

# Computing the Future of Medicine™

Interim results for six months  
ended 31 July 2023

26<sup>th</sup> October 2023

# Legal Disclaimer

## Forward looking statement

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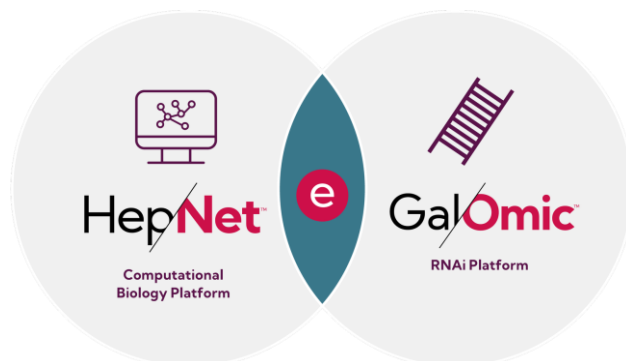
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# Company Overview

Driving innovation at the intersection of AI and precision medicine

## Our mission:

Integrating computational power and biology to discover life-transforming medicines



Cash and cash equivalents  
**£24.8m** 2022: £21.8m

Revenue  
**£0.2m** 2022: £0.3m

R&D spend  
**£5.3m** 2022: £3.1m

Operating loss  
**£7.0m** 2022: £4.6m

Loss after tax  
**£5.6m** 2022: £3.8m

R&D tax credit receivable  
**£2.5m** 2022: £2.2m

Multi-disciplinary team (exc NED)  
**34 FTE** 2022: 38

Share Price (25/10/23)  
**10.7p**

Shares outstanding (25/10/23)  
**583.8m**

Market cap (25/10/23)  
**£62.5m**



**London**  
Company HQ



**Boston**

*Interim results for six months ended 31 July 2023*

# Our Approach

Integrating computational power and biology to discover life-transforming medicines



World-class hepatocyte data resource with sophisticated network biology analytics for target ID and ability to automate early stages of preclinical development

Proprietary chemistry platform for potent and durable hepatocyte-specific mRNA knockdown of novel targets identified by HepNet™

In-house pipeline of GalOmic™ RNAi therapies across broad range of indications, with lead assets in cardiometabolic disease and haemophilia

# Traditional Approaches to Drug Development are Too Slow and Too Expensive

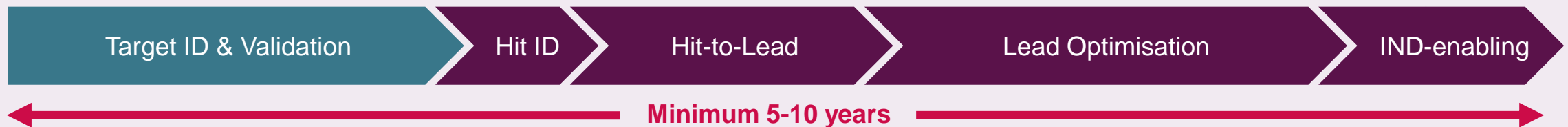
- Typical small molecule preclinical development takes a **minimum of 5-10 years**.
- Enabled by computation and use of the RNAi modality, we can go from gene target selection to disease model experiments in **6 months**, costing **less than \$500,000** and **IND ready in 3 years**.
- This means we can rapidly develop multiple life-transforming RNAi medicines for the people that need them.

## e therapeutics **Preclinical Development Timeline**

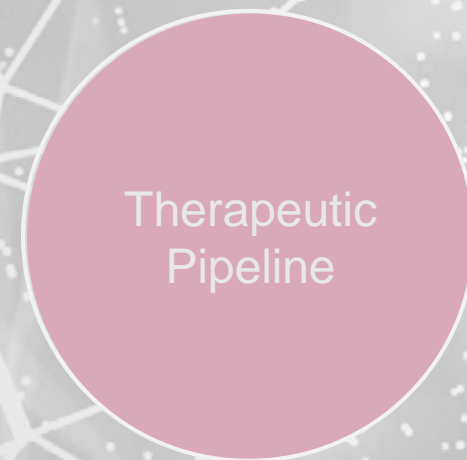
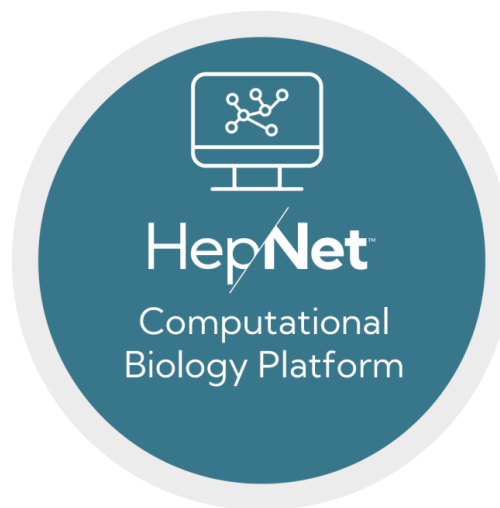


**ETX's RNAi platform enables rapid and cost-effective drug development**

## **Typical Small Molecule Preclinical Development Timeline**



# HepNet™





HepNet™ is our proprietary computational biology platform, built on the world's most comprehensive hepatocyte-specific knowledgebase.

