NAFLD: Potential Trial Designs & Suitable Study Populations

EMA Stakeholder Meeting on Medicinal Products for Chronic Non-Infectious Liver Diseases, London, December 2018

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Institute of Cellular Medicine,
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Disclosure Slide

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Consultancy (undertaken on behalf of Newcastle University)

Abbott Laboratories, Acuitas Medical, Allergan/Tobira, E3Bio, EcoR1, Eli Lilly & Company Ltd., Galmed, Genfit SA, Gilead, Grunthal, HistoIndex, Imperial Innovations, Intercept Pharma Europe Ltd., Inventiva, IQVIA, Janssen, Madrigal, MedImmune, NewGene, NGMBio, Novartis, Novo Nordisk A/S, Pfizer Ltd., Poxel, Raptor Pharma, Servier, Viking.

Speaker

Abbott Laboratories, Allergan/Tobira, BMS, Clinical Care Options, Falk, Genfit SA, Gilead, Kenes.

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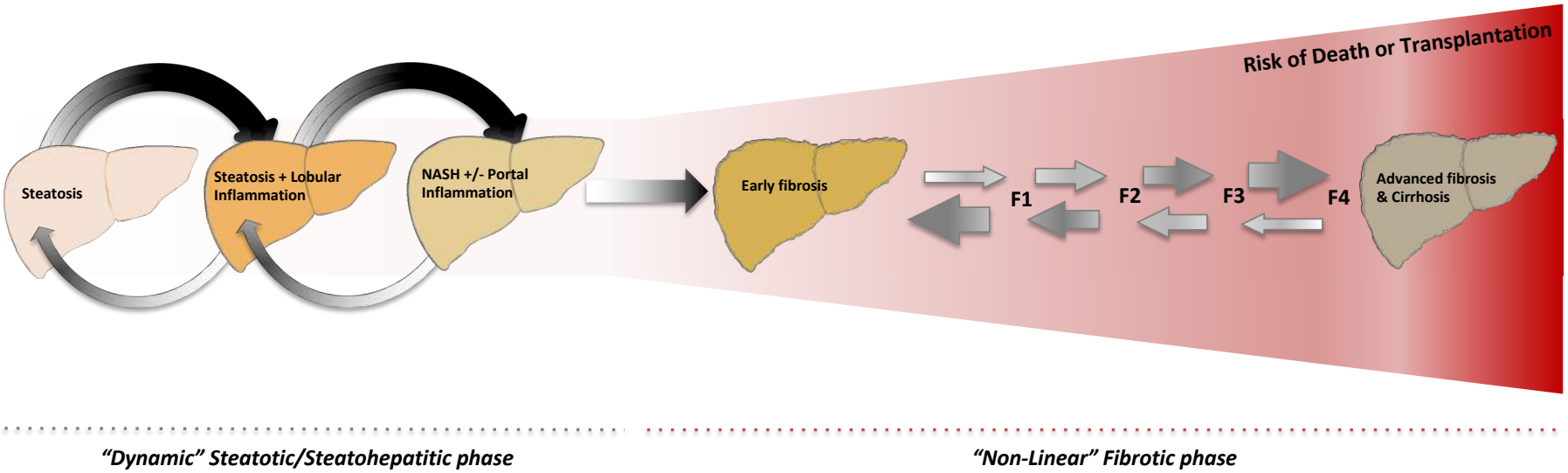
NAFLD Natural History



Steatohepatitis (NASH) is the *biological driver* of disease progression and fibrogenesis.
The presence of *advanced stage of fibrosis (F3-4) is the strongest predictor of long-term mortality*.

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Challenges of Trial Design & Drug Development in NAFLD

- **Highly variable Natural History** with evolving understanding of pathophysiology.
  - Confounding factors to be accounted for/controlled.
- **Long "asymptomatic" phase before Clinically Measurable Outcomes occur**.
  - Morbidity/Mortality may be non-liver related (e.g. Cardiovascular Disease).
- **Surrogate Endpoint validity not well established.**
  - **Clinical Benefit** of endpoints related to *changes* in NASH activity or Fibrosis stage have not been formally established.
- **Specific challenges related to how disease severity or response are assessed.**
  - **Biopsy**: Patient acceptance/safety, Sampling error, Interpretation variability.
  - **Non-invasive biomarkers**: none qualified at present.
    - Actively being addressed in the **EU-funded IMI2 "LITMUS"** project.
- **Wide range of differing Mechanisms of Action (MoA) being explored.**

Targeting Numerous Pathophysiological Processes to Treat NASH

Targets related to Insulin Resistance and/or Lipid Metabolism

PPARγ: Pioglitazone
GLP-1: Liraglutide, Semaglutide
MPCi: PXL065
SGLT1/2: LIK066
GLP-1/GR: MEDI0382
KHKi: PF-06835919
ACCi: GS-0976, PF-05221304
DGAT2i: PF-06865571
SCD1: Aramchol
FGF21: BMS-986036

Targets related to Lipotoxicity & Oxidative Stress

PPARα/∂: Elafibranor
PPARα/∂/γ: IVA337
PPARα/γ: Saroglitazar
THR-β: MGL-3196
mTOT: MSDC-0602K
FXR: OCA, GS-9674, LJN-452, LMB-763
TGR5: INT-767, INT-777
ASBT: Volixibat
FGF19: NGM282
AMPKi: PXL770
Vitamin E

Targets related to Inflammation and Immune activation

CCR2/5: Cenicriviroc
AOC3: BI 1467335
TLR4: JKB-121
Anti-LPS: IMM-124E

Targets related to Cell Death (Apoptosis and Necrosis)

ASK1: Selonsertib
Caspases: Emricasan

Targets related to Fibrogenesis & Collagen Turnover

LOXL2: Simtuzumab
Galectin: GR-MD-02

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Study Population

Endpoints

Trial Design

Pre-Cirrhotic NASH **vs.** **Cirrhotic NASH**

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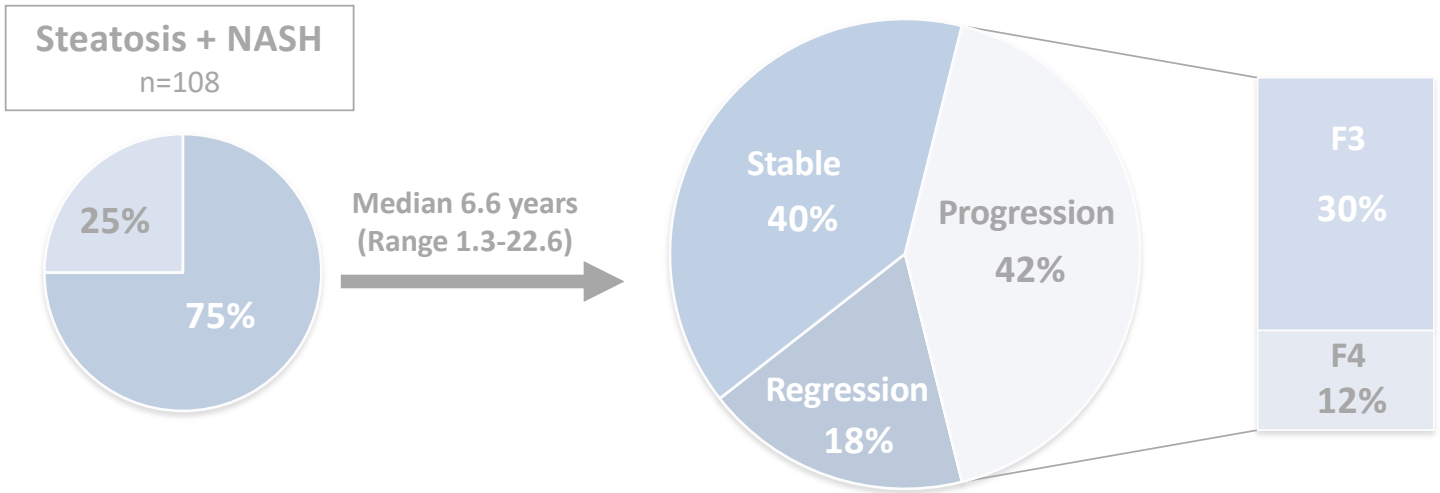
Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis & clinical management

