Boosting drug development in NASH through integrated research platforms: proposal of a master protocol for a NASH platform trial

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on Behalf of The EU-PEARL NASH Investigators

Introduction

Despite its high prevalence, there are no drugs currently approved to treat NASH. Amongst other reasons, the design, and the methodological and operational features of traditional clinical trials in NASH might impede optimal drug development. In this regard, **platform trials (PT)** might be an attractive complement or alternative to conventional clinical trials by using a master protocol which allows for evaluating multiple investigational medicinal products (IMP) concurrently or sequentially with a single control arm. Through **interim analysis**, these trials allow early exit of drugs from the trial based on success or futility, while **providing participants better chances of receiving active compounds** through adaptive randomization. Overall, platform trials represent an alternative for patients, pharmaceutical companies and clinicians in the quest for accelerating pharmacologic treatment for NASH.

Aims

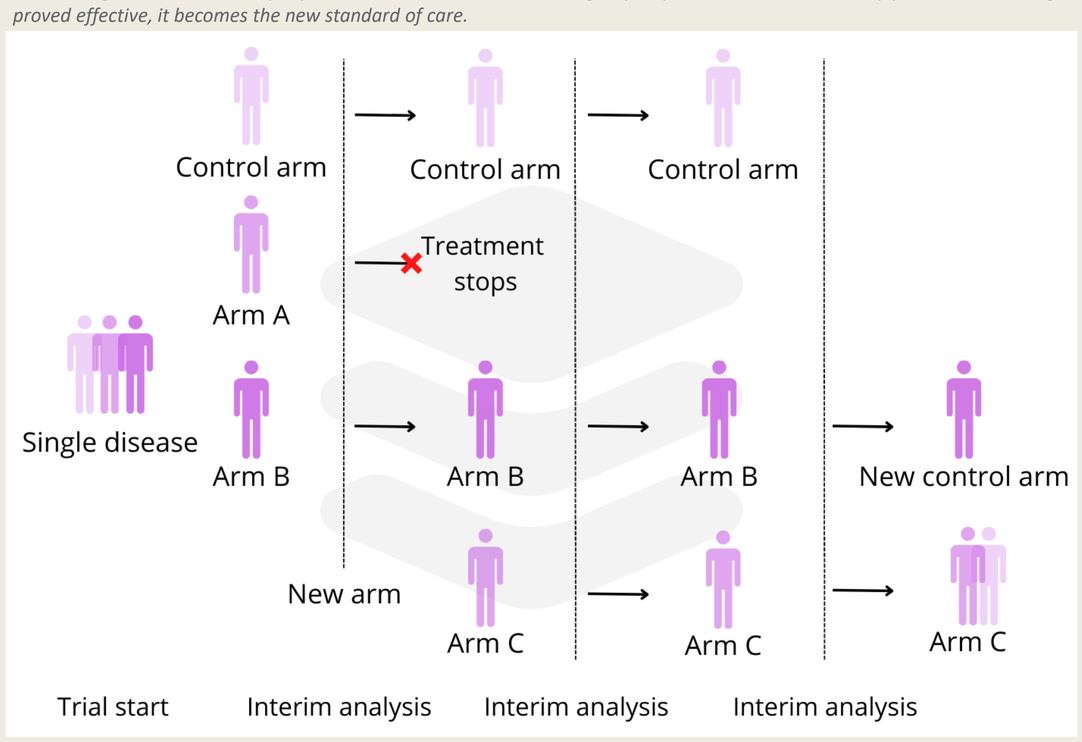
- ✓ Create a **Phase 2b Master Protocol** for a NASH IRP
- ✓ Set the basis for operationalizing a NASH IRP

Methods

The EU Patient-cENtric clinical tRIal pLatforms (EU-PEARL) consortium, created under an IMI (Innovative Medicines Initiative) project, aims to boost the use of platform trials (PT) to improve the efficiency of drug development, while putting the needs of participants and their community at the center.

