

Overview of the Liver Forum Proposal for a NIT-based RLSE in MASLD

Liver Forum 19 Meeting, September 2025

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Disclosure Slide

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AstraZeneca, Boehringer Ingelheim, Intercept.

Consultancy (undertaken on behalf of Newcastle University)

Alimentiv, Akeru, AstraZeneca, Axcella, 89Bio, Boehringer Ingelheim, Bristol Myers Squibb, Echosens, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKline, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janssen, Madrigal, Medpace, Merck, NGMBio, North Sea Therapeutics, Novartis, Novo Nordisk, PathAI, Pfizer, Pharmanest, Poxel, Resolution Therapeutics, Roche, Ridgeline Therapeutics, RTI, Shionogi, Terns

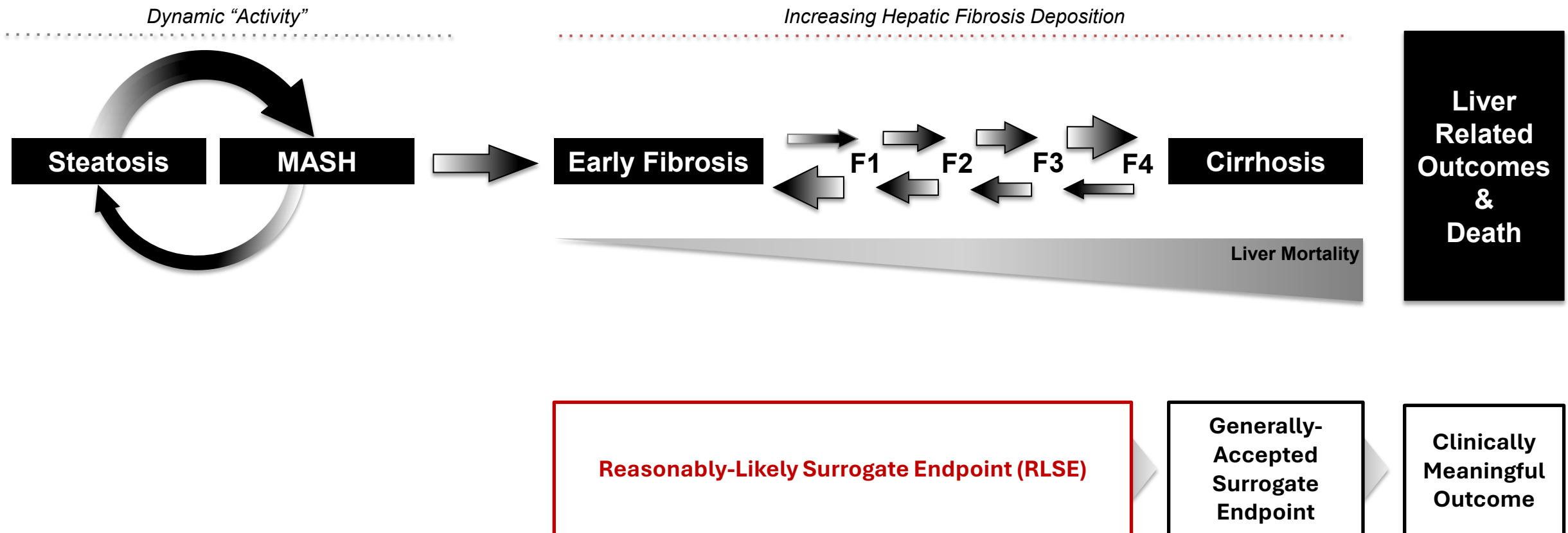
Speaker

Fishawack, Integritas Communications, Kenes, Novo Nordisk, Madrigal, Medscape, Springer Healthcare.

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MASLD Natural History



Rationale for Biomarker Selection as a RLSE

- 1. Biological plausibility** that biomarker change reflects alteration in disease state.
- 2. Robust evidence of adequate biomarker performance in relevant BEST Context(s) of Use PLUS supporting Scientific Consensus:**
 - Diagnostic CoU [1,2]
 - Prognostic CoU [3,4]
 - Sensitivity to change (epidemiological studies): Monitoring CoU [5]
 - Sensitivity to change (clinical trials): Response/Pharmacodynamic CoU [6, 7]

} **Meaningful magnitude of change defined**
- 3. Detailed characterization of analytical/technical performance** of biomarker.
- 4. Scalability** for implementation in Ph2/3 clinical trials & post-approval use:
 - Widely available / clinically adopted in routine care
 - Economically viable

[1] Vali et al. Biomarkers for staging fibrosis and non-alcoholic steatohepatitis in non-alcoholic fatty liver disease (the LITMUS project): a comparative diagnostic accuracy study. *Lancet Gastroenterol Hepatol* 2023;8:714-725. [2] Sanyal et al. Non-Invasive Biomarkers of Nonalcoholic Steatohepatitis: the FNIH NIMBLE project. *Nat Med* 2022;28:430-432. [3] Mozes et al. Performance of non-invasive tests and histology for the prediction of clinical outcomes in patients with non-alcoholic fatty liver disease: an individual participant data meta-analysis. *Lancet Gastroenterol Hepatol* 2023;8:704-713. [4] Lin et al. Vibration-Controlled Transient Elastography Scores to Predict Liver-Related Events in Steatotic Liver Disease. *JAMA* 2024;331:1287-1297. [5] Gawrieh et al. Increases and decreases in liver stiffness measurement are independently associated with the risk of liver-related events in NAFLD. *J Hepatol* 2024. [6] Harrison et al. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. *N Engl J Med* 2024;390:497-509. [7] Newsome et al. ESSENCE: Phase 3 ongoing, randomized, double-blind, placebo-controlled trial of semaglutide for patients with MASH [The Liver Meeting: San Diego, 2024; Late Breaker #5018]. *Hepatology* 2024;80:S1-S2011.