S. McPherson, T. Hardy, E. Henderson, A.D. Burt, C.P. Day & Q. M. Anstee

Journal of Hepatology **2015** vol. 62 | 1148–1155



Disease Activity (Steatohepatitis)

Baseline disease activity	Follow-up disease activity			
	Bland steatosis	Steatosis and mild inflammation	NASH	Total
Bland steatosis	7	6	4	17
Steatosis and mild inflammation	2	0	8	10
NASH	5	1	75	81
Total	14	7	87	108

Disease Stage (Fibrosis)

Baseline fibrosis	Follow-up fibrosis stage					
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Total
Stage 0	16	4	1	2	0	23
Stage 1	6	7	3	11	2	29
Stage 2	1	7	11	11	3	33
Stage 3	0	2	4	9	8	23
Stage 4	0	0	0	0	0	0
Total	23	20	19	33	13	108

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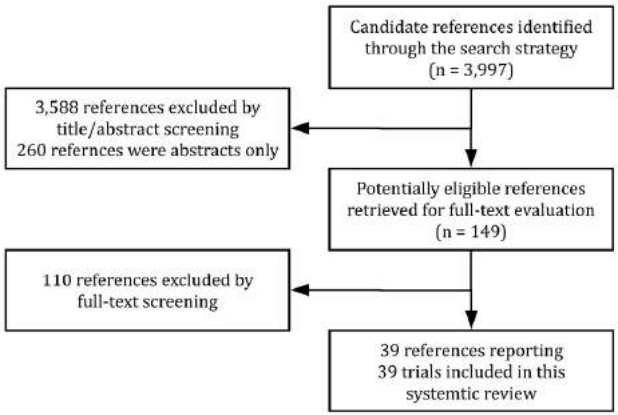
See also: Pais et al, 2013; Singh et al, 2015

Meta-analysis of Trial Placebo Arms



39 RCTs: 1463 Placebo Treated Patients

- **Histology (31 studies; N = 956)**
- **MRS Steatosis (13 studies; N = 295)**
- **MRI-PDFF (3 studies; N = 61)**

Median study duration 48 weeks (8-96)

Well known studies included:

PIVENS n=83
Sanyal, 2010

FLINT n=142
Neuschwander-Tetri, 2015

MOZART n=25
Loomba, 2015

GOLDEN-505 n=92
Ratziu, 2016

Pioglitazone n=51
Cusi, 2016

LEAN n=22
Armstrong, 2016

CENTAUR n=144
Friedman, 2017

FELINE n=21
McPherson, 2017

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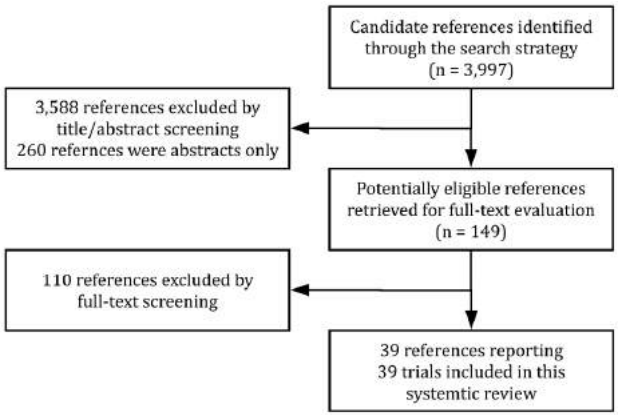
Thanda Han & Altayar et al, Clinical Gastroenterology & Hepatology, 2018 in press.

Meta-analysis of Trial Placebo Arms: Two-Point NAS Improvement



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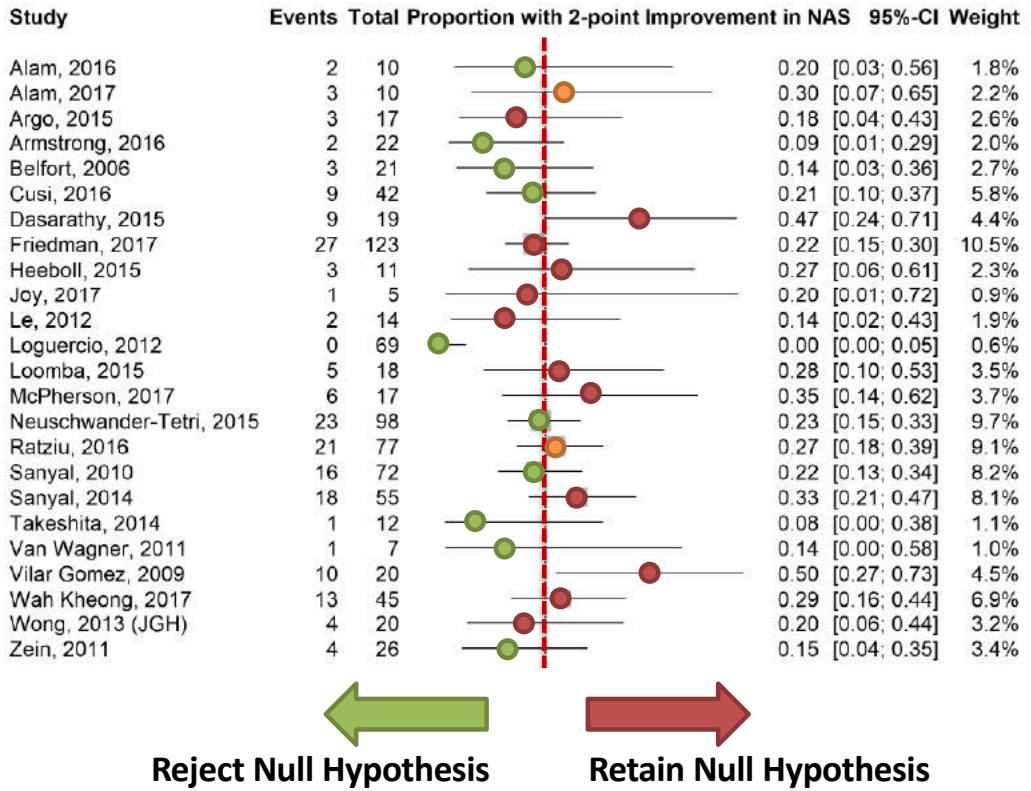

25% (95%CI 21-29%) of placebo patients had a ≥2 point NAS improvement

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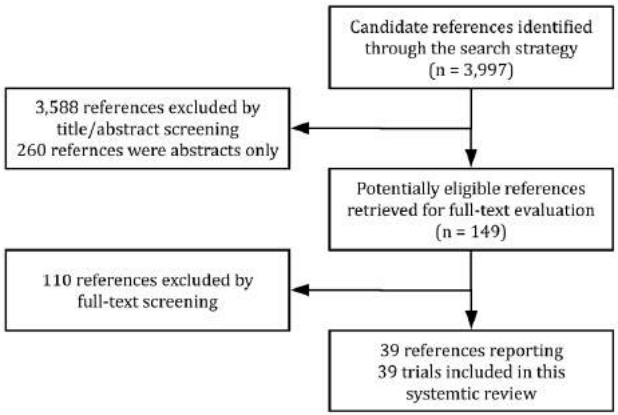
Thanda Han & Altayar et al, Clinical Gastroenterology & Hepatology, 2018 in press.

