uniQure

Leadership in Gene Therapy

Corporate Presentation
April 2023

Charles, Huntington's disease patient advocate

uniQure

Our mission is to deliver curative, one-time administered genomic medicines that transform the lives of patients.

Reimagining the future through ingenuity and innovation.

Ron, a clinical trial patient for etranacogene dezaparvovec

uniQure our history of innovation

A gene therapy pioneer with a 25-year history and deeply engrained culture of innovation across an increasingly validated platform

First approved AAV gene therapy in the world

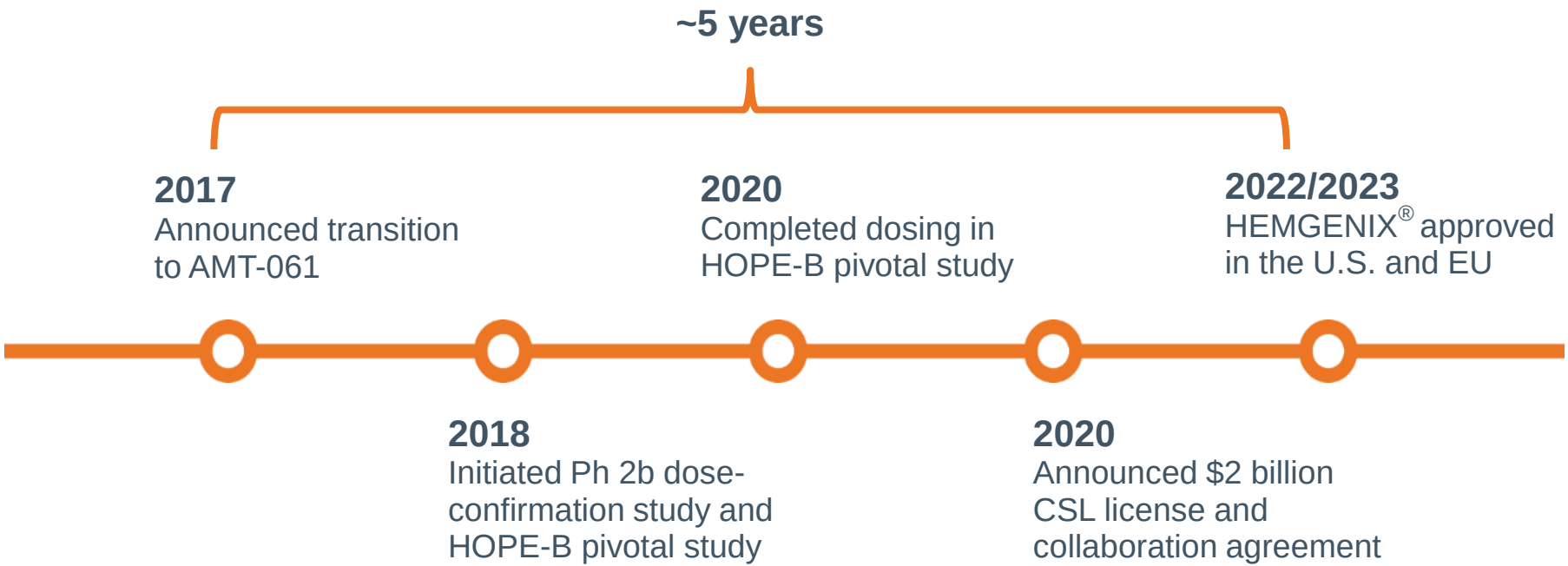
First commercially licensed AAV manufacturing facility

First AAV-delivered gene silencing for HD to enter clinic

First AAV vector demonstrated effective in patients with NABs

First Gene therapy approved for hemophilia B

Pursuing hemophilia B with a first and potential best-in-class gene therapy



uniQure leading the gene therapy revolution

- **Validated technology platform**
- **Industry-leading manufacturing capabilities**
- **Broad pipeline of first/best-in-class gene therapies**
- **Strong financial position**
- **Numerous near-term milestones**
  - One to two-year Huntington’s disease data from U.S. Ph 1/2
  - One-year Huntington’s disease data from Cohort 1 of EU Ph 1b/2
  - Initiate two new Ph 1/2 studies
  - Advance at least one new candidate to IND-enabling studies

uniQure manufacturing excellence for global, commercial opportunities

Establishing larger scale and highly cost-effective capabilities to address more prevalent disorders

uniQure expanding our capabilities

Completed construction of a second cGMP manufacturing facility in Amsterdam that will complement commercial manufacturing in Lexington, Massachusetts.

Amsterdam, NL
111,000 sq ft (~290 FTEs)

- Research
- Process Development
- Analytical Development
- Quality
- cGMP Manufacturing

Lexington, MA
100,000 sq ft (~200 FTEs)

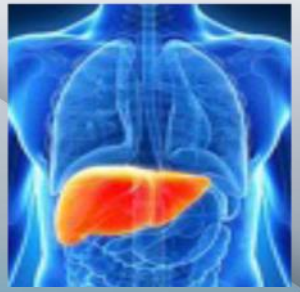
- Process Development
- Analytical Development
- Quality
- cGMP Manufacturing
- Research

our areas of focus

AAV Engine: Leveraging our leading technology platform to develop and commercialize products targeting the CNS and liver

CNS

Liver



AAV Technology Engine

Manufacturing & Enabling Tools

reimagining the R&D pipeline

Doubling the pipeline in 5 years

5-year Pipeline Goals:

- **3-4 Phase 3 commercial programs**
- **5-8 Phase 1/2 programs**
- **7-12 preclinical programs**

reimagining the R&D pipeline

Larger market opportunities built on validated targets and technologies

Key criteria:

- Best and/or first in class
- Human validation
- Leverage proven technologies
- Larger indications

recent transactions

In January 2023, completed global licensing deal for AMT-162 (formerly APB-102), a clinical stage gene therapy for SOD1 ALS

- $10 million up-front cash payment
- Up to $45 million upon achievement of regulatory approvals and pre-specified annual net sales milestones
  - Tiered royalties of a percentage of net sales starting in the mid-single to low double digits

Aligns with current neurodegenerative focus of pipeline and highly complementary with AMT-161 program for ALS caused by mutations in c9orf72 gene

Clinical-stage asset with cleared IND expected to enter development in 2H23

Fast-progressing patient population

Orphan Drug and Fast Track designations

Our Research and Development Pipeline

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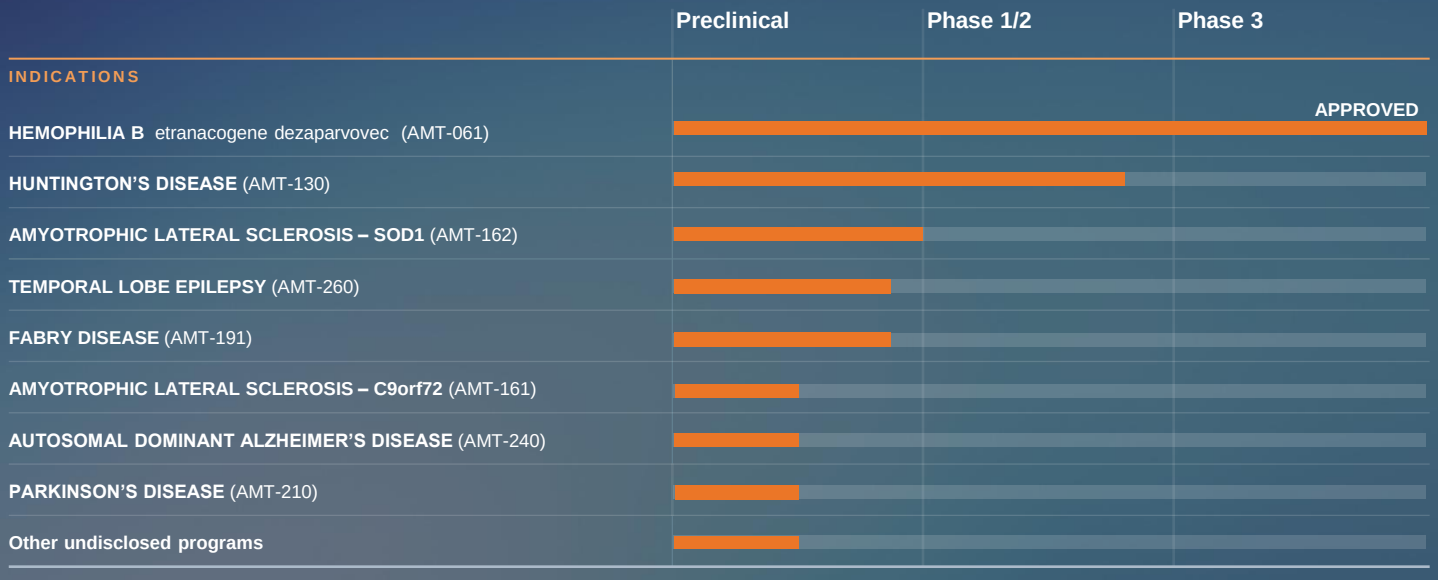

CSL Behring partnership ←

Proprietary programs ←

uniQure strong execution across all programs in 2022

Hemophilia B	✓ FDA approval of HEMEGENIX® ✓ Received $55 million in additional milestone payments from CSL Behring ✓ Positive CHMP opinion for European approval
Huntington's	✓ Announced 12-month data on lower-dose cohort in Phase I/II trial of AMT-130 ✓ Enrolled a total of 36 patients in U.S. and European trials to date ✓ Resumed European higher-dose enrollment following DSMB guidance
Research Pipeline	✓ Virtual R&D investor event highlighting TLE and manufacturing platform ✓ Initiated IND-enabling studies in TLE and Fabry
Manufacturing and Technology Platform	✓ Completed 2nd cGMP facility in Amsterdam with 500-liter capacity ✓ Completed process validation for etranacogene dezaparvovec ✓ Lexington manufacturing GMP certification from EMA and FDA