It enables:

- Identification of novel targets for a wide range of diseases through sophisticated network analytics that account for the true complexity of biology
- Increased speed of execution by automating drug discovery and design processes
- Mining of 100s of integrated data sources to distil new mechanistic knowledge of hepatocyte biology

### ETX data and knowledge covers...

- 12,091 expressed genes
- 1039 secreted proteins
- 461 proteins secreted to blood
- 700 biological processes

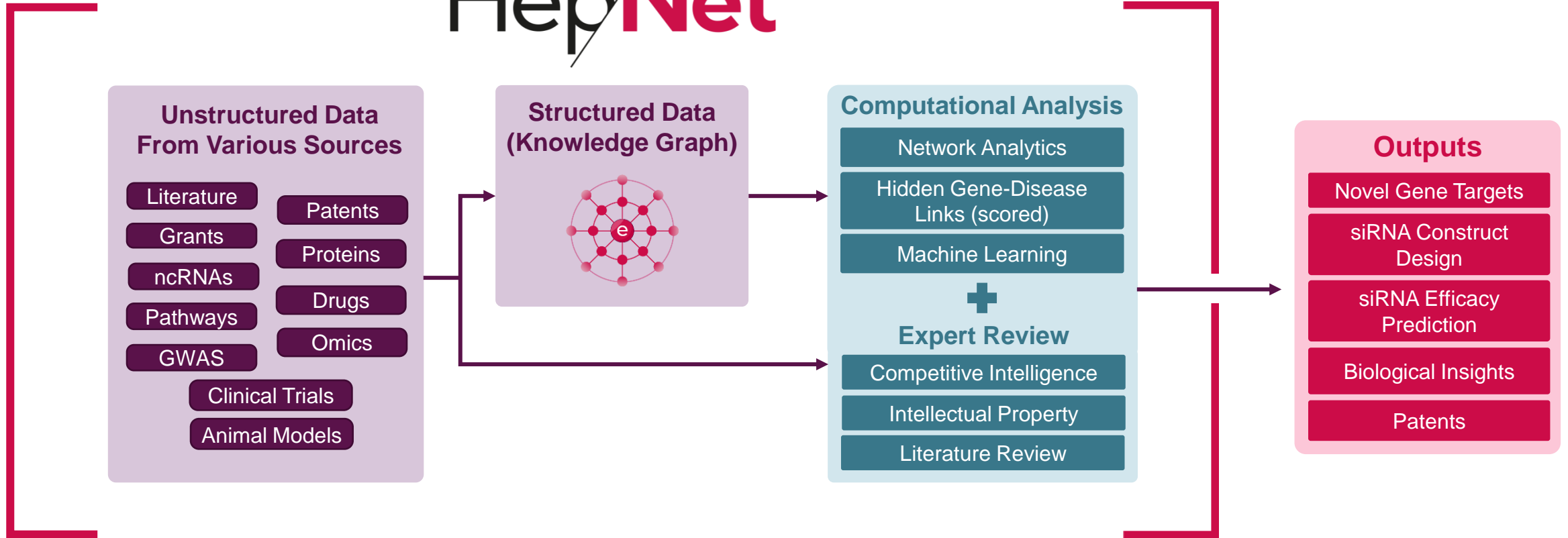


# HepNet™

Our world-class hepatocyte-specific computational biology platform



## HepNet™



**HepNet™ increases automation and provides us with the ability to identify novel targets and rapidly design siRNA constructs.**