Meta-analysis of Trial Placebo Arms: Improvement in Fibrosis



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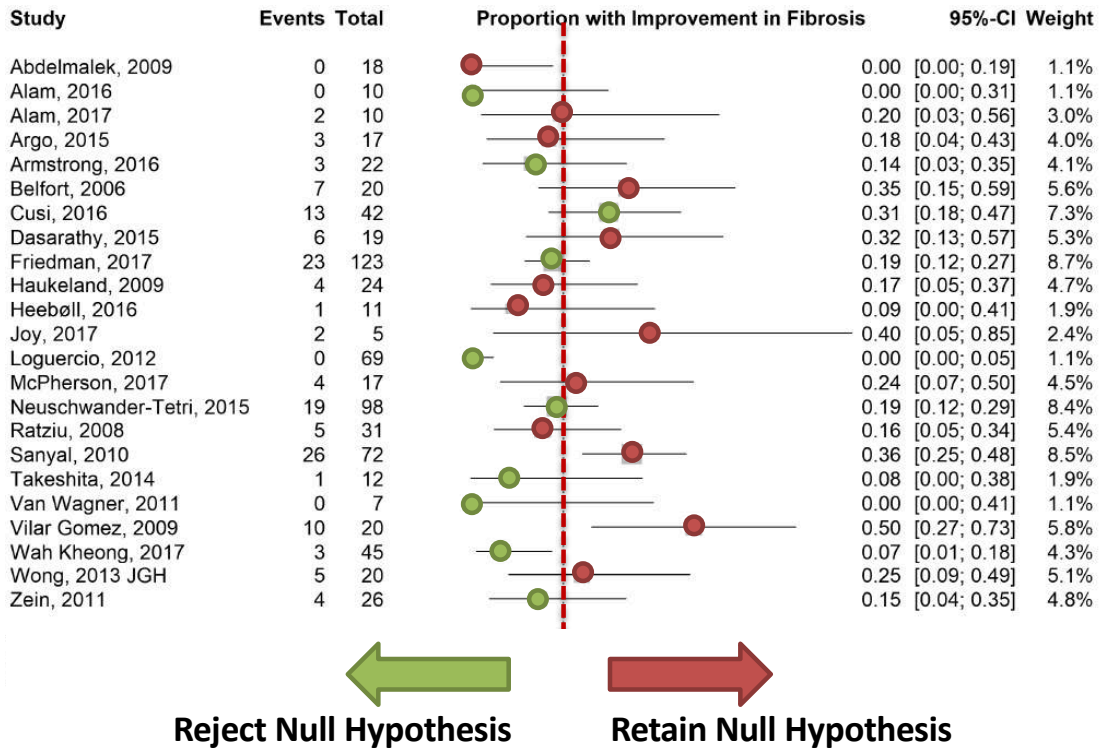

21% (95%CI 16-26%) of placebo patients had a ≥1 stage Fibrosis improvement

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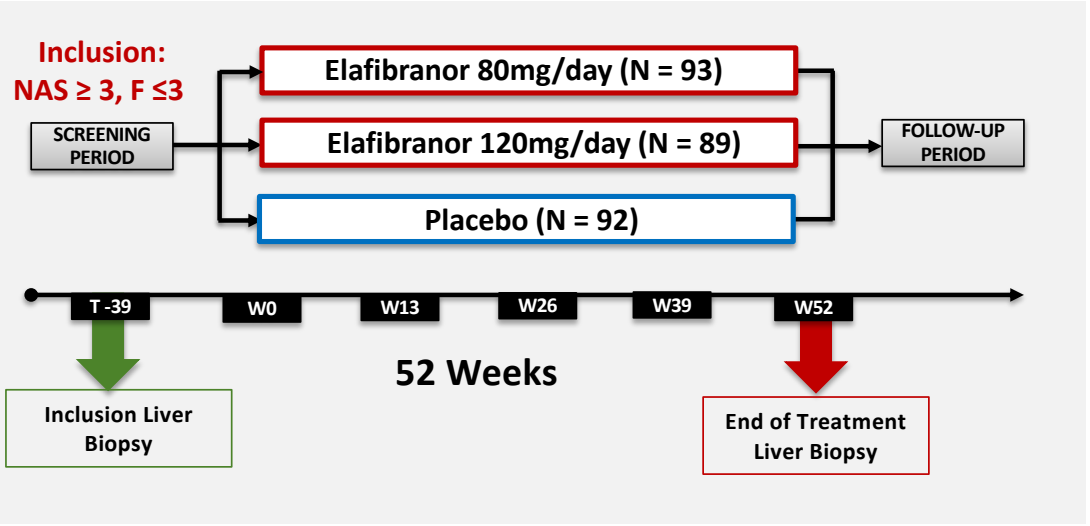
(See also Roskilly A, et al. EASL 2018).
Thanda Han & Altayar et al, Clinical Gastroenterology & Hepatology, 2018 in press.

The Phase 2b GOLDEN-505 Study

274 diabetic and non-diabetic adults with biopsy proven NASH



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Ratziu et al, Gastroenterology, 2016

Greater Placebo Response at Lower Baseline NAS/Fibrosis Stage

Placebo Arm % NASH Resolution

NAS	n	Placebo, n (%)
Protocol-defined primary outcome		
Total	274	92 (17)
NAS ≥4 (moderate and severe)	234	76 (11)
NAS 3 (mild)	40	16 (50)
Modified definition of response		
Total	274	92 (12)
NAS ≥4 (moderate and severe)	234	76 (9)
NAS 3 (mild)	40	16 (25)

Placebo % NASH Resolution by Fibrosis Stage

Population	Selection n (%)	Placebo n (%)
All NAS ≥4	**202**	**63 (11)**
NAS ≥4 with fibrosis (any stage)	**176**	**55 (13)**
NAS ≥4 with moderate/advanced fibrosis (F2, F3)	**99**	**32 (9)**

Placebo response rate changed 5% (17% >>> 12%) by how "NASH Resolution" endpoint defined

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Ratziu, et al. Gastroenterology. 2016

Pre-Cirrhotic Study Populations

- **Placebo responsive rate 10-40% (FRR ~20% a reasonable estimate)**.
- **Higher NAS** and/or **greater Fibrosis Stage/Hepatic Collagen** at baseline implies lower probability of substantial spontaneous regression.