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HEMGENIX®

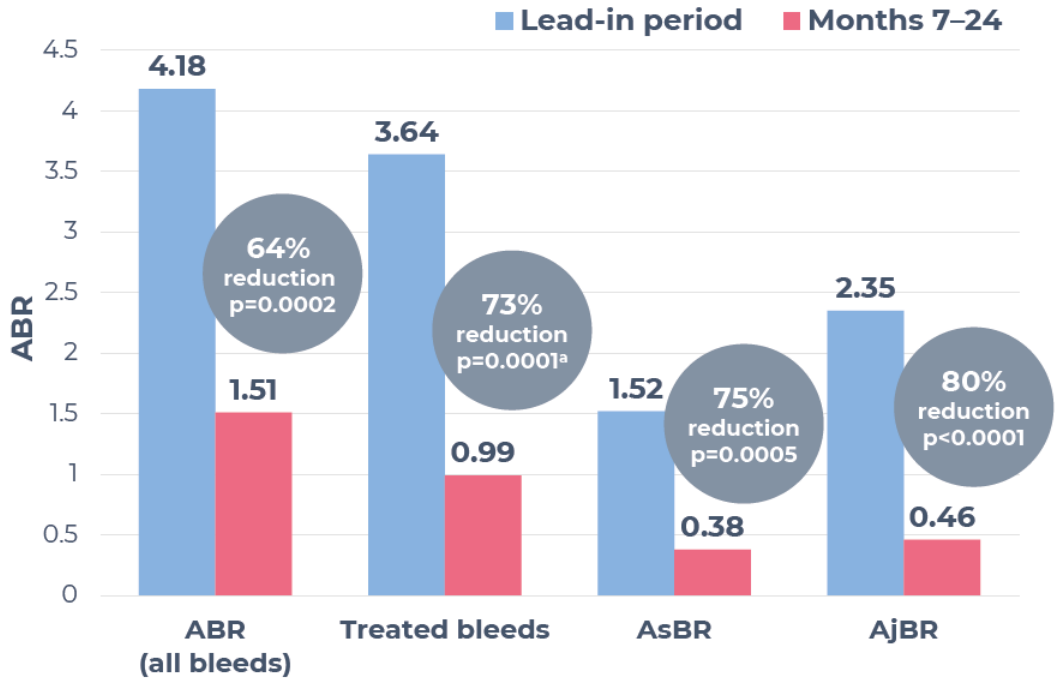
etranacogene dezaparvovec-drlb

CSL's HEMGENIX® was approved by the FDA in November 2022 and by the EMA in February 2023

- **First and only FDA and EMA-approved gene therapy** for adults with hemophilia B who:
  - Currently use factor IX prophylaxis therapy, or
  - Have current or historical life-threatening bleeding, or
  - Have repeated, serious spontaneous bleeding episodes*

* Bullet-point copy as it appears on U.S. prescribing label

HOPE-B pivotal trial: improvement in average bleeding rate (ABR)



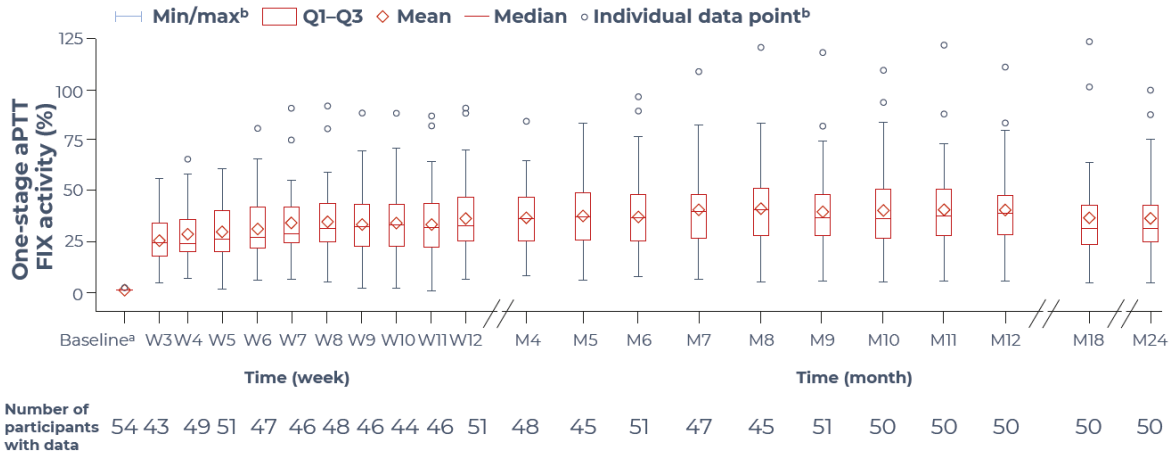
[a] P-value for treated bleeds is not Type I error controlled.
ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate; AsBR, annualized spontaneous bleeding rate.

Courtesy of CSL Behring

Compared with ≥ 6-month lead-in period, mean ABR for all bleeds during Month 7-24 post-treatment was significantly reduced by 64%.

- Mean ABR lead-in period vs Months 7-24: 4.18 vs 1.51; p=0.0002
- The bleed reduction that satisfied the primary endpoint for the trial during Months 7-18 was sustained for Months 7-24
- Mean ABR for all other bleed types was reduced at Months 7-24 compared with the ≥ 6-month lead-in period

HOPE-B pivotal trial: FIX activity levels over 24 months



[a] Baseline FIX was imputed based on participant's historical hemophilia B severity documented on the CRF. If the participant had documented severe FIX deficiency (FIX<1%), their baseline FIX activity level was input as 1%. If the participant had documented moderately severe FIX deficiency (FIX≥1% and ≤2%), their baseline FIX activity level was input as 2%. The standard error was not provided at baseline.
[b] Min/max within 1.5x interquartile range of the bottom and top of the box, respectively. Any points outside of the whiskers are plotted individually.
aPTT, activated partial thromboplastin time; CRF, case report form; FIX, factor IX; M, Month; max, maximum; min, minimum; W, Week.

Mean (standard deviation [SD]; minimum-maximum) FIX activity levels were sustained throughout 24 months post-treatment.

- Month 6: 39.0% (±18.7; 8.2-97.1) (n=51)
- Month 18: 36.9% (±21.4; 4.5-122.9) (n=50)
- Month 24: 36.7% (±19.0; 4.7-99.2) (n=50)

These values represented a significant increase from baseline (mean 1.19%; SD: 0.39) with a least squares mean FIX activity increase of:

- Month 6: 36.2% (standard error [SE]: 2.3; 95% confidence interval [CI]: 31.7-40.7; p<0.0001)
- Month 18: 34.4% (SE: 2.3; 95% CI: 29.8-39.9; p<0.0001)
- Month 24: 34.1% (SE: 2.3; 95% CI: 29.6-38.7; p<0.0001); p-value not adjusted for multiplicity)

Courtesy of CSL Behring

HOPE-B pivotal trial: most frequent adverse events (all causality ≥13%)

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	All causality AEs		Treatment-related AEs	
	Participants n (%)	Events n	Participants n (%)	Events n
Participants with ≥1 AE	**54 (100)**	**557**	**38 (70.4)**	**93**
Arthralgia	19 (35.2)	34	3 (5.6)	3
Headache	16 (29.6)	31	8 (14.8)	9
Nasopharyngitis	15 (27.8)	20	1 (1.9)	1
Fatigue	14 (25.9)	17	4 (7.4)	4
ALT increased	11 (20.4)	12	9 (16.7)	10
COVID-19	10 (18.5)	10	0	0
Back pain	9 (16.7)	12	1 (1.9)	1
Pain in extremity	9 (16.7)	10	0	0
Blood CPK increased	8 (14.8)	11	4 (7.4)	6
AST increased	8 (14.8)	9	5 (9.3)	6
Influenza-like illness	7 (13.0)	12	7 (13.0)	8
Toothache	7 (13.0)	11	0	0
Oropharyngeal pain	7 (13.0)	7	0	0

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase

The safety profile is consistent with previously presented data

- Most AEs were mild (76.1%; moderate: 20.6%; severe 3.2%)

Alanine aminotransferase increase (with or without increased aspartate transaminase) occurred in 11 participants

- Nine (16.7%) received supportive care with reactive corticosteroids for a mean duration of 79.8 days (SD: 26.6; range: 51-130 days)
- All participants discontinued steroid use prior to Week 26
- FIX expression was maintained

No serious AEs related to treatment

One death was reported, unrelated to study treatment

- A 77-year-old participant died from cardiogenic shock (at 65 weeks following infusion), preceded by a urinary tract infection

One case of hepatocellular carcinoma (previously reported) – unrelated to study treatment following a detailed molecular analysis

Courtesy of CSL Behring

strong, future economics from CSL Behring

Global licensing agreement is a historic collaboration in gene therapy and hemophilia with uniQure eligible to receive more than $2B in total economics

- $450M upfront payment received in 2021
- $1.45B in regulatory and commercial milestones
- Near term milestones of $100M for first US sale and $75M for first EU sale if before July 1, 2023
- Double-digit royalty payments starting in mid-teens up to low-twenties percentage of global net product sales