# siRNA Efficacy Prediction

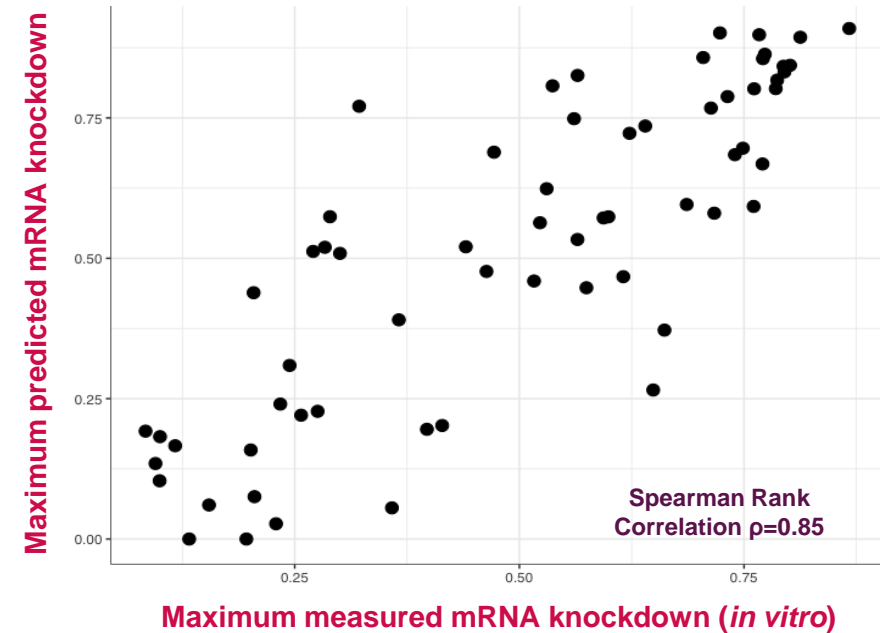
Using machine learning to predict siRNA efficacy and bypass *in vitro* screening



- Highly accurate model trained on proprietary, high-quality training datasets
- Trained model demonstrates high prediction accuracy, performance is superior to widely used algorithms (BioPredSi, ThermoComposition21)
- Enables identification of lead siRNA sequences *in silico*, minimising number of sequences that require screening
- We are now exploring further enhancement of predictions using large language models (LLMs) trained on mRNA sequences

	Pre-AI Approach	Post-AI Approach
Number of siRNA screened	Up to 400	<10
Time to lead identification (potential clinical candidate)	6 months	1 month
Cost of screening	\$500,000	\$50,000

## Predicted vs measured siRNA efficacy (Validation Dataset)



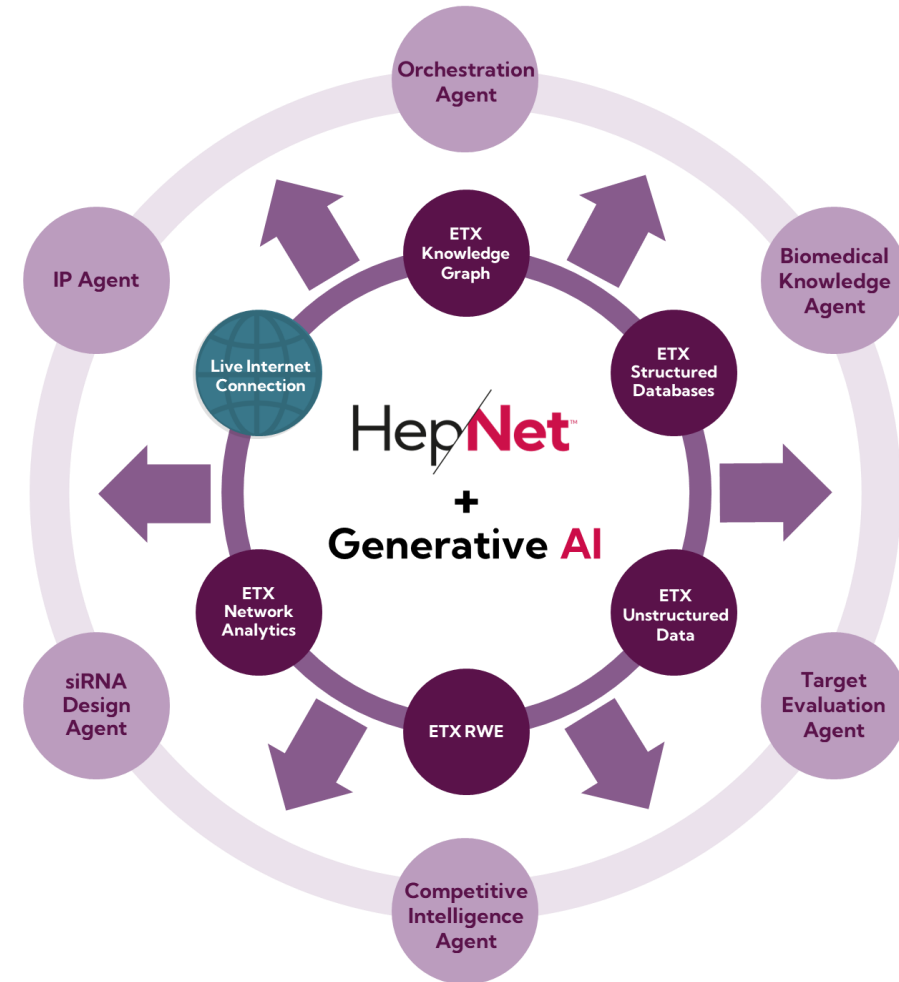
**HepNet™’s siRNA efficacy prediction already reduces preclinical development timelines and costs, with potential to enable bypassing of *in vitro* screening**