Phase 2a: Histologically defined study populations not mandated

Phase 2b/3/4: Histologically defined study populations with NASH + Fibrosis

Baseline Evidence of NASH:	**NAS ≥4 (≥1 for each component)**
Baseline Evidence of Fibrosis:	**F2 minimum, F3 preferred**

Cirrhotic Study Populations

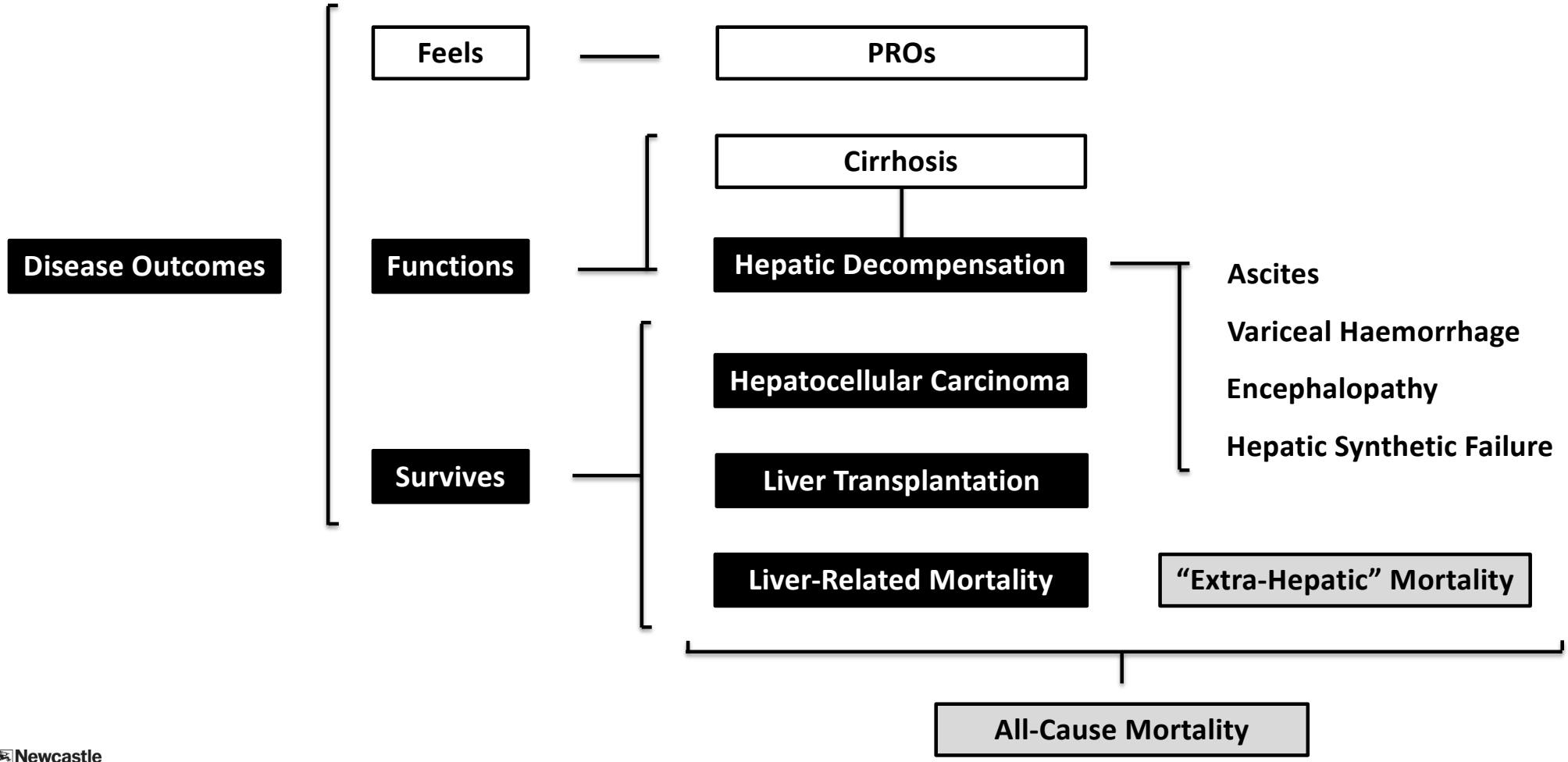
- **Placebo responsive rate 10-40% (FRR ~20% a reasonable estimate)**.
- **Higher NAS** and/or **greater Fibrosis Stage/Hepatic Collagen** at baseline implies lower probability of substantial spontaneous regression.

Phase 2a: Histologically defined study populations not mandated but advisable

Phase 2b/3/4: Histologically defined study populations with NASH + F4 Fibrosis

Baseline Evidence of NASH:	**NAS ≥3 (≥1 for each component)**
Baseline Evidence of Fibrosis:	**F4 minimum**

Endpoints



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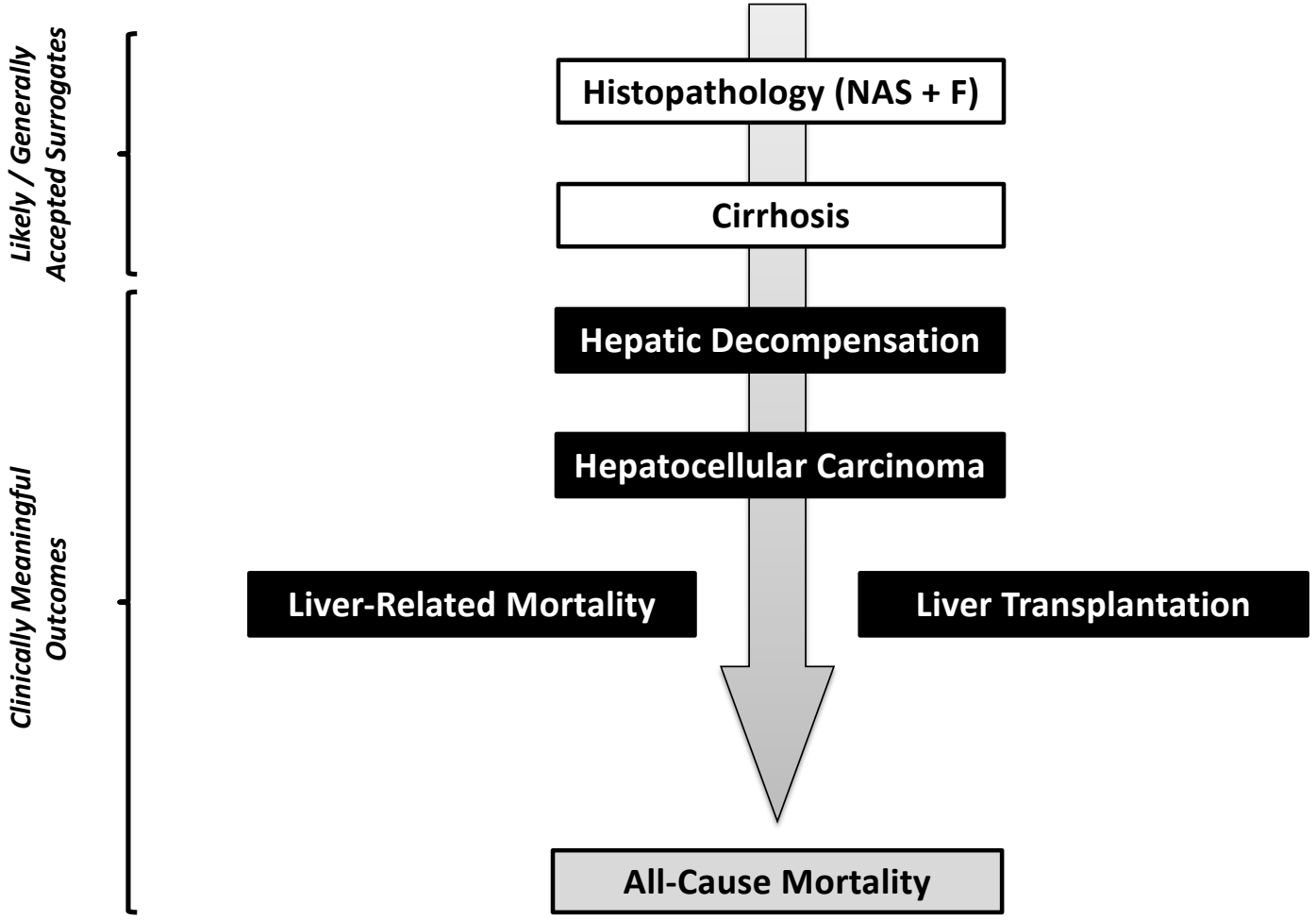
Relevant Trial Endpoints & Outcomes for NAFLD