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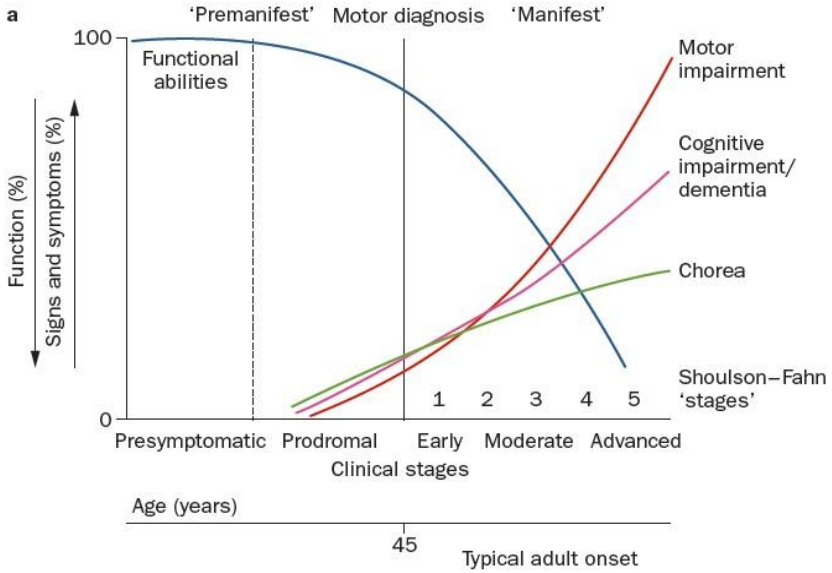
Huntington's Disease

AMT-130

Charles, Huntington's disease patient advocate

Huntington's disease (HD): an overview

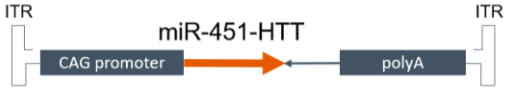
- Autosomal dominant inherited disorder (50% risk if your parent has HD)
- Affects ~25,000 patients each in U.S./EU[1]
- Initially described based upon characteristic chorea
- Dystonia, incoordination, ataxia, and later rigidity and bradykinesia contribute to functional impairment
- Cognitive and behavioral symptoms may occur early
- Progressive course from onset ~age 45 to death over 10-15 years[2]



1) Neuroepidemiology 2016; 46:14-153 2) Ross CA, et al Nat Rev Neurol 2014; 10:204-216

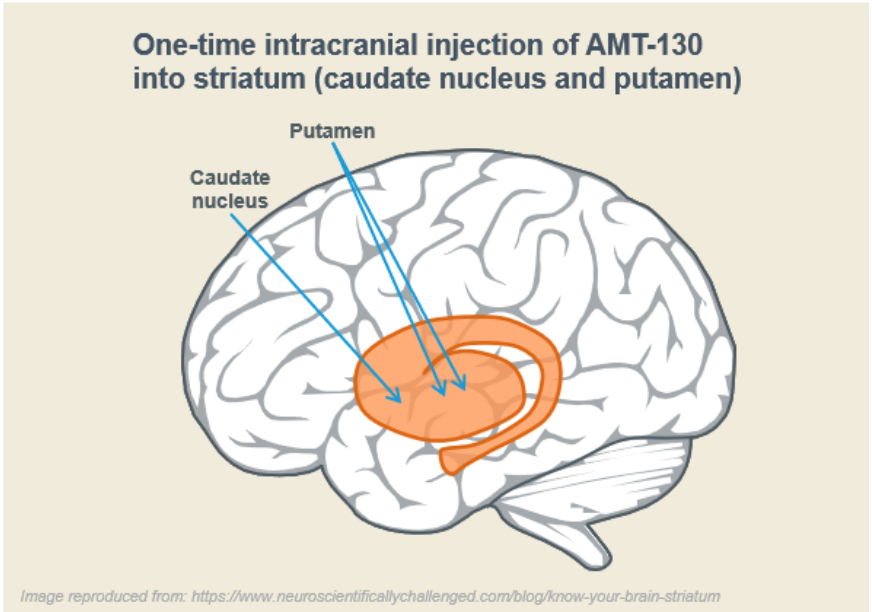
AMT-130: a gene therapy approach for early manifest HD

- **AAV5-miHTT (AMT-130)**
  - Replication-deficient adeno-associated viral vector serotype 5 (AAV5)
  - Codes for microRNA (miRNA) that targets the HTT mRNA at exon 1
  - Blocks expression of HTT protein



Extensive preclinical validation

Model	Efficacy	Safety	Distribution
Cultured human neurons	✓	✓	
Rodents (HD rat[4]) (4 types HD mouse[3])	✓	✓	
NHP (Non-human primate[1])	✓	✓	✓
Pig (tgHD Minipig[2])	✓	✓	✓



1) Samaranch L, et al. Gene Ther 2017;24:253-261; 2) Evers M, et al. Mol Ther 2017;5(Suppl. 1):247; 3) Spronck EA, et al. Hum Gene Ther 2017;28:A78; 4) Miniarikova J, et al. Gene Therapy 2017;24:630-639; 5) Evers MM et al. Mol Ther. 2018;26(9):2163-2177; 6) Spronck EA et al. Mol Ther Methods Clin Dev. 2019 Mar 16;13:334-343; 7) Keskin S et al. Mol Ther Methods Clin Dev. 2019 Oct 4;15:275-284; 8) Caron NS et al. Nucleic Acids Res. 2019 Nov 20. pii: gkz976. doi: 10.1093/nar/gkz976

two ongoing studies in the U.S., EU and UK

CT-AMT-130-01 (Phase Ia/II)
double-blind sham-controlled

HD GeneTRX1

26 Patients

- Low-dose 6e12 AMT-130 (6 Drug, 4 Control)
- High-dose 6e13 AMT-130 (10 Drug, 6 Control)
- Surgical Adaption

Crossover of eligible patients after 1 year following DSMB review

CT-AMT-130-02 (Phase Ib/II)
open-label

HD GeneTRX2

15 Patients

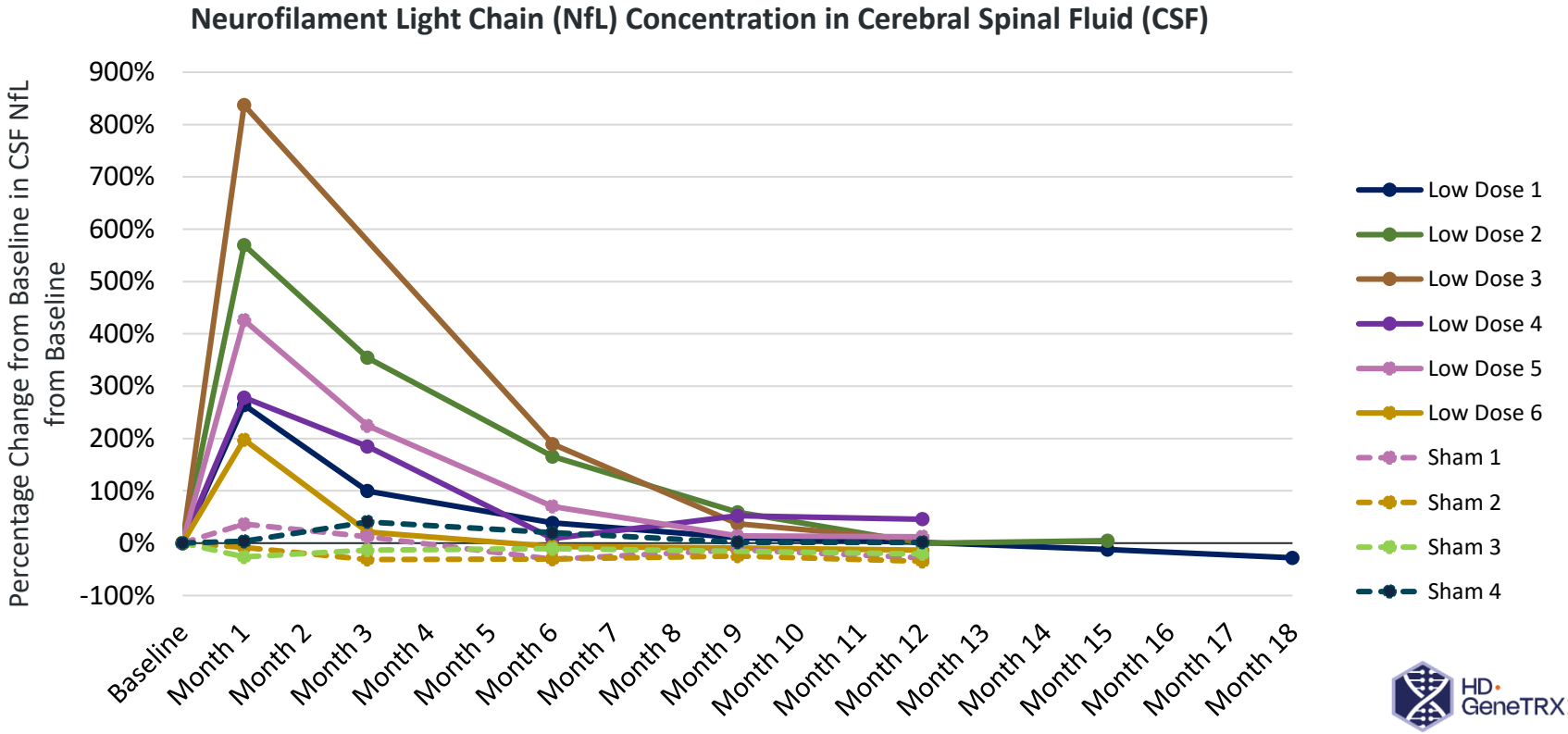
- Low-dose 6e12 AMT-130 (6 patients)
- High-dose 6e13 AMT-130 (9 patients)

encouraging 12-month data from lower dose cohort in U.S. Ph I/II study

- AMT-130 was generally well-tolerated at lower dose, with no reported adverse drug reactions or serious unexpected suspected adverse reactions
- CSF NfL increased as expected following surgical administration of AMT-130 and neared baseline at 12 months
- Trends in CSF mHTT support target engagement at the low dose of AMT-130