# Enhancing Computation with LLMs

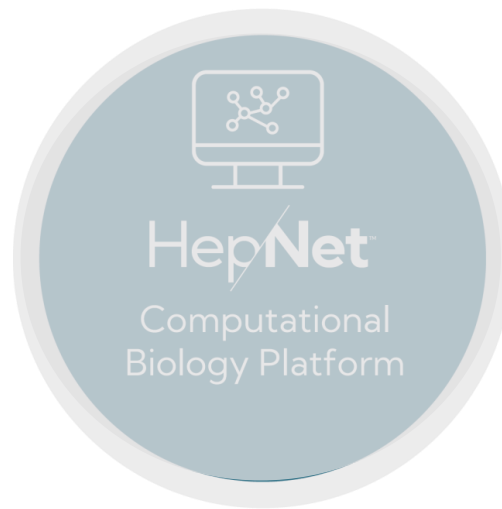
Transforming HepNet™ into a dynamic knowledge resource



- We are fully embracing the latest advances in generative AI and LLMs through integration with HepNet™ and creation of specialist LLM agents
- LLM agents trained on specific data such as scientific papers, mRNA sequences, hepatocyte-specific data, patents etc. will support target ID, target-indication evaluation and drug design
- This will enhance our ability to understand, reason, and infer from vast amounts of data, increasing automation and speed of ETX processes