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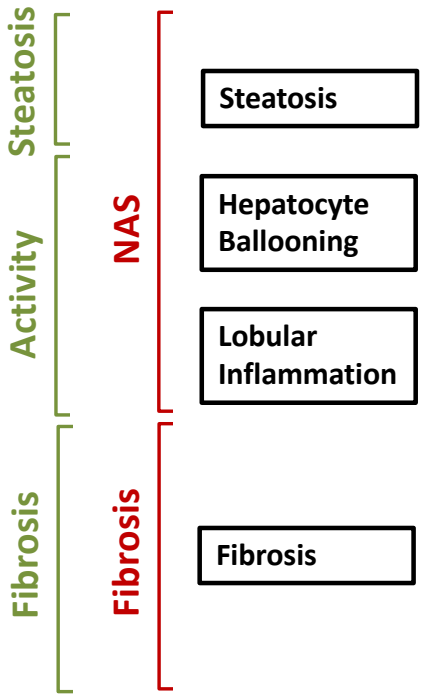
Histological Features of NAFLD & NASH



NIDDK NASH Activity Score

Category definition	
0	<5%
1	5–33%
2	34–66%
3	>66%
PLUS	
0	None
1	Few
2	Many
PLUS	
0	None
1	1–2 foci per ×20 field
2	2–4 foci per ×20 field
3	>4 foci per ×20 field
Total=NAFLD Activity score 0–8	
0	No fibrosis
1a	Zone 3 mild perisinusoidal fibrosis
1b	Zone 3 moderate perisinusoidal fibrosis
1c	Periportal/portal fibrosis only
2	Zone 3 plus portal/periportal fibrosis
3	Bridging fibrosis
4	Cirrhosis
Fibrosis score 0–4	

Kleiner et al, Hepatology 2005

FLIP "SAF" Score

Category definition	
0	<5%
1	5–33%
2	34–66%
3	>66%
(S) Steatosis score 0–3	
0	None
1	Clusters of hepatocytes with rounded shape and pale cytoplasm
2	Same as grade 1 with enlarged hepatocytes (>2× normal size)
PLUS	
0	None
1	<2 foci per 20× field
2	>2 foci per 20× field
(A) Total=Activity score 0–4	
0	No fibrosis
1a	Zone 3 mild perisinusoidal fibrosis
1b	Zone 3 moderate perisinusoidal fibrosis
1c	Periportal/portal fibrosis only
2	Zone 3 plus portal/periportal fibrosis
3	Bridging fibrosis
4	Cirrhosis
(F) Fibrosis score 0–4	

Bedossa et al, Hepatology 2012

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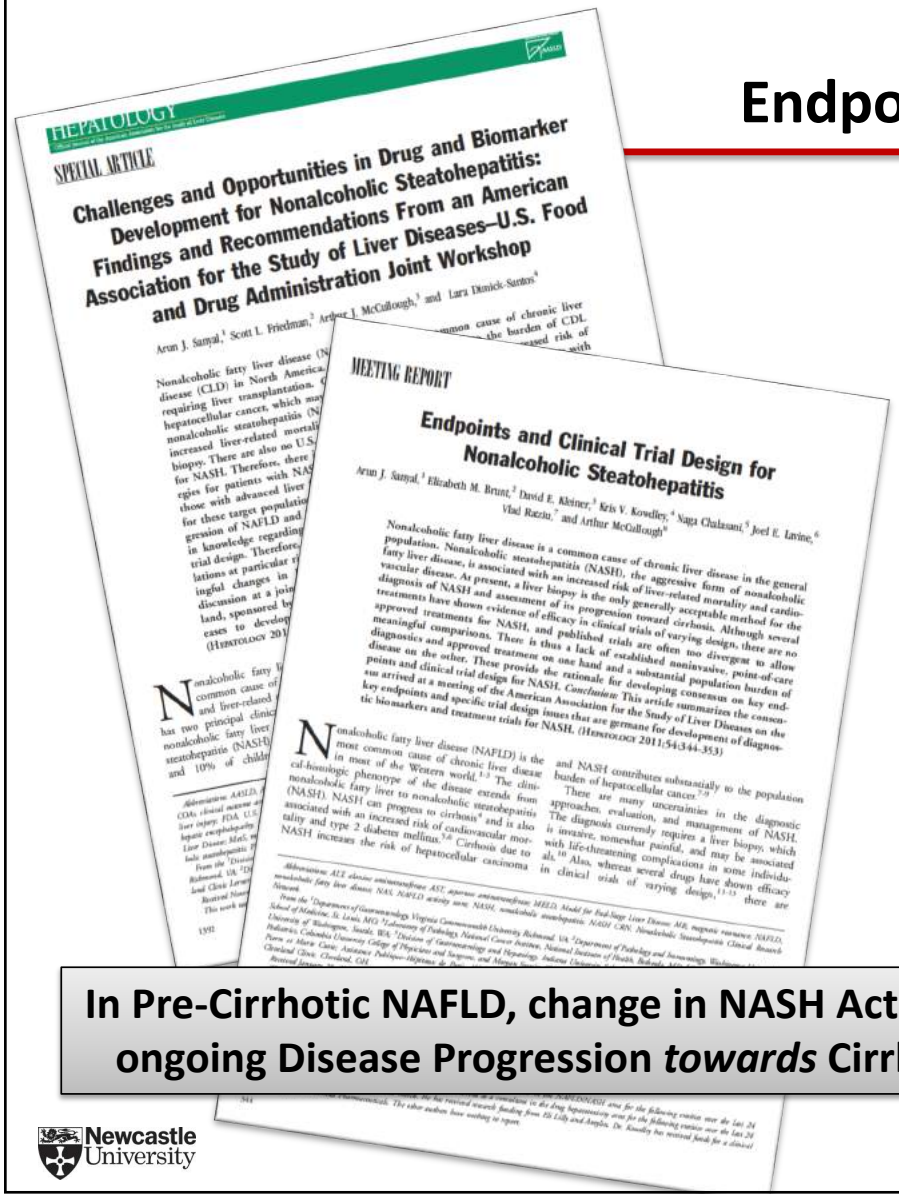
Table: Dyson et al, J Clin Pathol 2013