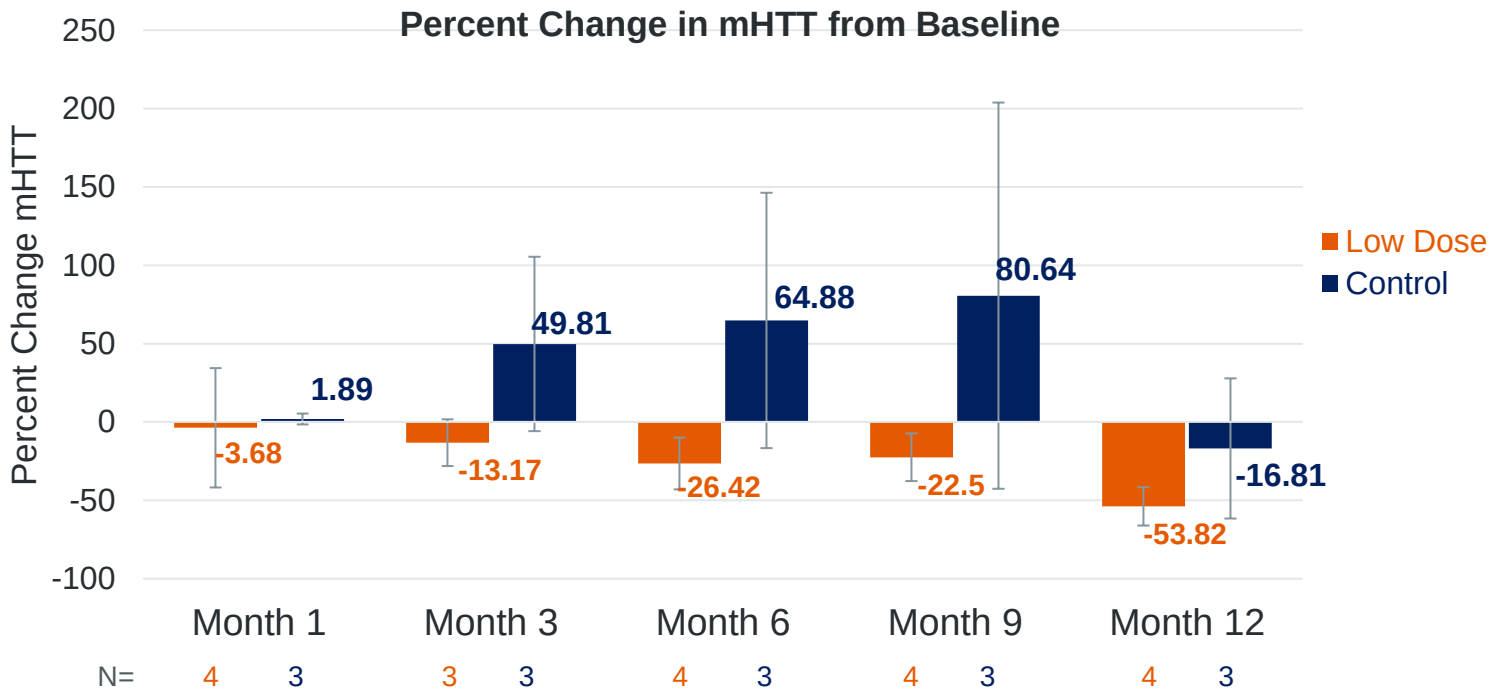
As of time of database lock for analysis on 05.13.22

NfL levels near baseline at 12-months in treated patients



HD GeneTRX1

uniQure declines in CSF mHTT support target engagement



AMT-130: appears to be well tolerated with no significant related safety issues in U.S. low-dose cohort

- No adverse drug reactions were reported
- No serious unexpected suspected adverse reactions were reported
- Two serious adverse events were reported, both in the peri-operative period:
  - Deep venous thrombosis in the upper arm - treated with anticoagulants and resolved
  - Transient post-operative delirium – resolved

- 95 treatment emergent adverse events (TEAS) unrelated to AMT-130 were reported in 10 subjects
- Most common adverse events were procedural pain, procedural headache, post-lumbar puncture syndrome and procedural complications from anesthesia (examples: fatigue, leg spasms, low-body temperature)

As of time of database lock for analysis on 05.13.22

AMT-130: U.S. ph I/II clinical update 2Q23

Low-dose cohort

10 patients

- 6 treated
- 4 control*

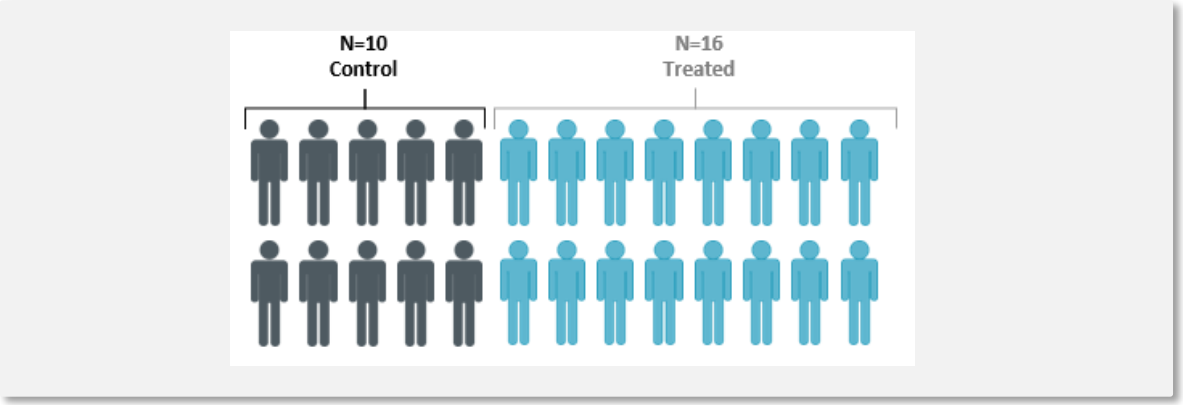
} Followed up to 2 years

High-dose cohort

16 patients

- 10 treated
- 6 control*

} Followed up to 1 year



* Control groups are followed out to the 12-month blinding period only

AMT-130: U.S. ph I/II clinical update 2Q23

General

- Safety
- Overall tolerability

Biomarkers

- Nf-L (neurofilament light)
- mHTT in CSF

Imaging

- Volumetric MRI

Functional

- Motor function

AMT-130: ph I/II clinical data anticipated over next 12-18 months

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2Q 2023

- U.S. ph I/II clinical update low & higher doses
- 26 patients
- Followed up to 2 years

2H 2023

- EU ph I/II clinical update low dose
- 6 patients
- Followed up to 1 year

2024

- EU ph I/II clinical update higher dose
- 9 patients
- Followed up to 1 year

HD GeneTRX1

AMT-130: ph I/II clinical data anticipated over next 12-18 months

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- Several clinical data announcements featuring longer duration and larger number of evaluable patients

- Data on all 41 patients in 2024
  - One-year follow up on all patients
  - Up to three-year follow up on low-dose cohort

- Opportunity to observe separation between treated and control patients on functional and imaging endpoints