# GalOmic™



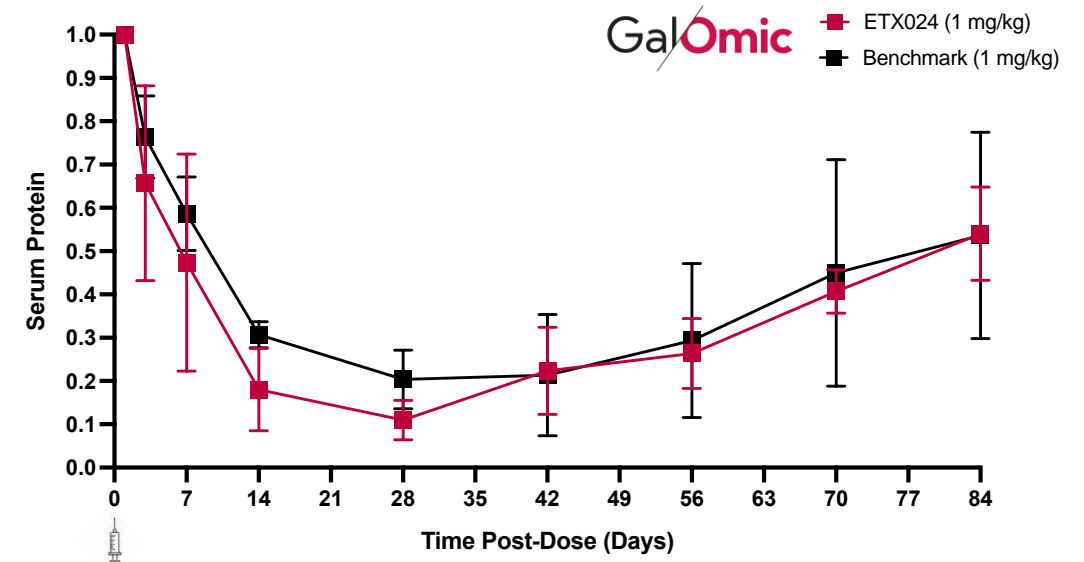
# GalOmic™

Our proprietary RNA interference chemistry platform

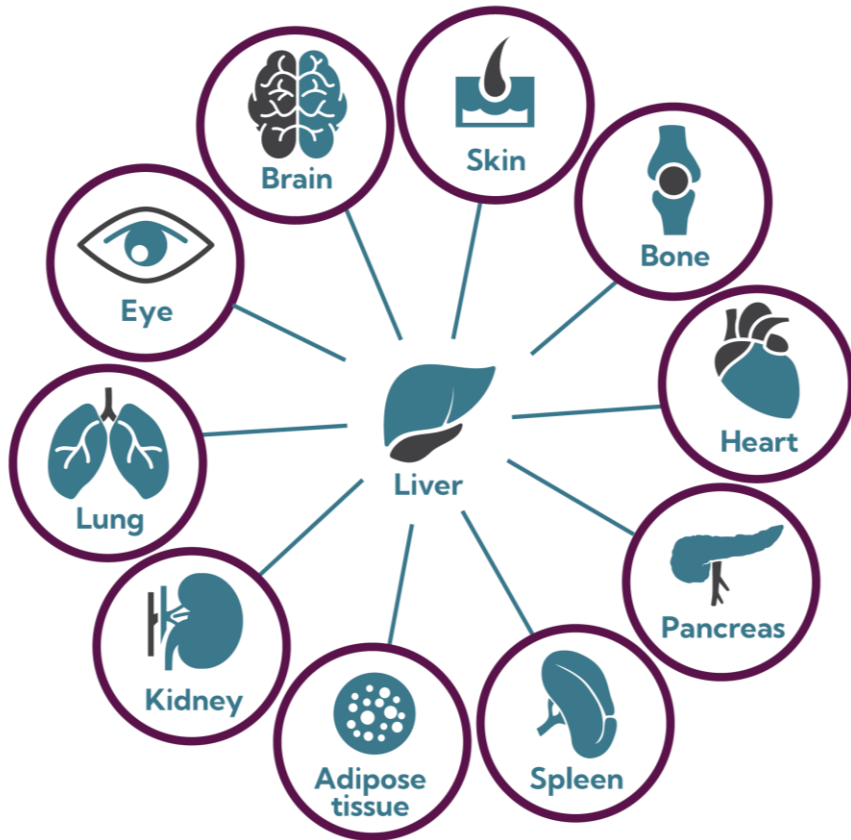


- GalOmic™ enables generation of GalNAc-siRNA drug candidates for hepatocyte-specific gene silencing via RNAi of any target gene identified by HepNet™
- Benchmarking data demonstrates at least equivalent knockdown compared to market leads across multiple genes
- Data from in-house pipeline further highlights potent and durable silencing profile of GalOmic™ siRNA constructs, supporting infrequent, subcutaneous dosing
- Platform is protected by IP covering conjugate design and chemical modifications, including modification patterns

## Typical performance profile of our RNAi platform in non-human primate



siRNA - small-interfering RNA | RNAi - RNA interference



### Hepatocyte-associated Disease Areas

Cardiovascular

Metabolic

Diabetes

Haematology

Obesity

NASH

Renal

Rare

& More

Hepatocytes are highly influential cells, allowing us to develop GalOmic™ RNAi medicines for a broad range of diseases

# Therapeutic Pipeline



# ETX-291: A HepNet™ Identified Target for Cardiovascular Disease Risk

Pursuing a novel target with human validation and mechanism of action beyond LDL-C modulation



HepNet™ predicted link between the target and metabolic disease risk



Human genetic evidence links target to reduced cardiovascular disease risk in otherwise healthy individuals

## Target Product Profile:

- **Meaningful CVD risk reduction** independent of statins and PCSK9s
- **Holistic treatment potential** for metabolic co-morbidities by modulating insulin sensitivity, promising applicability beyond LDL-C modulation
- Ease of use: **long-acting**, aiming for quarterly+ duration of action
- Using ETX's **GalOmic™ GaINAc-siRNA** technology for highly specific liver targeting

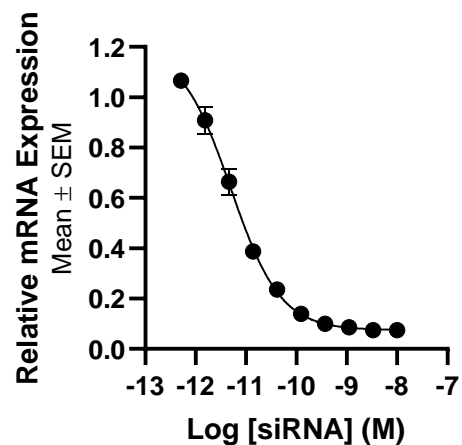


# ETX-291 is a Potent siRNA Utilising ETX's GalOmic™ Chemistry

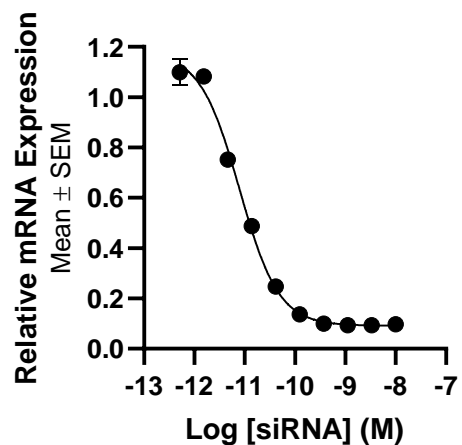
Lead siRNA identified *in vitro* and tested in healthy mice