Proposal: A Non-Invasively Assessed Fibrosis RLSE

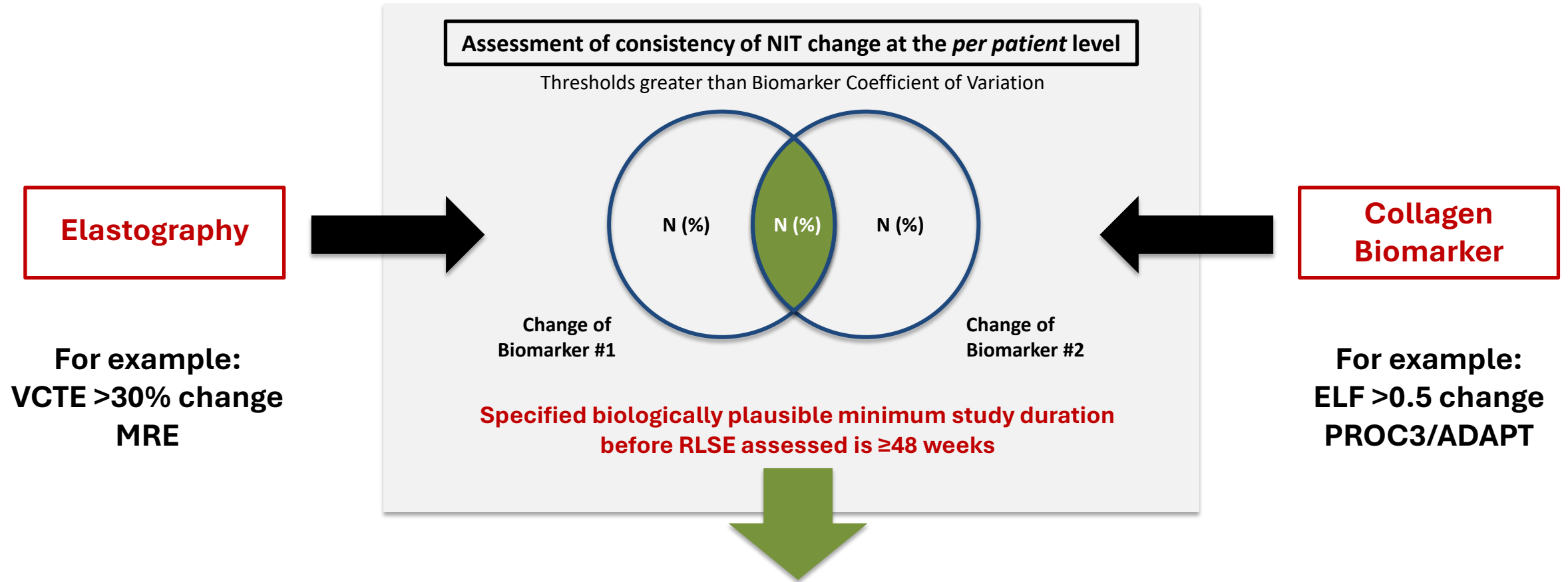
1. Change in Hepatic Fibrosis should be the basis for a NIT-based RLSE.

- Non-invasive Fibrosis biomarkers have robust evidence of high **diagnostic** and **prognostic** performance as well as demonstrating **sensitivity to change** in multiple studies.
- To establish Treatment Response it is proposed to demonstrate **concordance of change in two biomarkers at the individual patient level**.

2. Change in Liver Fat Content (steatosis) and/or markers of Disease Activity may provide supportive evidence of treatment effect but do not form part of the proposed RLSE.