HD GeneTRX1

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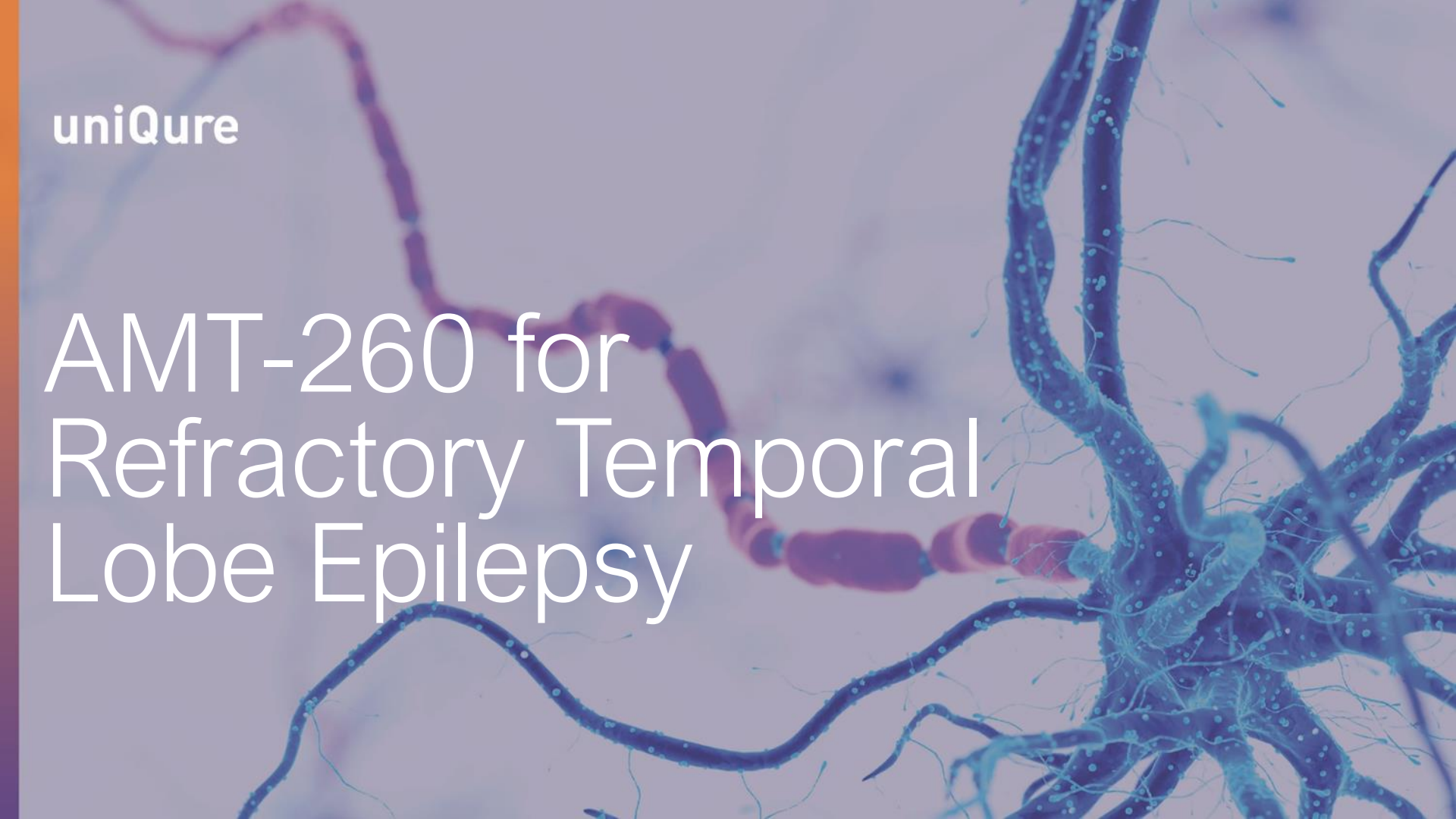
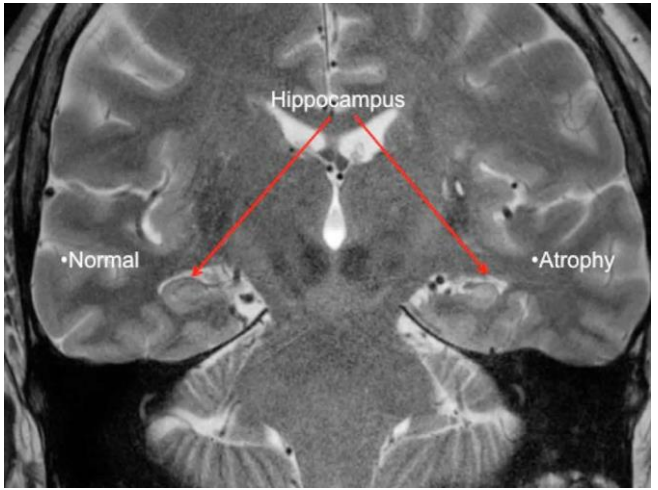
AMT-260 for Refractory Temporal Lobe Epilepsy



uniQure refractory temporal lobe epilepsy (rTLE)

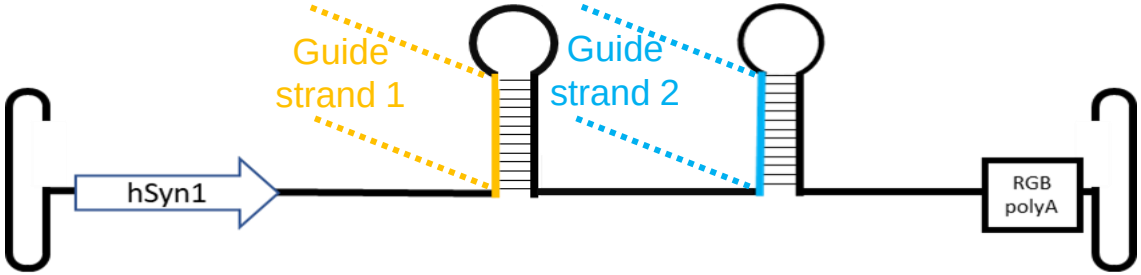
- TLE is the **most common type** of focal epilepsy[1]
- TLE is associated with damage to the **temporal lobe and hyperexcitability of the hippocampus**
- It's often caused by brain injury, tumors or a prolonged febrile seizure
- TLE affects approximately 1.3 million people in the U.S. and Europe[2]; **~750,000-800,000 patients are inadequately treated[3]**
- Refractory TLE patients have a poor quality of life and a reduced lifespan
- The standard of care is lobectomy or laser tissue ablation but **only 1-2% of eligible patients undergo surgery[4]**

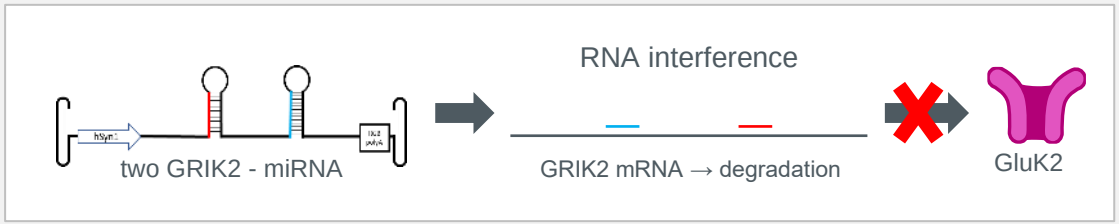


1. "Epilepsy: Hope Through Research", NINDS, Publication date April 2015. NIH Publication No. 15-15 2. Téllez-Zenteno JF, Hernández-Ronquillo L. A review of the epidemiology of temporal lobe epilepsy. Epilepsy Res Treat. 2012;2012:630853. doi:10.1155/2012/630853 3. Asadi-Pooya AA, Stewart GR, Abrams DJ, Sharan A. Prevalence and Incidence of Drug-Resistant Mesial TLE in the US. World Neurosurg. 2017 Mar;99:662-666. doi:10.1016/j.wneu.2016.12.074. Epub 2016 Dec 27. PMID: 28034810. 4. Engel J Jr: The current place of epilepsy surgery. Curr Opin Neurol. 2018; 31(2):192–7.

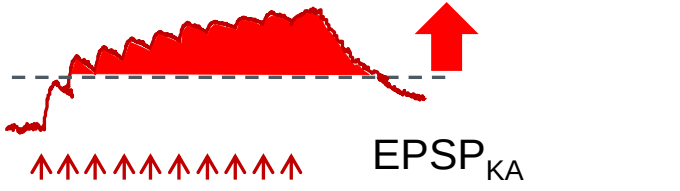
AMT-260: an AAV9-LinQURE™ targeting GRIK2, the kainate glutamate receptor

- AAV9 delivery of engineered miRNAs to reduce the expression of a glutamate receptor subtype that triggers seizures in focal epilepsies
- AMT-260 targets the GluK2 subunit of the kainate receptors

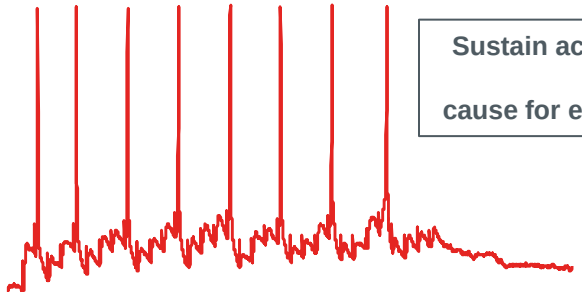




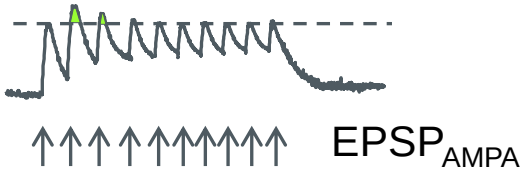
kainate receptor activation triggers epileptic activity



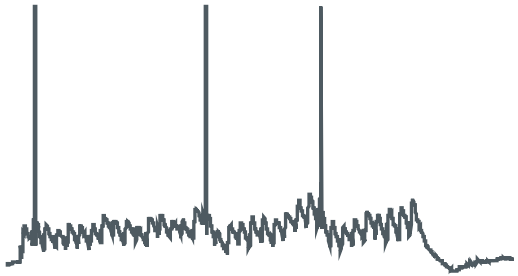
Repeated GluK2 stimulation accumulate over time



Sustain activity of GluK2
=
cause for epileptic activity

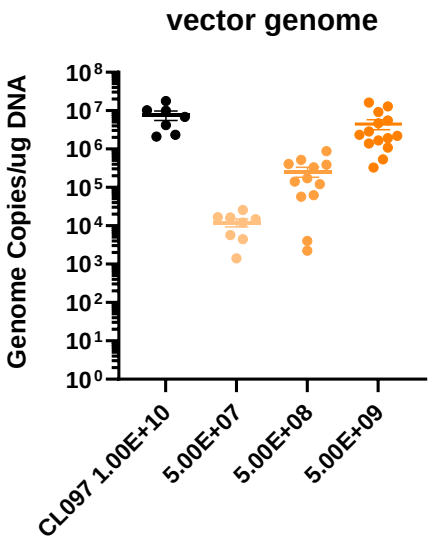


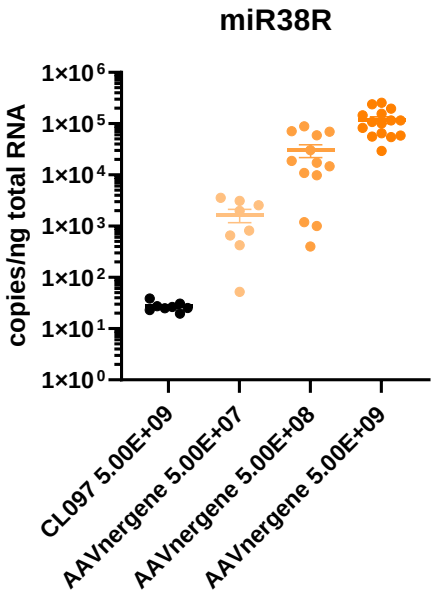
Repeated AMPA stimulation **does not** accumulate over time