## ETX-291 mRNA Knockdown *in vitro*

Huh7

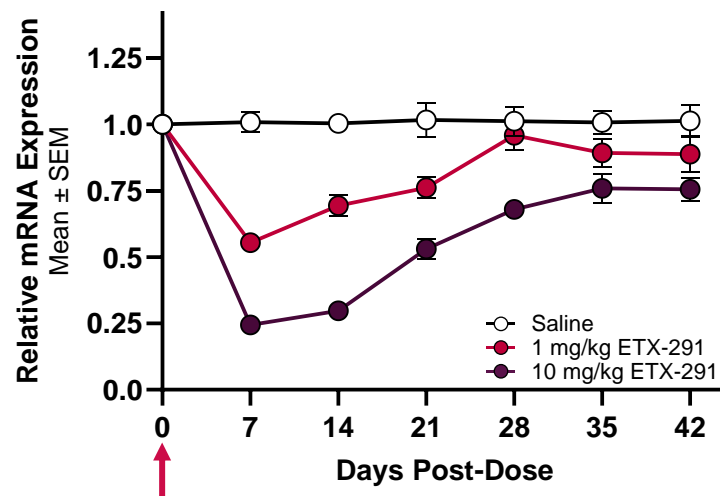


Primary Human Hepatocytes

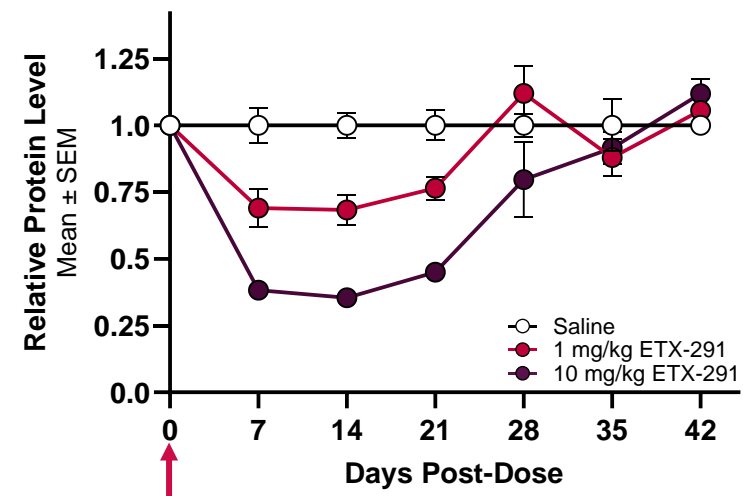


## ETX-291 Knockdown in Healthy Mice

mRNA Levels by RT-qPCR



Protein Levels by LC-MS



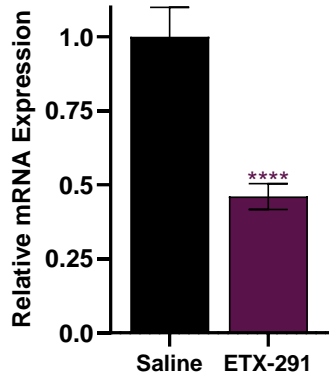
Constructs used in *in vivo* murine models demonstrate deep and sustained mRNA and protein knockdown, with a duration of action that supports quarterly subcutaneous dosing in humans

mRNA – messenger RNA | siRNA – small interfering RNA | RT-qPCR – Real-Time Quantitative Reverse Transcription PCR | LC-MS – Liquid Chromatography-Mass Spectrometry

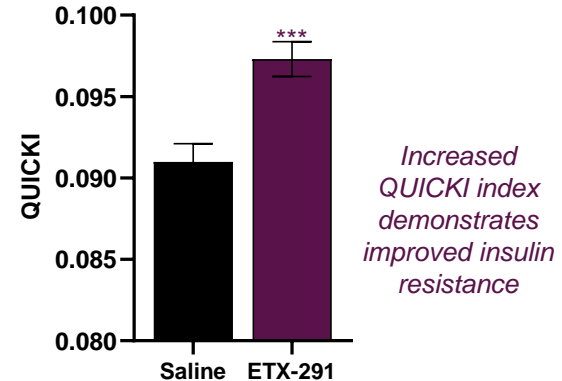
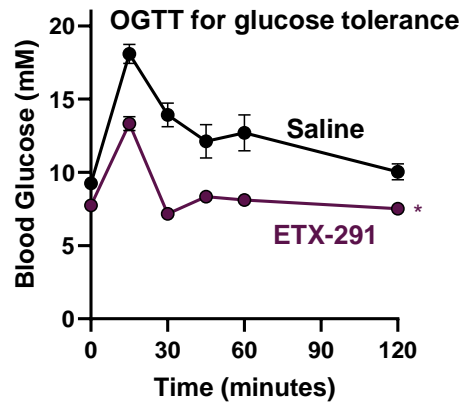
# Pleiotropic Effects of ETX-291 on Key Cardiometabolic Risk Factors

Results from a 12-week study in an ApoE\*3L.CETP mouse model of metabolic syndrome