Results

*Platform trial representation. The figure depicts the structure of a platform trial. **Platform trials** have a common randomized trial structure and its main characteristic is that therapeutic arms can enter and exit the study continuously based on a decision algorithm. Moreover, platform trials use a common control group or placebo and can last many years. When a drug is proved effective, it becomes the new standard of care.*



Differences between traditional clinical trials and platform trials

Traditional clinical trials	Platform trials
Multiple control arm vs. One single active compound arm	Single common control arm vs Multiple treatment arms
Defined duration	Unlimited duration
Sponsor is the IMP owner	Sponsor is often an academic or non-profit organization
All decisions made by the pharmaceutical or start-up company	Governance bodies make decisions related to treatment arms
Drugs enter only at the beginning of the trial	Drugs enter and exit the trial depending on interim analysis
Protocol for each trial	Master protocol for all the trial and ISA for each drug

Inclusion criteria for the NASH Master Protocol

Participants must be 18 to 75 years of age inclusive at the time of signing ICFs
Body Mass Index must be within the range 25 (23 if Asian ethnicity) – 45kg/m^2 inclusive
Female participants must be not of childbearing potential OR of childbearing potential and practicing a highly effective method of contraception
Histological evidence of NASH with fibrosis stage 2 or 3 based upon a liver biopsy obtained no more than 26 weeks prior to baseline visit and NAS of ≥4 with at least a score of 1 in each component of the NAS
Participant must sing a Master ICF
Participant must sign the applicable ISAs ICF
Participant must sign a separate ICF if he or she agree to provide an optional DNA sample for research

Summary of the most relevant features of a Phase 2b NASH Master Protocol Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of study intervention(s) compared to placebo on NASH histology after 48 weeks of treatment relative to baseline	▪ Experiencing at least 1-stage fibrosis improvement without worsening of NASH, or ▪ Experiencing resolution of NASH without worsening of fibrosis
Secondary	
To evaluate the efficacy of study intervention(s) compared to placebo on other histologic parameters after 48 weeks of treatment relative to baseline	▪ Experiencing both NASH resolution and 1-stage improvement in fibrosis ▪ Experiencing at least 2-stage improvement in fibrosis without worsening of NASH ▪ Change in steatosis score ▪ Change in inflammation score ▪ Change in ballooning score ▪ Change in NAFLD activity (NAS) score ▪ Change in steatosis-activity-fibrosis (SAF) score ▪ Change in NASH activity (inflammation and ballooning)
To evaluate the efficacy of study intervention(s) compared to placebo on biomarkers over time and after 48 weeks of treatment relative to baseline	▪ Absolute and percentage change from baseline in liver function tests (i.e., ALT, aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], total bilirubin, direct bilirubin, and alkaline phosphatase [ALP]) ▪ Absolute and percentage change from baseline in fibrosis biomarkers: pro-C3, pro-C6, ELF score and its individual components (i.e., type III procollagen peptide (PIIINP), hyaluronic acid (HA), and tissue inhibitor of metalloproteinase-1 (TIMP1)) ▪ Absolute and percentage change from baseline in liver stiffness as measured by vibration-controlled transient elastography ▪ Absolute change in simple scores (i.e., FIB-4, APRI, and NFS)
To evaluate safety and tolerability of the study intervention(s) throughout the study based on the incidence, change from baseline in continuous measures, or clinically significant findings relative to baseline	▪ Adverse events ▪ Clinical laboratory tests (including hematology, blood chemistry, blood coagulation, lipids, metabolic parameters [fasting plasma glucose, fasting insulin, HOMA-IR, and HbA1c)] and urinalysis) ▪ 12-lead electrocardiogram ▪ Vital signs (including body weight) ▪ Physical examination
Exploratory	
To evaluate the change from baseline in Patient Reported Outcomes (PROs) following treatment with study intervention(s) relative to placebo over time and at week 48	▪ NASH-CHECK score ▪ CLDQ NASH score ▪ EQ-5D score
To evaluate the change from baseline in exploratory biomarkers following treatment with study intervention(s) relative to placebo over time and at week 48	▪ RNA biomarkers ▪ Proteomics ▪ Genomics ▪ Metabolomics

Conclusions

- ✓ A NASH IRP will **benefit patients** due to better access to available drugs being tested and more probability of receiving active treatment due to one shared control arm.
- ✓ A platform trial allows IMP owners to access a clinical trial with a **ready-to-operate set-up and network**.

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