Endpoints for Clinical Trials

- Histology-based Endpoints for NASH Trials:
  - **Reversal of Steatohepatitis, with no worsening of fibrosis.**
    - Minimum 2-point improvement in NAS (with ≥1 point improvement in >1 category)
    - Resolution of NASH (with Ballooning 0 & Inflammation 0-1)
  - **Improvement of Fibrosis, with no worsening of NASH.**
    - Minimum 1-point improvement of Fibrosis Stage
- Disease Outcomes as Long-Term Endpoints

In Pre-Cirrhotic NAFLD, change in NASH Activity or Stage of Fibrosis (F1-3) are most relevant as indicators of ongoing Disease Progression *towards* Cirrhosis or Efficacy of Intervention and Regression *from* Cirrhosis.

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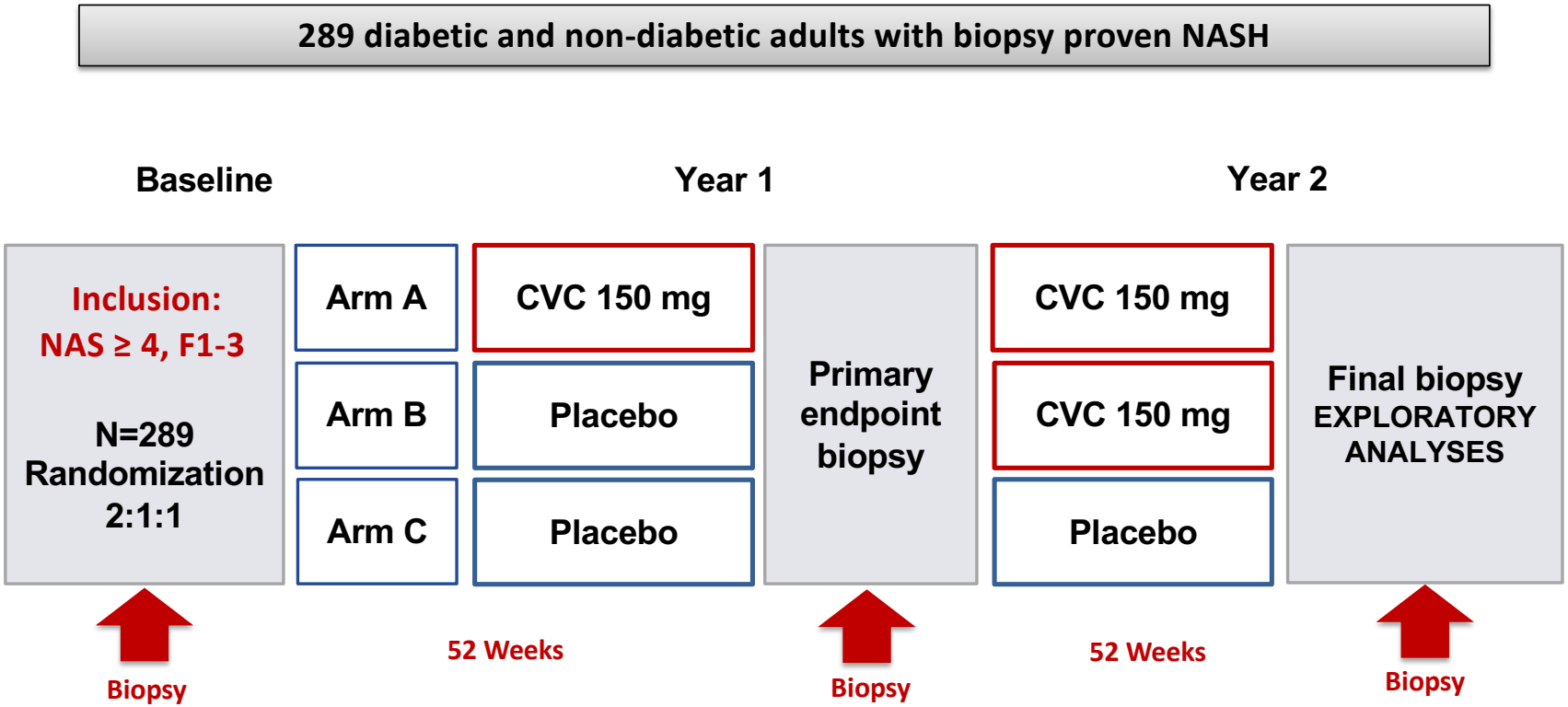
The Phase 2b CENTAUR Study



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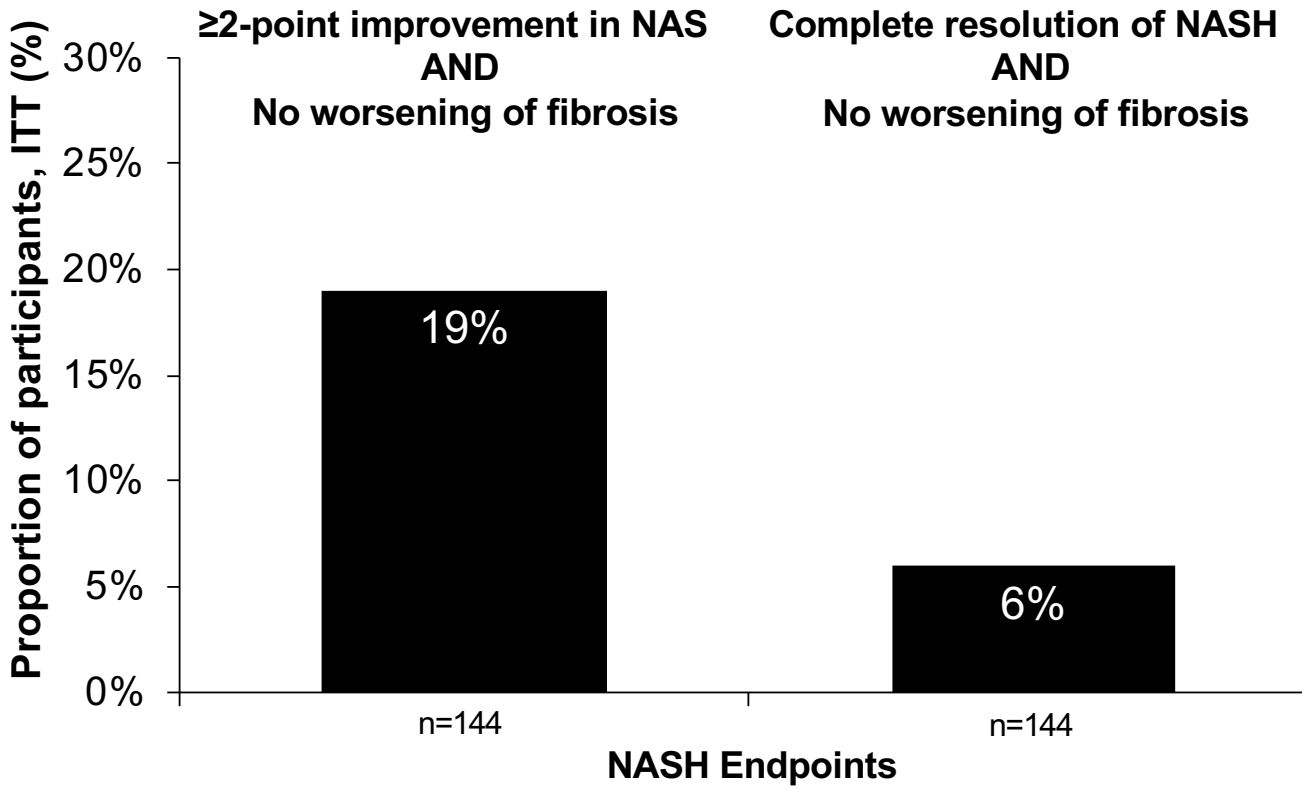
Friedman et al, Hepatology 2017; Image courtesy of Allergan