Reduced target mRNA expression

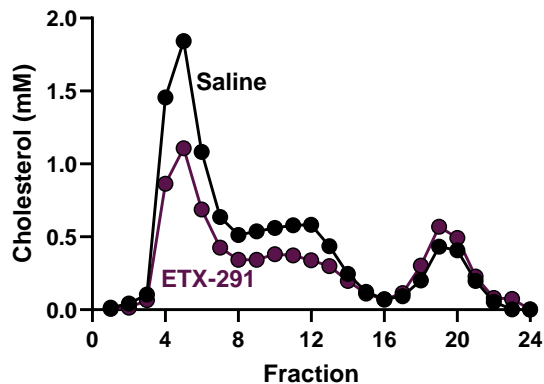


Improved glucose tolerance and insulin sensitivity

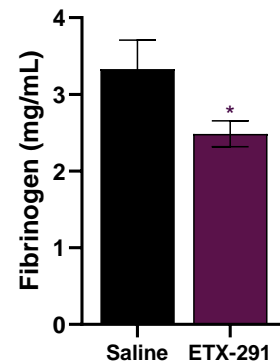


Treatment with ETX-291 provides a holistic treatment potential for cardiometabolic diseases beyond LDL-C modulation

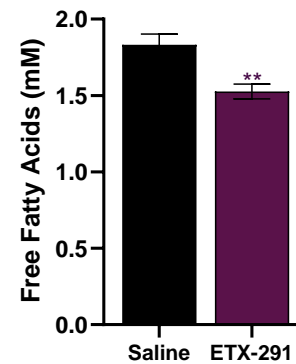
Reduced plasma cholesterol



Reduced fibrinogen



Reduced FFA



12-week study with weekly subcutaneous 10 mg/kg dose of ETX-291. Error bars: mean  $\pm$  SEM

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ , \*\*\*\*  $p < 0.0001$

# ETX-148: A HepNet™ Identified Pan-Haemophilia Target

Pursuing a novel pan-haemophilia rebalancing agent with good joint protection and leading safety profile



HepNet™ established link between the target and haemophilia through haemostasis network analysis



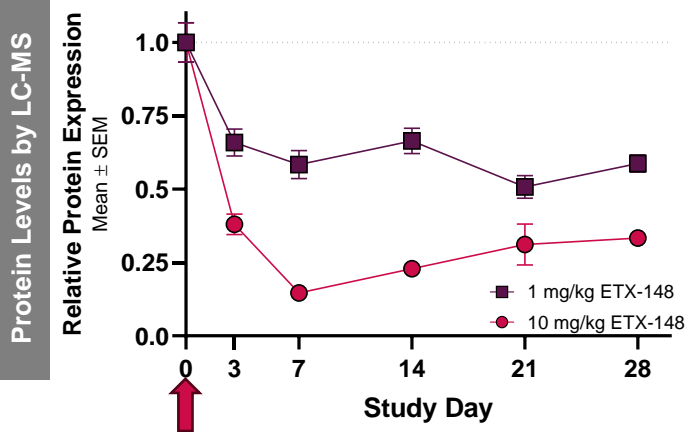
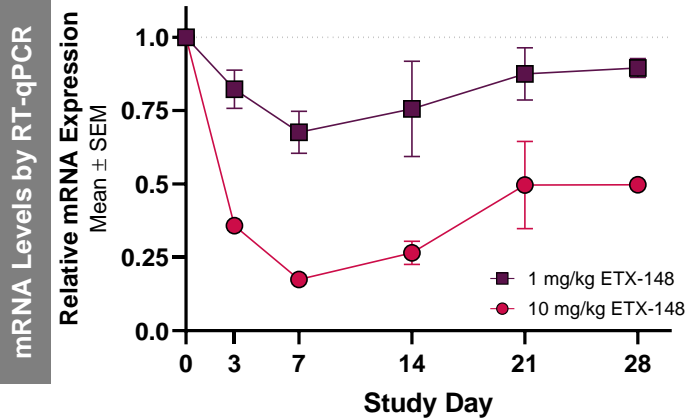
Human genetic evidence suggests reduced target expression not linked to increased risk of thrombosis unlike other rebalancing agents

## Target Product Profile

- **Combining good joint protection and a long duration of action** (aiming for quarterly+ duration)
- **Safe** in combination with **Factor replacement** (for emergency use)
- **Patient-friendly** subcutaneous administration
- Using ETX's proprietary **GaOmic™ GaINAc-siRNA** technology

