1.24 points at 18 months for the low- and high-dose, respectively (baseline values: 14.1 in low-dose and 14.9 in high-dose).
    - *Total Functional Capacity (TFC)*: AMT-130 showed a favorable difference in TFC of 0.95 points at 30 months in the low-dose and 0.49 points at 18 months in the high-dose (baseline values: 11.9 in low-dose and 12.2 in high-dose).
    - *Total Motor Score (TMS):* AMT-130 showed a favorable difference in TMS of 2.80 points at 30 months in the low-dose and 1.70 points in the high-dose at 18 months (baseline values: 13.3 in low-dose and 12.1 in high-dose).

Biomarkers and Volumetric Imaging Data

- *Neurofilament Light Chain (NfL*): Mean CSF NfL for the low-dose cohort remained below baseline through month 30 and was 6.6% below baseline. Mean CSF NfL for the high-dose cohort also further declined and is near baseline at month 18. These data suggest a reduction in neurodegeneration when compared to an expected increase from baseline in CSF NfL based on natural history data. As expected, all patients treated with AMT-130 experienced a transient increase in CSF NfL related to the surgical procedure that peaked at approximately one month following the procedure and declined thereafter. These transient increases were not dose-dependent.
- *Mutant Huntingtin Protein (mHTT)*: Given AMT-130 is directly administered deep within the brain, the pharmacodynamics of mHTT in the CSF are not believed to be materially representative of mHTT in the targeted brain regions. Mean changes in mHTT levels measured in CSF samples compared to baseline continue to be variable and impacted by baseline levels near or below the lower limit of quantification.
- *Total Brain Volume:* Changes in the total brain volume of patients treated with AMT-130 were observed after the surgical procedure and trended below natural history. The volumetric changes do not appear to be clinically meaningful or associated with protracted increases in neurodegeneration as measured by NfL.

Safety and Tolerability

AMT-130 was generally well-tolerated, with a manageable safety profile at both the lower dose of $6x10^{12}$ vector genomes and the higher dose of $6x10^{13}$ vector genomes. The most common adverse events in the treatment groups were related to the surgical procedure.

There were four serious adverse events (SAE) unrelated to AMT-130 (post-operative delirium, major depression, suicidal ideation and epistaxis) in the low-dose cohort, six unrelated SAEs in the high-dose cohort (back pain, hypothermia, post procedural hematoma, post-lumbar puncture syndrome (n=2), pulmonary embolism), and one SAE (deep vein thrombosis) in the control group. In addition, there were four AMT-130-related serious adverse events in the high-dose cohort (central nervous system inflammation (n=3), and severe headache (1) that, retrospectively, also was attributable to central nervous system inflammation.

Patients with symptomatic central nervous system inflammation improved with glucocorticoid medication. Additionally, six high-dose patients have received perioperative steroids with the administration of AMT-130 to reduce the risk of inflammation.

Next Steps

Based on the promising data from this interim analysis, uniQure anticipates the following next steps:

- uniQure began enrolling patients in a third cohort to further investigate both doses in combination with perioperative immune suppression with a focus on evaluating near-term safety. Up to 12 patients will be treated in this cohort, all of whom will receive AMT-130 using the current, established stereotactic neurosurgical delivery procedure.
- In the first quarter of 2024, uniQure plans to initiate regulatory interactions to discuss the U.S. and European data and potential strategies for ongoing development of AMT-130.
- In mid-2024, uniQure expects to present another clinical update from the ongoing Phase I/II studies of AMT-130, including additional follow-up data from the treated patients in the U.S. and European trials.

Investor Conference Call and Webcast Information

uniQure management will host an investor conference call and webcast today, Tuesday, December 19, 2023 at 8:30 a.m. ET. The event will be webcast under the Events & Presentations section of uniQure's website at https://www.uniqure.com/investors-media/events-presentations, and following the event a replay will be archived for 90 days. Interested parties participating by phone will need to register using this online form. After registering for dial-in details, all phone participants will receive an auto-generated e-mail containing a link to the dial-in number along with a personal PIN number to use to access the event by phone. If you are joining the conference call, please dial in 15 minutes before the start time.