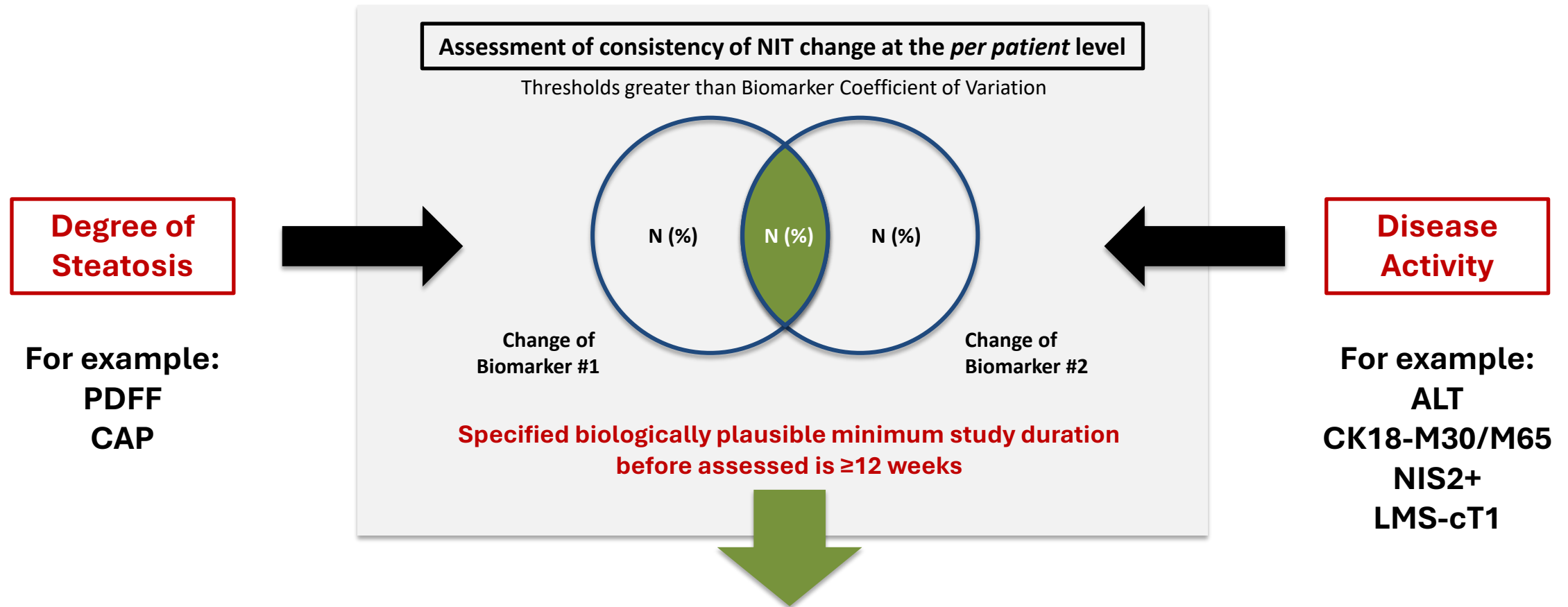
- Steatosis and Activity biomarkers have evidence for diagnostic performance and sensitivity to change, but **lack strong evidence of prognostic performance**.

Analysis #1: Fibrosis (Proposed New RLSE)



Change (improvement) of both biomarkers > Pre-defined thresholds = Disease Regression (Responder)
Discordance, worsening, or change of biomarkers < Pre-defined thresholds = Non-responder

Analysis #2: Steatosis & Activity (Supportive evidence only, not RLSE)



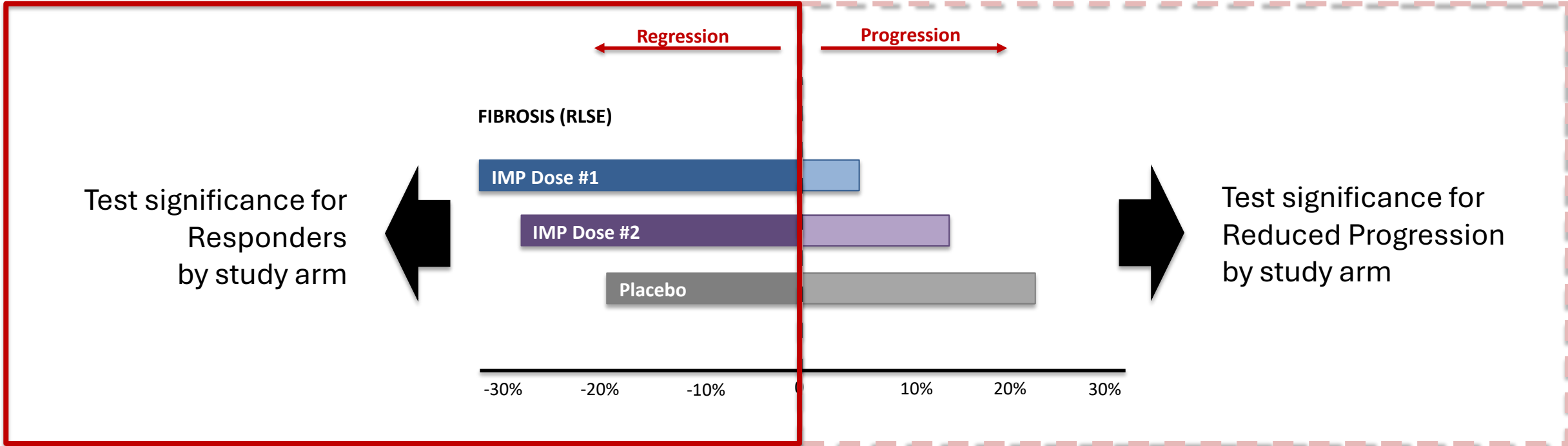
Change (improvement) of both biomarkers > Pre-defined thresholds = Disease Regression (Responder)
Discordance, worsening, or change of biomarkers < Pre-defined thresholds = Non-responder