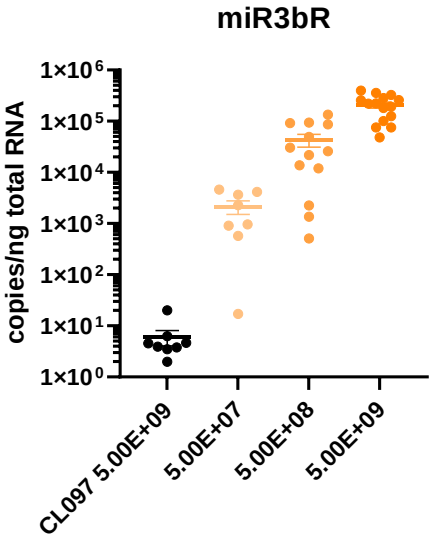


Artinian et al 2011

AMT-260: shows a dose-dependent increase in the expression of miRNAs in mouse hippocampus







AMT-260: inhibits epileptic activity also improves health in the pilocarpine mouse model of TLE

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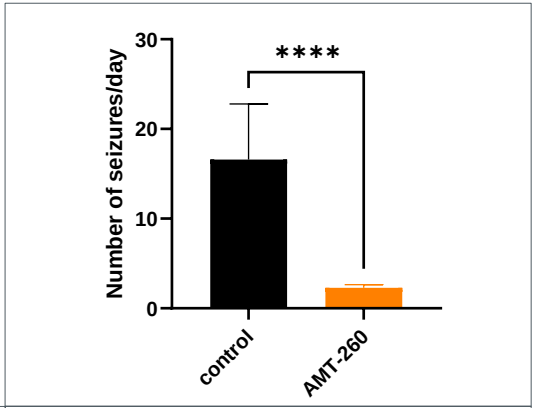
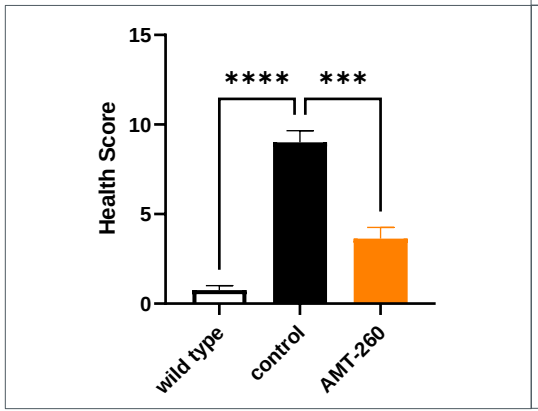
Before AMT-260

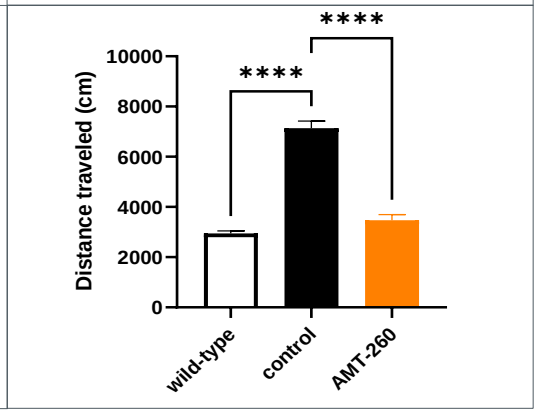
After AMT-260

AMT-260 treatment:

- Reduces seizure
- Ameliorates general health
- Decreases hyperactivity



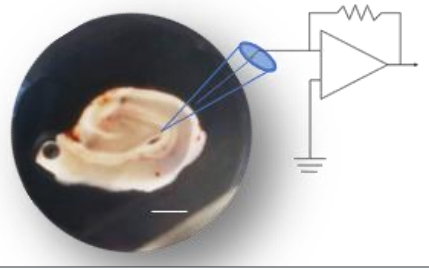




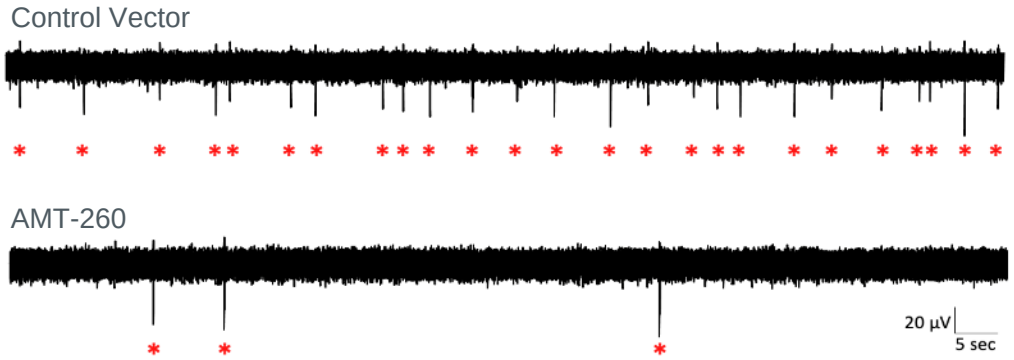
AMT-260: suppression of spontaneous epileptic activity in hippocampal slices from patients with refractory TLE

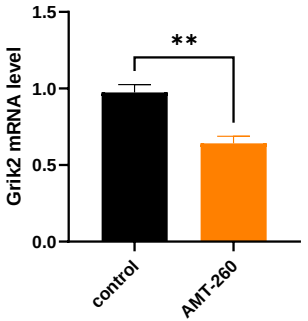
Electrophysiological recordings on hippocampus resected from patient with rTLE

Hippocampal slices prepared from patients transduced with control vectors and AMT-260



AMT-260 suppresses epileptic activity from the hyperexcitable hippocampus excised from patients with rTLE





AMT-260: reduces GRIK2 gene expression by 90% in the hippocampus of non-human primates

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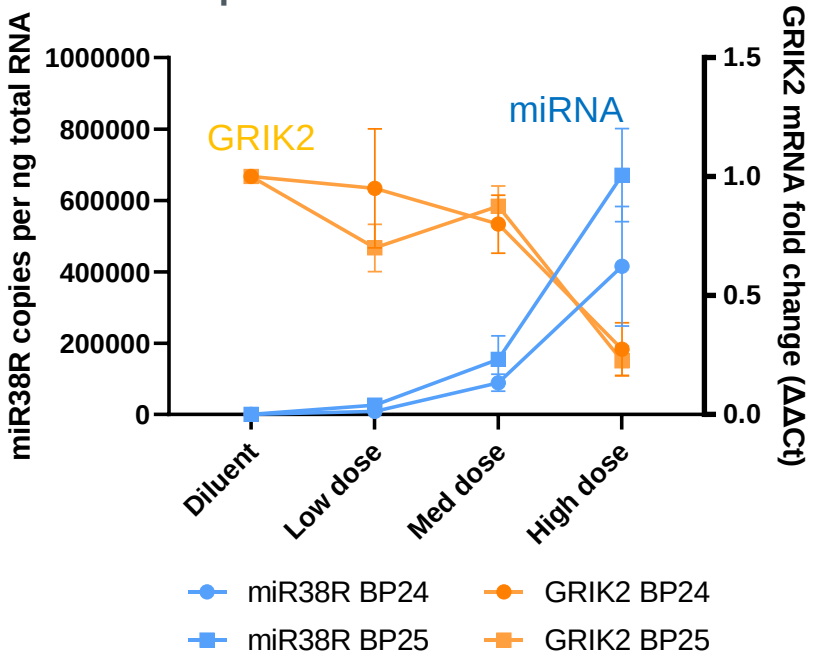
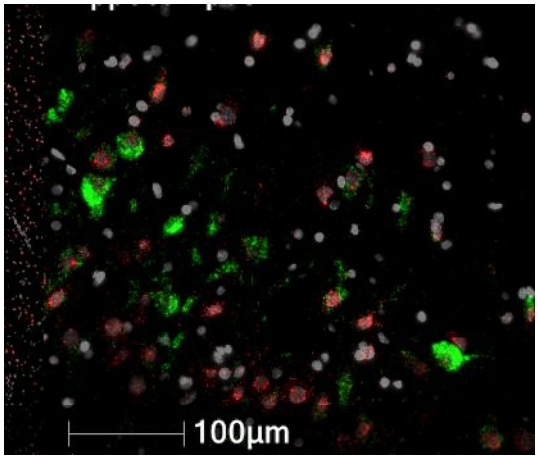
Knock down of GRIK2 mRNA in the hippocampus is proportional to the expression of the miRNAs



The higher the expression of miRNA in hippocampal neurons the lower the expression of GRIK2