About the Phase I/II Clinical Program of AMT-130

The U.S. Phase I/II clinical trial of AMT-130 for the treatment of Huntington's disease is exploring the safety, tolerability, and efficacy signals in 26 total

patients with early manifest Huntington's disease split into a 10-patient low-dose cohort followed by a 16-patient high-dose cohort; patients are randomized to treatment with AMT-130 or an imitation (sham) surgery. The multi-center trial consists of a blinded 12-month core study period followed by unblinded long-term follow-up for five years. A total of 16 patients in the clinical trial were randomized to treatment and received a single administration of AMT-130 through MRI-guided, convection-enhanced stereotactic neurosurgical delivery directly into the striatum (caudate and putamen). An additional four control patients in the high-dose cohort crossed over to treatment. Additional details are available on www.clinicaltrials.gov (NCT04120493).

The European, open-label Phase Ib/II study of AMT-130 enrolled 13 patients with early manifest Huntington's disease across two dose cohorts; a low-dose cohort of six patients and a high-dose cohort of seven patients. Together with the U.S. study, the European study is intended to establish safety, proof of concept, and the optimal dose of AMT-130 to take forward into Phase III development or into a confirmatory study should an accelerated registration pathway be feasible.

AMT-130 is uniQure's first clinical program focusing on the CNS incorporating its proprietary miQURE ® platform.

About Huntington's Disease

Huntington's disease is a rare, inherited neurodegenerative disorder that leads to motor symptoms including chorea, behavioral abnormalities and cognitive decline resulting in progressive physical and mental deterioration. The disease is an autosomal dominant condition with a disease-causing CAG repeat expansion in the first exon of the huntingtin gene that leads to the production and aggregation of abnormal protein in the brain. Despite the clear etiology of Huntington's disease, there are no currently approved therapies to delay the onset or to slow the disease's progression.

About uniQure

uniQure is delivering on the promise of gene therapy – single treatments with potentially curative results. The recent approvals of uniQure's gene therapy for hemophilia B – an historic achievement based on more than a decade of research and clinical development – represent a major milestone in the field of genomic medicine and usher in a new treatment approach for patients living with hemophilia. uniQure is now leveraging its modular and validated technology platform to advance a pipeline of proprietary gene therapies for the treatment of patients with Huntington's disease, refractory temporal lobe epilepsy, ALS, Fabry disease, and other severe diseases. www.uniQure.com

uniQure Forward-Looking Statements

This press release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as "anticipate," "believe," "could," "establish," "estimate," "expect," "goal," "intend," "look forward to", "may," "plan," "potential," "predict," "project," "seek," "should," "will," "would" and similar expressions and the negatives of those terms. Forward-looking statements are based on management's beliefs and assumptions and on information available to management only as of the date of this press release. Examples of these forward-looking statements include, but are not limited to, statements concerning: the potential clinical and functional effects of AMT-130, including as an important treatment option for patients with Huntington's disease; the company's plans to continue clinical development of AMT-130 and to initiate interactions with regulatory authorities; the potential for accelerated regulatory pathways; the company's use of a natural history cohort as a basis for comparison with respect to the efficacy of AMT-130; the company's enrollment plans with respect to the third cohort studying AMT-130 in combination with perioperative immune suppression; the utility of mHTT or NfL in CSF as an effective biomarker; and the company's plans for further clinical updates. uniQure's actual results could differ materially from those anticipated in these forward-looking statements for many reasons. These risks and uncertainties include, among others: risks related to the company's Phase I/II clinical trials of AMT-130, including the risk that such trials will be unable to demonstrate efficacy data sufficient to support further clinical development and the risk that interim data from the trials may not be predictive of later data readouts; risks related to the company's financial position and stock price, including the company's ability to raise sufficient capital to support further development of the company's clinical programs, as needed and on acceptable terms; risks related to the company's reliance on third parties to conduct, supervise, and monitor its preclinical studies and clinical trials and to manufacture components of its drug product, including the clinical trials for AMT-130; and the company's ability to obtain, maintain and protect its intellectual property. These risks and uncertainties are more fully described under the heading "Risk Factors" in uniQure's periodic filings with the U.S. Securities & Exchange Commission (SEC), including its Annual Report on Form 10-K filed with the SEC on February 27, 2023, its Quarterly Reports on Form 10-Q filed with the SEC on May 9, 2023, August 1, 2023 and November 7, 2023, and in other filings that the company makes with the SEC from time to time. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements and, except as required by law, uniQure assumes no obligation to update these forward-looking statements, even if new information becomes available in the future.

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