Analysis #3: Presentation of Results & Testing Significance

Overview of bi-directional NIT changes *per study arm*

RSLE Primary Endpoint: Fibrosis Reduction

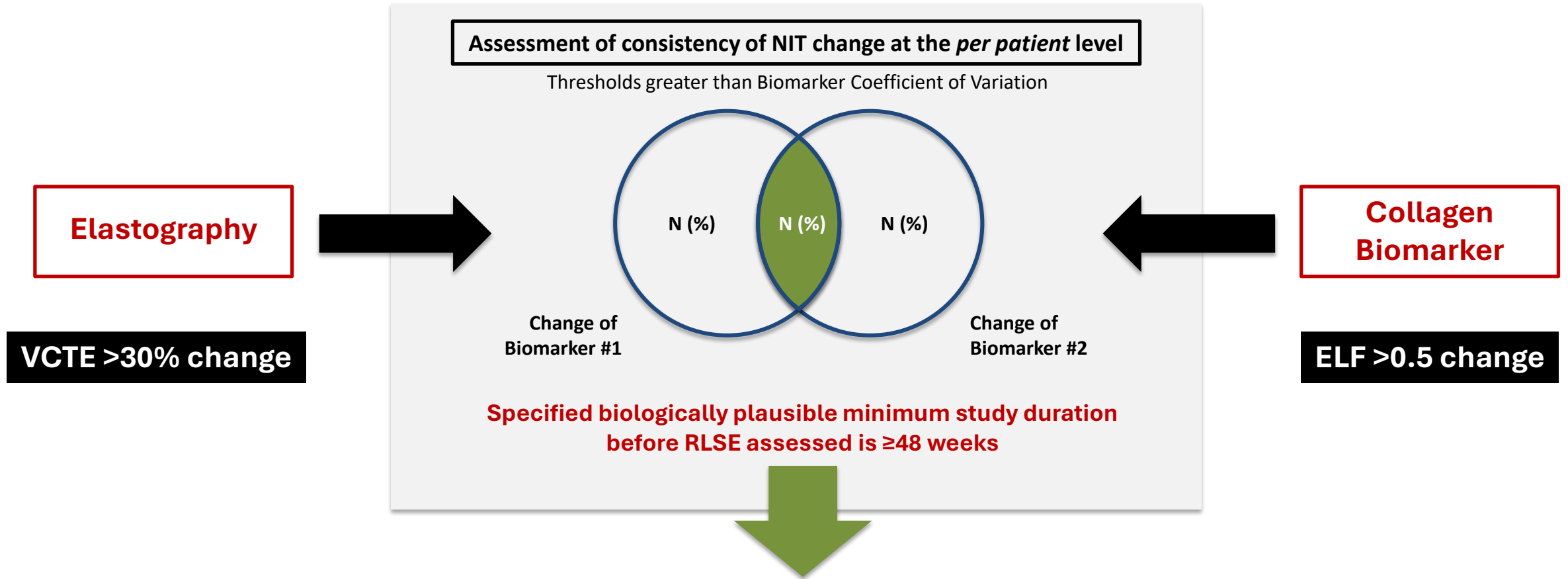
Supportive



Three Real World Examples

Thanks to Kitty Yale (Akeru), Andrew Billen (Gilead) & Michelle Long (Novo)

Worked Examples of Proposed Non-Invasive Fibrosis RLSE

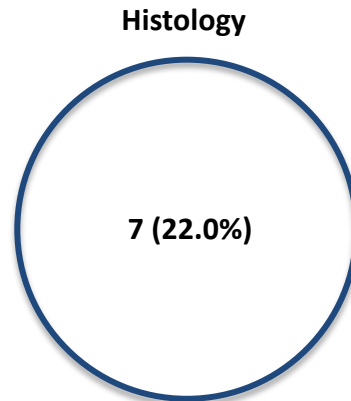


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Examples of New RLSE Application with Existing Trial Datasets

#1: Positive Trial with concordant Histological RLSE & NIT -based RLSE: Akero HARMONY, week 96.

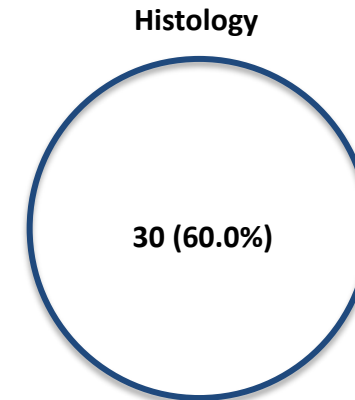
PLACEBO



Total N in Study Arm

(responders and non-responders) = 32 (100%)