Changes in NAS & NASH Resolution after 1-Year



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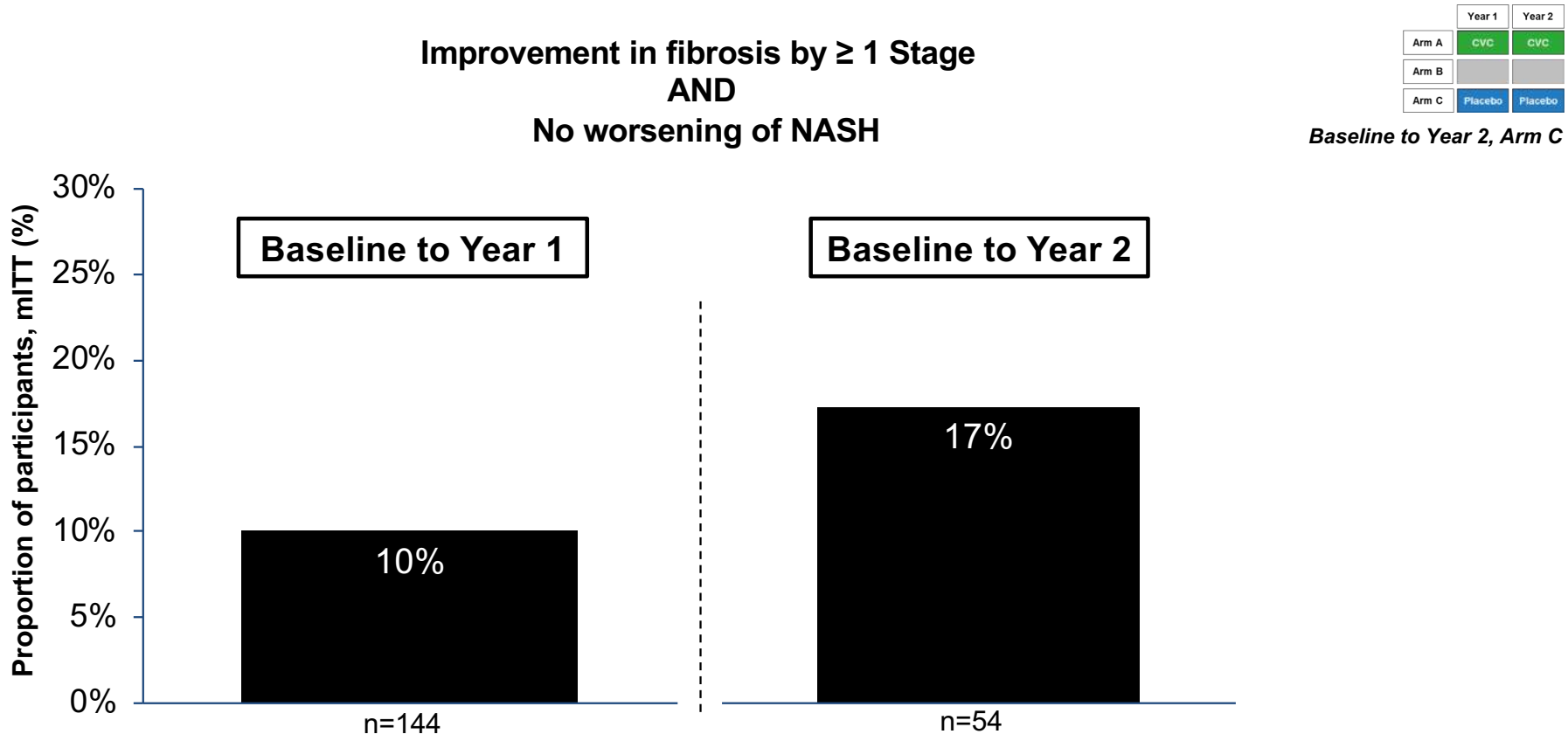
Friedman et al, Hepatology 2017; Image adapted from slide courtesy of Allergan

Change in Fibrosis by ≥1-stage after 1-Year & 2-Years



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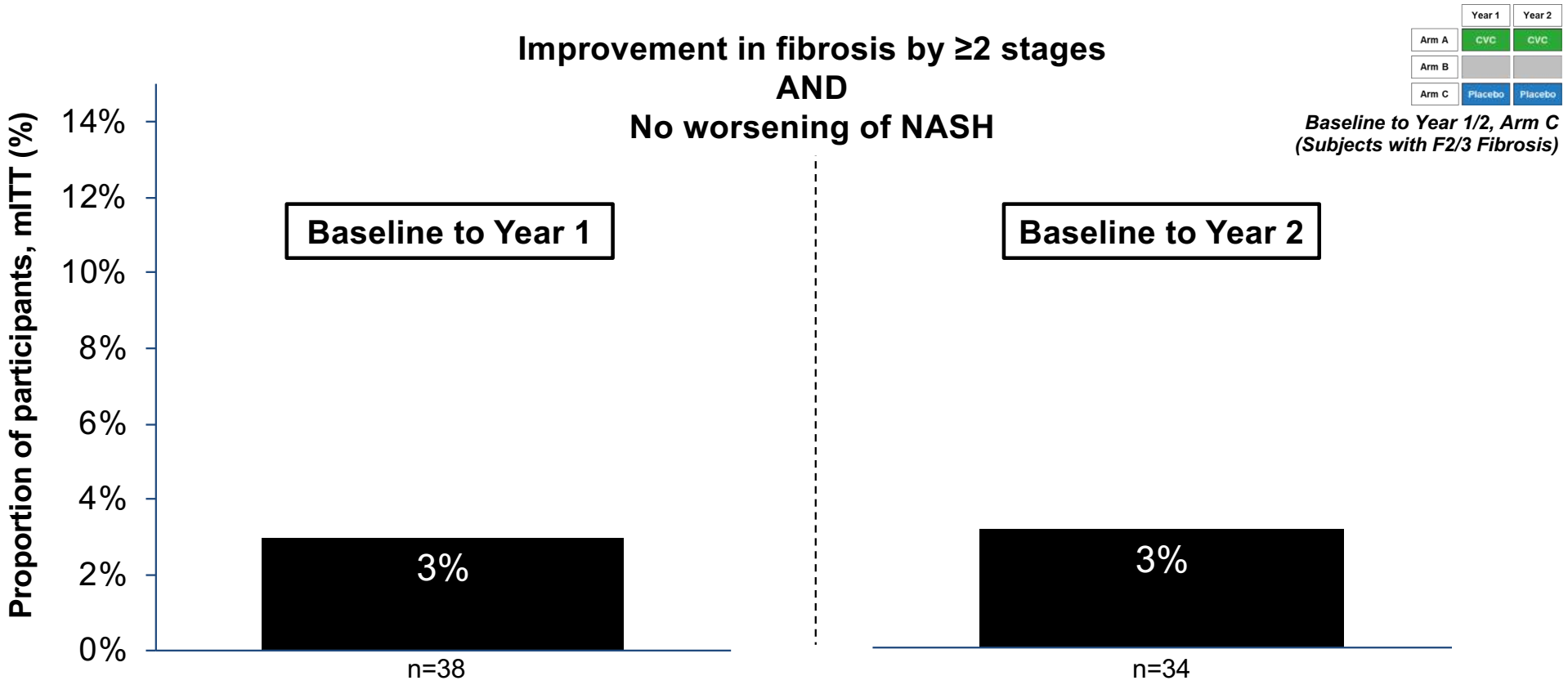
Friedman et al, Hepatology 2017; Image adapted from slide courtesy of Allergan