Red=GRIK2 Green=miR38R

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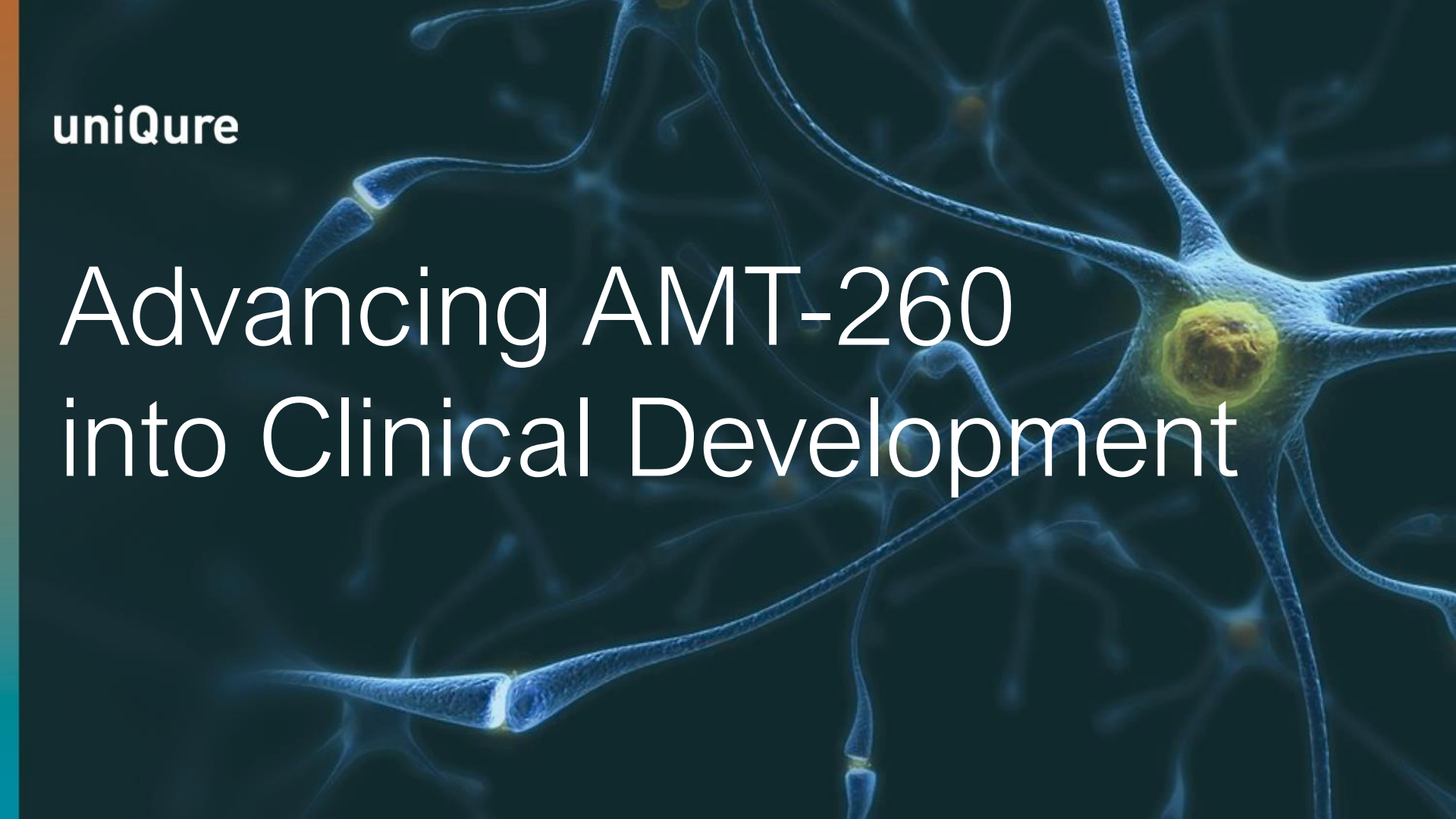
Advancing AMT-260 into Clinical Development



AMT-260: route of administration demonstrated focal biodistribution

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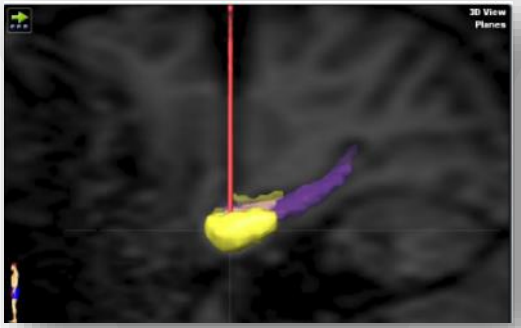
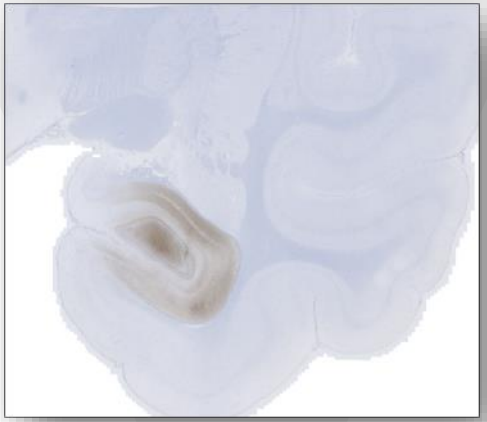
Injection accuracy in NHPs



Purple – Hippocampus
Yellow – Gadoteridol
Red - Trajectory

Injection into effected brain areas is targeted and accurate

Transduction efficacy in NHP hippocampus



Post-administration demonstrated full transduction within the hippocampus

uniQure AMT-260: targeted patient population for phase 1/2 study

Targeted Phase 1/2 Population

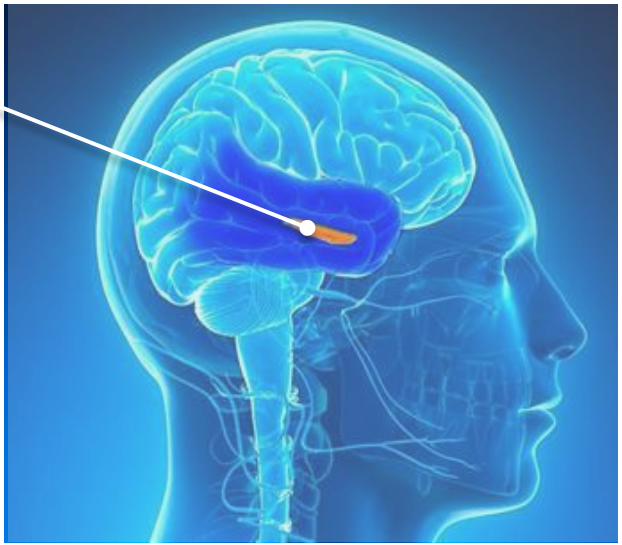
Mesial (MTLE)

- **Hippocampal sclerosis***

**Considered pathologies for Phase 1/2 study covering approx. 30-40% of all refractory TLE patients*

Temporal Lobe Epilepsy (TLE)

a subsection of focal epilepsy



Development Focus

Drug-resistant / Refractory TLE

(approx. 60% of all TLE patients)

uniQure AMT-260: anticipated phase 1/2 clinical study

Study Overview

- Objective: assess safety, tolerability and efficacy
- Multi-center, open-label, controlled, randomized 2:1 over standard of care*
- Subjects 1-month baseline period
- Dose-finding of 2 cohorts with a total of 24 patients

Patient enrollment criteria

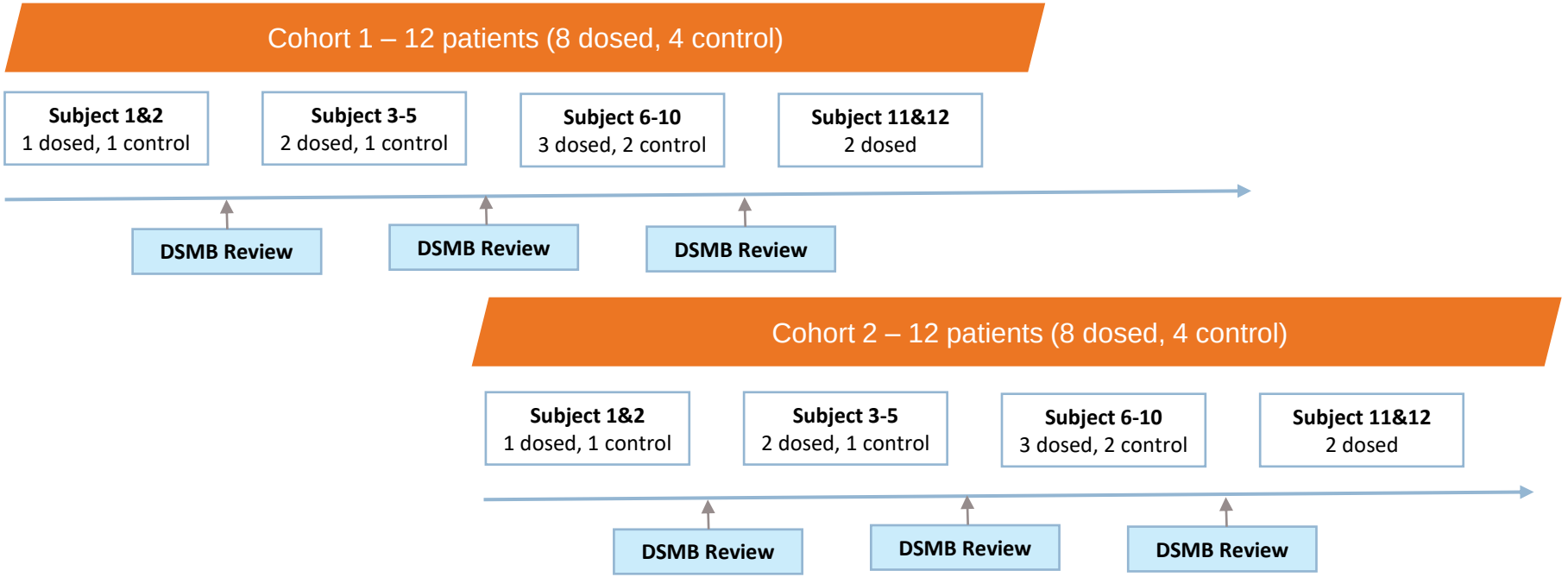
- Adult subjects, age 18-65
- Clinical diagnosis of refractory mesial temporal lobe epilepsy
- Confirmed disease severity based on seizure frequency