EFX both doses combined



Total N in Study Arm

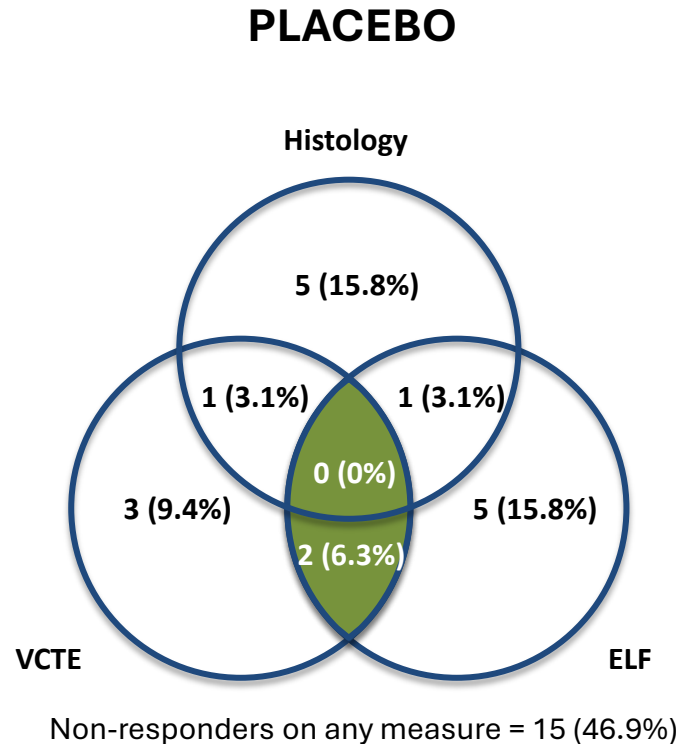
(responders and non-responders) = 50 (100%)

Endpoints:

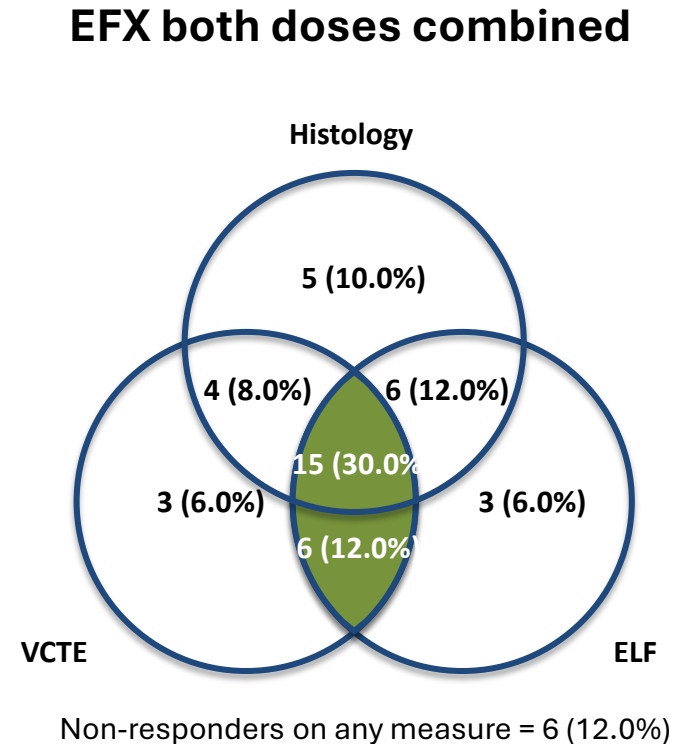
- Histology: ≥ 1 point Fibrosis reduction without worsening of MASH
- Fibroscan (VCTE): $\geq 30\%$ reduction from baseline
- ELF: ≥ 0.5 unit drop from baseline

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**Total N in Study Arm
(responders and non-responders) = 50 (100%)**

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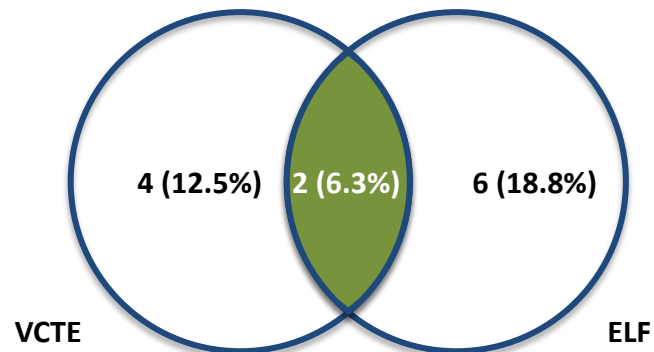
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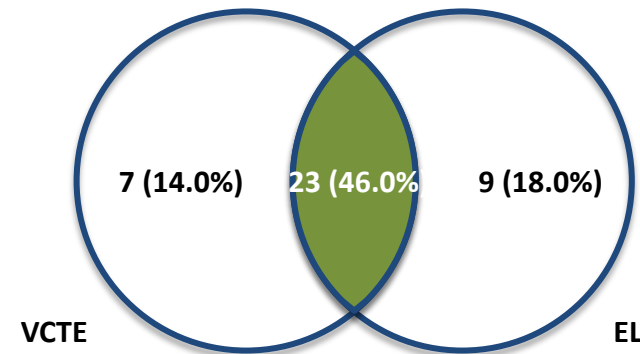
EFX both doses combined



Non-responders on any measure = 20 (62.5%)

Total N in Study Arm

(responders and non-responders) = 32 (100%)



Non-responders on any measure = 11 (22.0%)

Total N in Study Arm

(responders and non-responders) = 50 (100%)