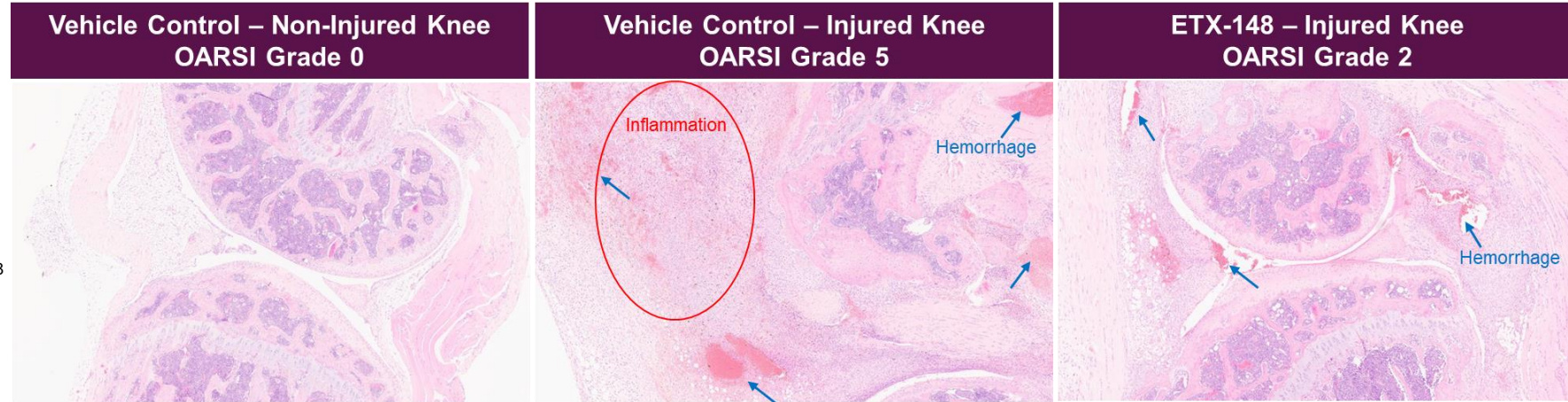
# ETX-148 is a Potent siRNA That Demonstrates Joint Protective Effects in a Haemophilia A Haemarthrosis Mouse Model

## ETX-148 Knockdown in Healthy Mice



Data normalised to saline-treated mice on Study Day 0

## A Haemarthrosis Study in Haemophilia A Mice



- Administration of ETX-148 resulted in improved haemarthrosis knee joint pathology, reduced inflammation, and resulted in smaller areas of haemorrhage
- Additional studies have demonstrated safe administration of ETX-148 in combination with Factor Replacement in Haemophilia A mice (not shown)

# Therapeutic Pipeline

Broad pipeline of GalOmic™ constructs targeting novel genes, guided by insights from HepNet™

Program	Indication	Target ID	Drug Design	Proof-Of-Concept	Candidate Declaration
ETX-291	Cardiometabolic Disease				
ETX-148	Haemophilia				
ETX-312	Metabolic Disease				
ETX-407	Undisclosed				
ETX-258	Undisclosed				
Multiple Targets					

# Outlook



# Outlook

Continuing to build on the strong foundation of HepNet™ and GalOmic™

## Key H1 2024 Progress

## Looking Ahead

✓	Generated positive proof-of-concept data for lead GalOmic RNAi assets, ETX-291 and ETX-148	Complete data packages for lead assets by YE2024
✓	Expansion of our GalOmic™ therapeutic pipeline	Complete data package for at least one additional GalOmic™ asset by YE2024, progress further assets into preclinical development
✓	Increased pool of novel targets identified and assessed <i>in silico</i> by HepNet™	Continue growth of target pool, expansion into new therapeutic areas
✓	Validated our siRNA design and straight to <i>in vivo</i> siRNA efficacy prediction	Further enhance AI-driven <i>in vivo</i> siRNA efficacy prediction with cutting-edge technology to accelerate drug design
✓	Continued development and integration of Generative AI and LLMs into HepNet™	Begin development of novel platform based on LLM technology
✓	Filed additional patent applications protecting our targets, chemistry, and therapeutics	Continue to generate novel IP and protect our inventions



# Appendix



# Leadership



**Ali Mortazavi**  
Chief Executive Officer



**Alan Whitmore**  
Chief Scientific Officer



**Alison Gallafent**  
Chief Intellectual Property  
Officer



**Timothy Bretherton**  
Chief Financial Officer



**Laura Roca-Alonso**  
Chief Operating & Business  
Officer

## Board of Directors

**Ali Mortazavi**  
Chief Executive Officer

**Professor Trevor Jones CBE**  
Non-Executive Chairman

**Michael Bretherton**  
Non-executive Director  
CEO Sarossa Plc

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Former CTO, Pfizer

**Professor John Mattick**  
Former CEO, Genomics England  
Professor RNA Biology, UNSW Sydney

**Dr Bill Harte**  
Chief Translational Officer  
Case Western Reserve University