*regular anti-seizure medication

Planning for the clinical studies is currently in progress, current approach could change

uniQure AMT-260: anticipated phase 1/2 clinical study

Phase 1/2 open-label against standard of care to establish safety, dose and evaluate efficacy



uniQure AMT-260: anticipated phase 1/2 endpoints

Clinical Parameters

- Safety
- Seizure count/reduction

Biomarkers

- Long–term EEG monitoring
- Interictal discharges

Imaging (MRI and PET)

- Hippocampal volume
- Metabolic function

Biosensor data

- Continuous health monitoring via smart watch

uniQure AMT-260: potential clinical timelines

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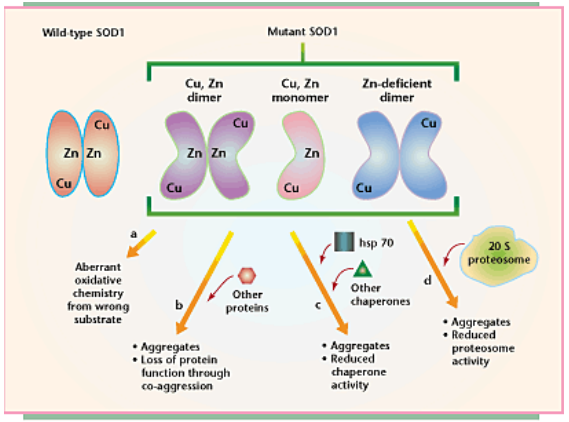
Amyotrophic Lateral Sclerosis (SOD1 ALS)

AMT-162

SOD1 Amyotrophic Lateral Sclerosis (ALS)

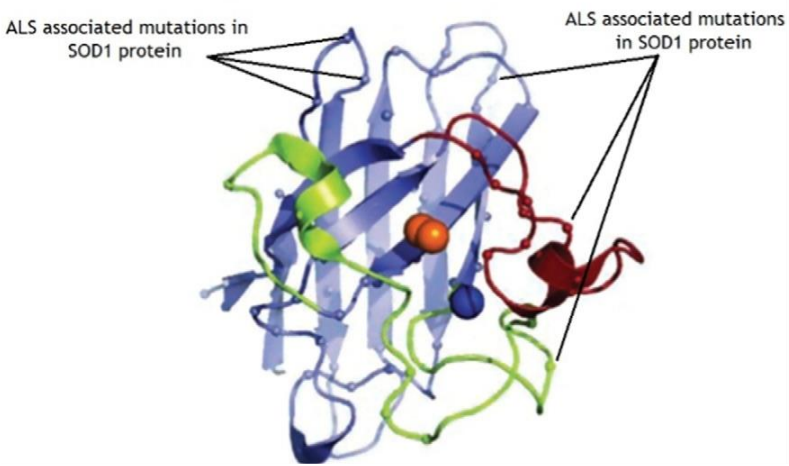
- **ALS** (aka Lou Gehrig's disease) is a progressive neurodegenerative disease that results in loss of motor neurons, involuntary movement, and death
- Average age of diagnosis is mid 50's; average lifespan of 2-4 years[1]
- Most cases are sporadic but ~10% are found to have a dominant genetic causation (familial), e.g., C9orf72*, SOD1, TPD42, FUS
- Mutations in SOD1 are found in ~20% of familial and up to 2% of sporadic cases of ALS[2]
- Approx 300 incident cases / year in US/EU5[2]



- **SOD1** (superoxide dismutase) is an enzyme that is responsible for catalyzing toxic superoxide to hydrogen peroxide and dioxygen
- While the exact mechanism for disease is not known, it is believed that a toxic gain of function in SOD1 results in oxidative stress and cell death of motor neurons

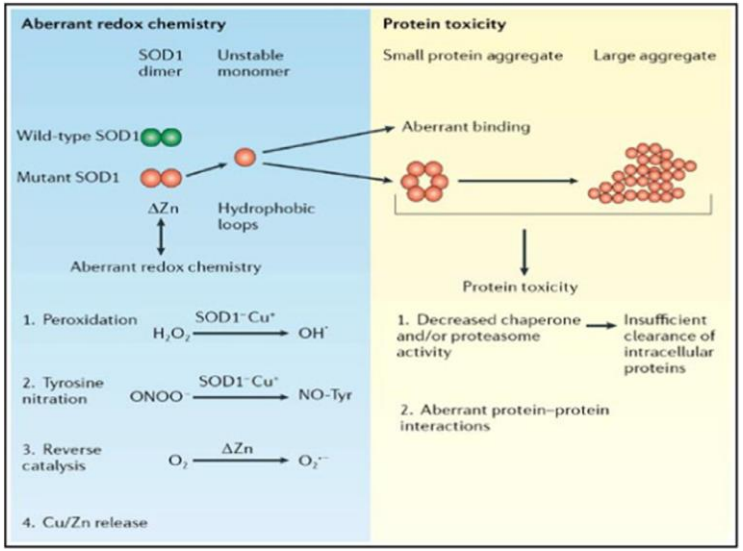
1) Brown RH, Al-Chalabi A. Amyotrophic Lateral Sclerosis. N Engl J Med. 2017 Jul 13
2) Brown CA, Lally C, Kupelian V, Flanders WD. Estimated Prevalence and Incidence of Amyotrophic Lateral Sclerosis and SOD1 and C9orf72 Genetic Variants. Neuroepidemiology. 2021

SOD1 genetics and pathophysiology



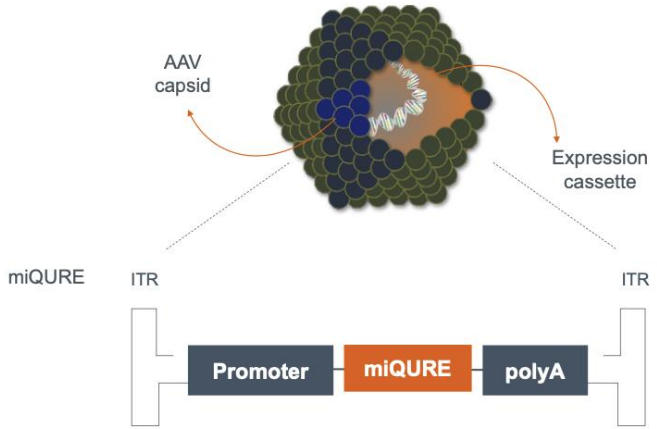
- More than 100 Pathogenic SOD-1 have been identified.
- Mutations are concentrated in a few regions of the protein.
- Mutations can be both dominant and recessive.
- Most common mutations: D90A, G93A, A4H, D46R
- Patients with different mutations progress at different rates

Mutations in SOD1 are a toxic gain of function that can affect many aspects of neuronal biology



uniQure AMT-162 (formerly APB-102) for SOD1-ALS

- Recombinant AAVrh10 vector expresses an artificial micro ribonucleic acid (miRNA) designed to knock down the expression of SOD1
- Intrathecally administered
- *In vivo* mouse data demonstrates greatly enhanced survival
- *In vivo* mouse and NHP data supports biodistribution with SOD1 reduction in spinal cord motor neurons



uniQure strategic rationale for global licensing with Apic Bio

- Aligns with current neurodegenerative focus of pipeline and highly complementary with AMT-161 program for ALS caused by mutations in c9orf72 gene
- Expands uniQure's ALS familial franchise allowing for synergistic clinical development and potential commercialization
- Clinical-stage asset with cleared IND expected to enter development in 2H23
- Fast-progressing patient population
- Orphan Drug and Fast Track designations

uniQure global licensing details

- $10 million up-front cash payment
- Up to $45 million upon achievement of regulatory approvals and pre-specified annual net sales milestones
  - Tiered royalties of a percentage of net sales starting in the mid-single to low double digits

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Near-term milestones

uniQure well-funded to meet our future needs

Significant cash runway to advance our pipeline

$393M* of cash, cash equivalents and investment securities > Runway to mid-2024 2024

+$175M in near-term milestones > Extends runway into 1H 2025 2025

+$1.3B in potential other milestones + royalties > Extends runway into 2026 and beyond 2026+

*Cash as of December 31, 2022

key value drivers in 2023

Hemophilia B	✓ European approval of HEMGENIX® • CSL commercial launches in U.S. and Europe • Milestone payments up to $175 million for first product sales
Huntington's	• Complete EU patient enrollment in Phase Ib/II clinical trial • Announce clinical update from U.S. Ph I/II trial • Announce clinical data from European low-dose cohort • Begin third cohort in U.S. Phase I/II clinical trial
Research Pipeline	• Submit IND and enter clinic for AMT-260 in refractory temporal lobe epilepsy • Submit IND for AMT-191 in Fabry disease • Initiate IND-enabling studies for another research program
Manufacturing and Technology Platform	• Provide global supply for commercial launches of HEMGENIX® • Achieve process validation for 500L STR for AMT-130 in Huntington's disease

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