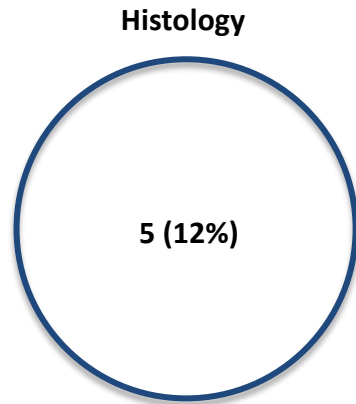
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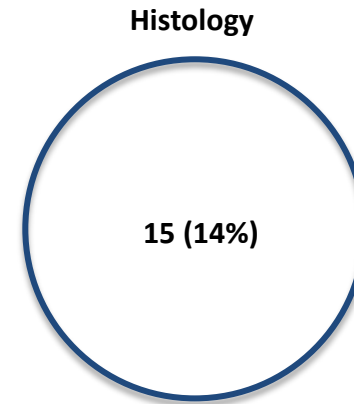
#2: Negative Trial with concordant Histological RLSE & NIT -based RLSE: Gilead STELLAR-3, week 48.

PLACEBO



Total N in Study Arm
(responders and non-responders) = 35 (100%)

SEL both doses combined



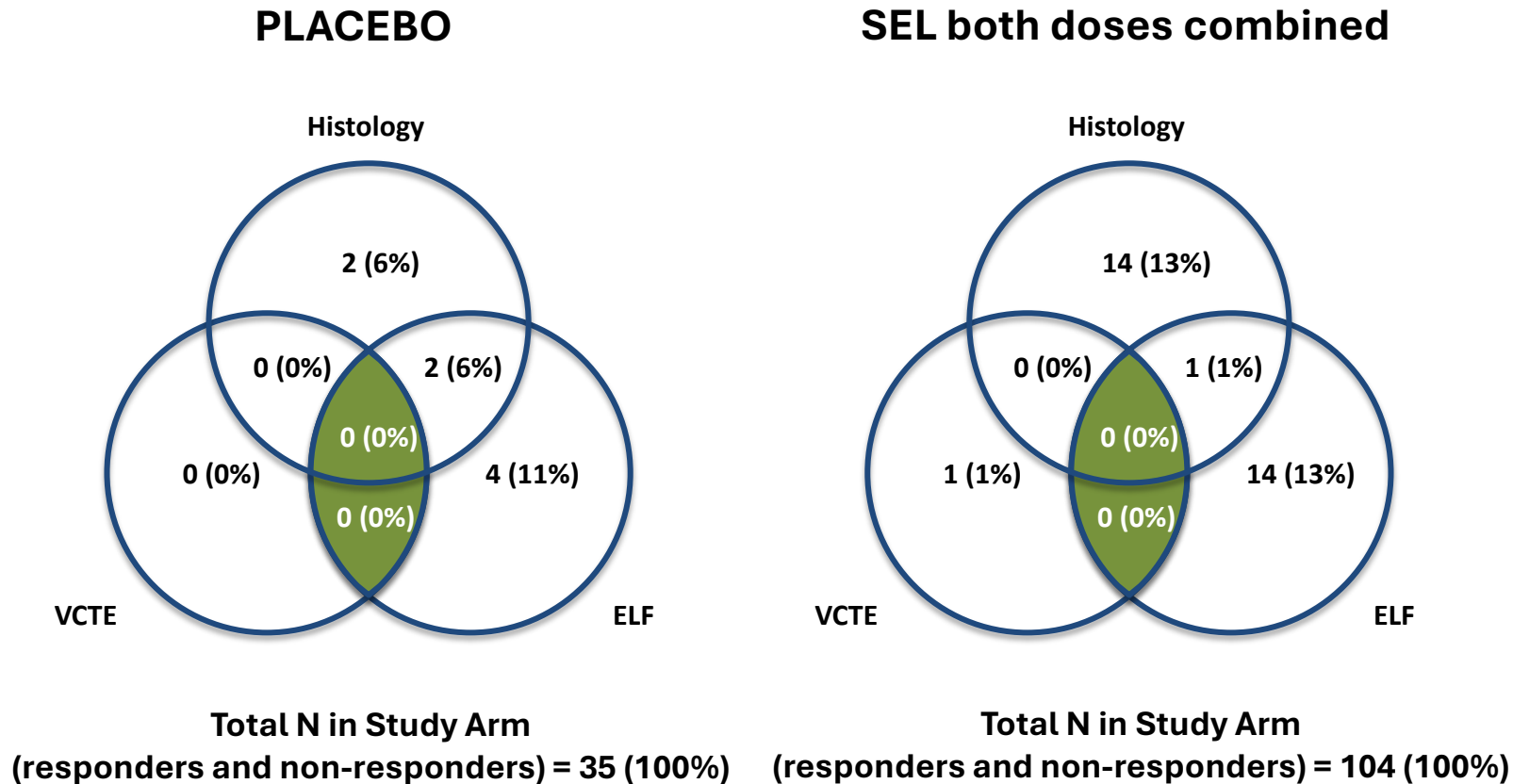
Total N in Study Arm
(responders and non-responders) = 104 (100%)

Endpoints:

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Examples of New RLSE Application with Existing Trial Datasets

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Endpoints:

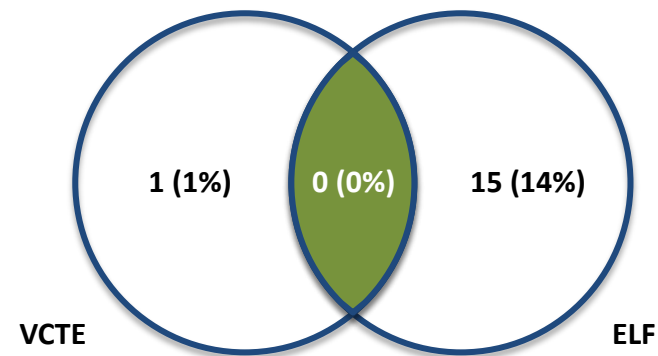
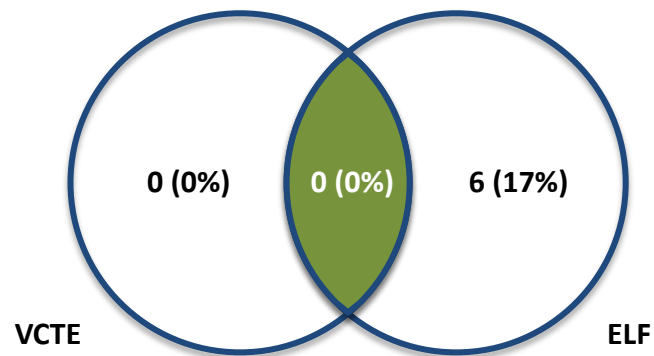
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PLACEBO

SEL both doses combined



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Total N in Study Arm
(responders and non-responders) = 104 (100%)

Endpoints:

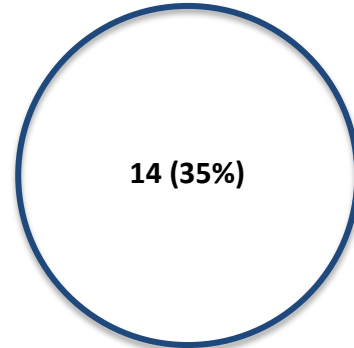
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Examples of New RLSE Application with Existing Trial Datasets

#3: Trial with discordant Histology RLSE & NIT -based RLSE: Novo Nordisc SEMA Ph2, week 72.

PLACEBO

Histology

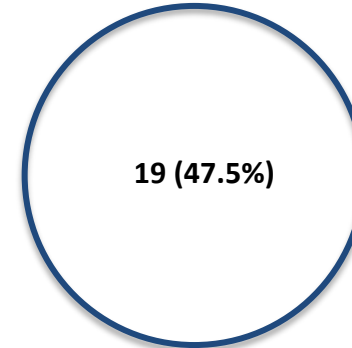


Total N in Study Arm

(responders and non-responders) = 40 (100%)

SEMA 0.4 mg

Histology



Total N in Study Arm

(responders and non-responders) = 40 (100%)

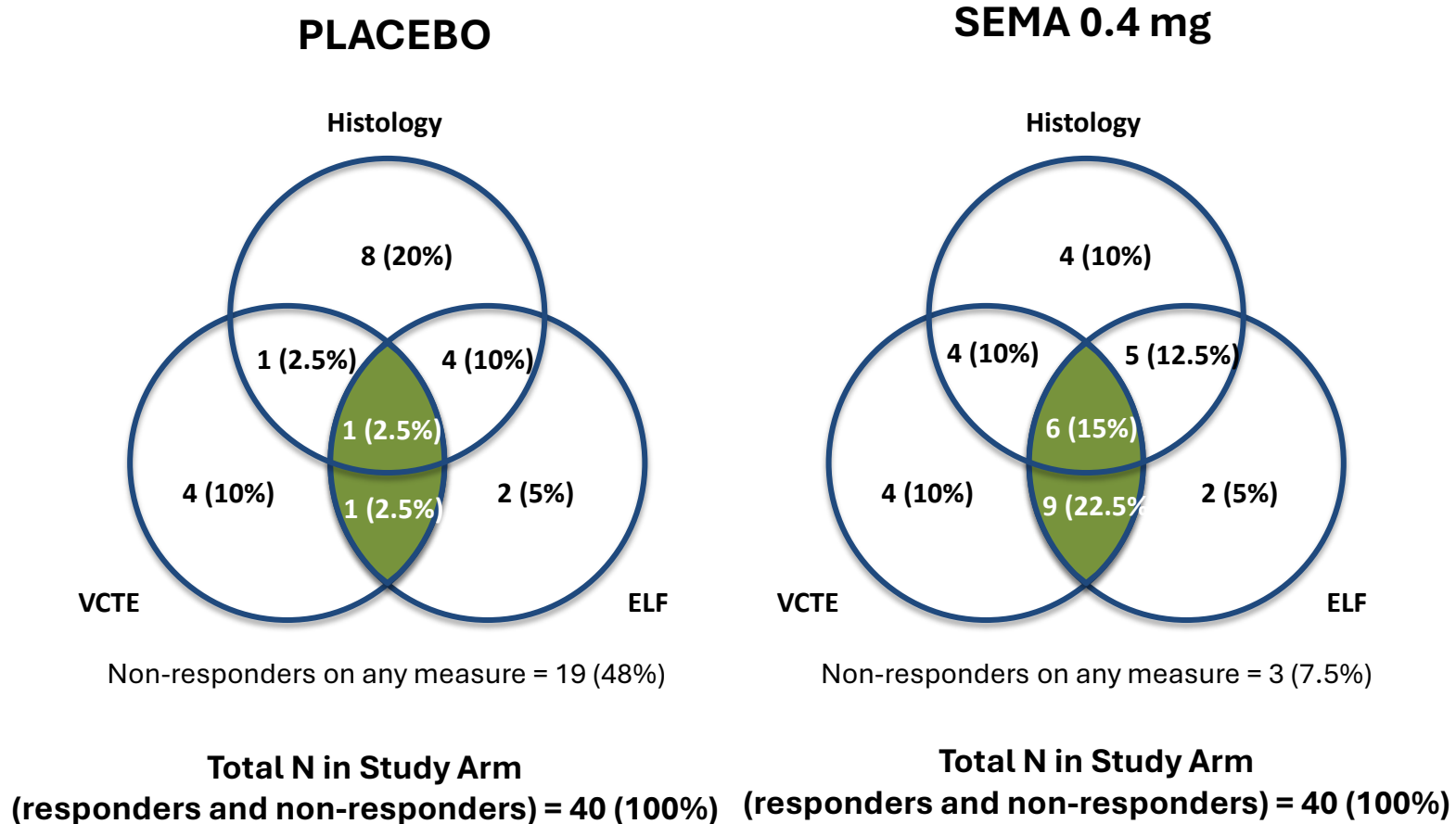
Endpoints:

- Histology: ≥ 1 point Fibrosis reduction
- Fibroscan (VCTE): $\geq 25\%$ reduction from baseline
- ELF: ≥ 0.5 unit drop from baseline

[1] Anstee et al, Fibrosis response assessed by enhanced liver fibrosis and FibroScan liver stiffness measurement in patients with non-alcoholic steatohepatitis treated with subcutaneous semaglutide, EASL 2021

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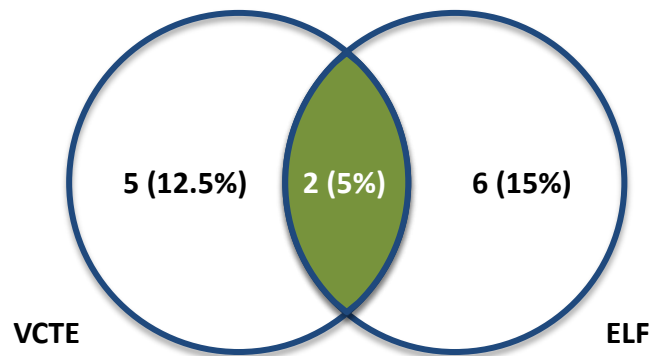
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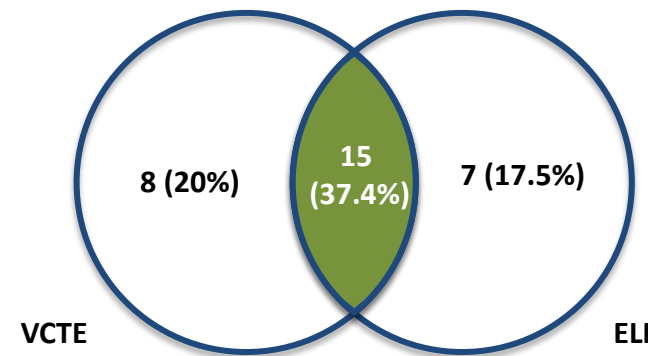
SEMA 0.4 mg



Non-responders on any measure = 27 (68%)

Total N in Study Arm

(responders and non-responders) = 40 (100%)



Non-responders on any measure = 10 (25%)

Total N in Study Arm

(responders and non-responders) = 40 (100%)

Endpoints:

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Conclusions

The current histology-based MASH drug development paradigm was founded on the evidence available in 2013^[1]. Over a decade later, it is timely to reconsider endpoints in light of substantial advances in our understanding, the availability of new technologies and data that support NITs as a viable tools to assess therapeutic efficacy.

- **Liver histology is an imperfect biomarker. Histological assessment of ballooning, and therefore ‘MASH resolution’ as currently defined, is *scientifically untenable* as an endpoint.**
- **The field has matured: well-evidenced, tractable non-invasive biomarkers are available to support drug development.**
 - **Trial Enrolment should be based on non-invasive Prognostic Enrichment**
 - **Pharmacodynamic/Response – Reasonably-Likely Surrogate Endpoints (RLSE):**
 - There is substantial evidence that fibrosis biomarkers directly link to outcome and change with progression/regression of disease, exhibiting greater inter-test consistency than histology for outcomes.
 - Thresholds based on clinically meaningful magnitude of change that exceeds the coefficient of variation have been defined.
 - Phase 2/3 trial data demonstrate that biomarkers track improvement with efficacious therapies.
 - In absence of a single ‘perfect’ biomarker, **response can be defined by assessment based on concordance of response** at the per-patient level of complementary fibrosis biomarkers (ie elastography + direct collagen).
 - As currently, the requirement to ultimately demonstrate outcome benefit remains and complements this approach.

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