Change in Fibrosis by ≥2-stages after 1-Year and 2-Years



Sustained improvement in fibrosis ≥ 2 stages is unlikely to occur in placebo groups over 24 months

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Friedman et al, Hepatology 2017; Image adapted from slide courtesy of Allergan

Pre-Cirrhotic Study Endpoints

- **Selection of robust and exacting study endpoints** to minimise placebo response.
  - NASH Resolution vs. NAS improvement
  - Fibrosis reduction ≥1 vs. ≥2 stages
- ***Consistency* of change in histology and supporting biomarkers** are important to counter effects of biopsy sampling error, especially in smaller early phase trials.

Phase 2a: Histologically defined study endpoints not mandated*

Phase 2b/3: Histologically defined study endpoints with NASH + Fibrosis*

Resolution of NASH, without worsening of Fibrosis
(NAS component Ballooning = 0 and Inflammation = 0-1)

Improvement of Fibrosis by ≥1 stage(s), without worsening of NASH

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* No increase in Cardiovascular disease or other extra-hepatic events

Pre-Cirrhotic Study Endpoints

Phase 2a: Histologically defined study endpoints not mandated*

Phase 2b/3: Histologically defined study endpoints with NASH + Fibrosis*

Resolution of NASH, without worsening of Fibrosis
(NAS component Ballooning = 0 and Inflammation = 0-1)

Improvement of Fibrosis by ≥1 stage(s), without worsening of NASH

Phase 3/4: Event-driven endpoints*

Composite endpoint composed of histopathologic progression to cirrhosis, liver-related clinical outcomes, and all-cause mortality

Event Free Survival
(Hepatic Decompensation, HCC, OLT, Liver-Related and/or All-Cause Mortality)

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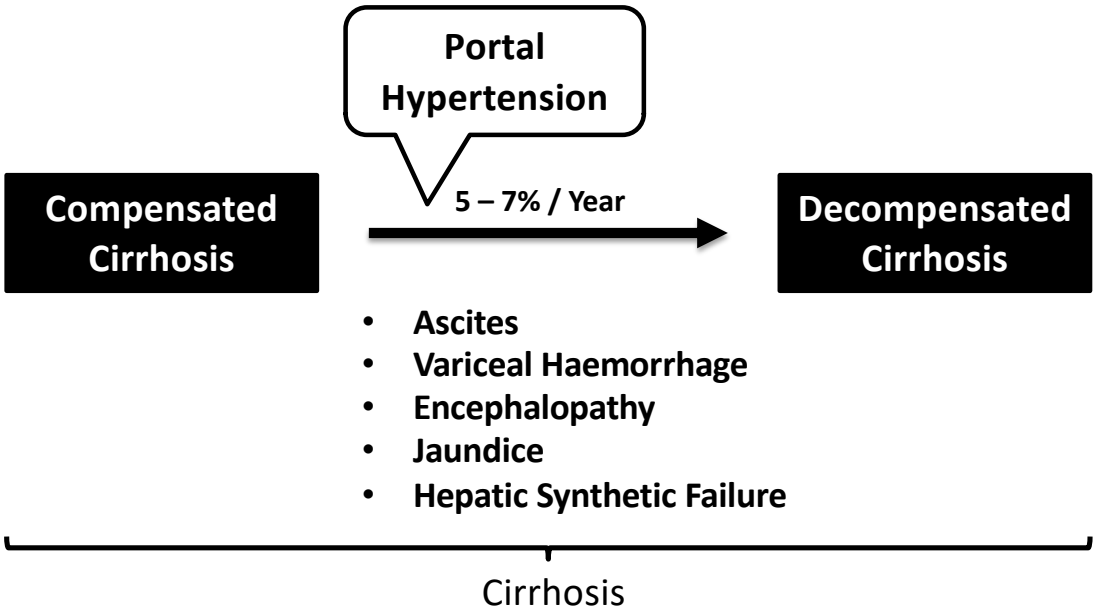
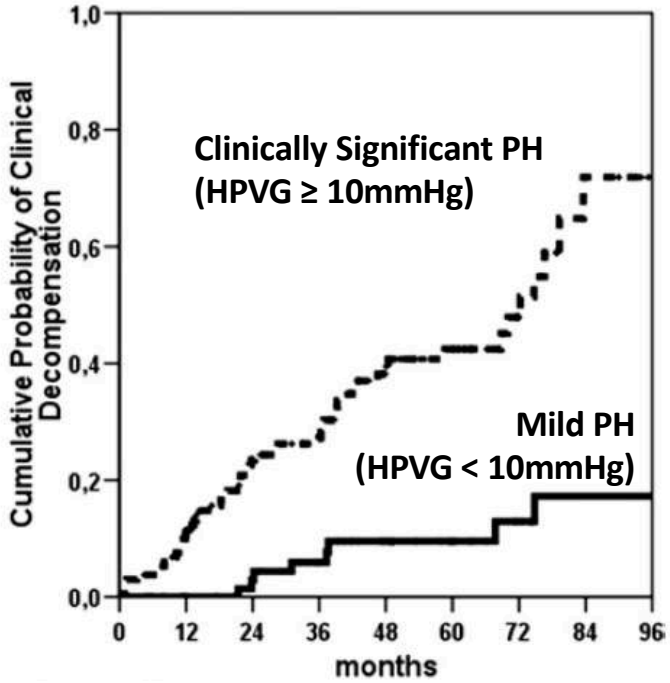
* No increase in Cardiovascular disease or other extra-hepatic events

Portal Hypertension is a Key Predictor of Cirrhotic Decompensation





Each 1 mmHg rise in HPVG above 10 mmHg associated with an 11% rise in risk of Hepatic Decompensation

HVPG <10 mmHg implies a 90% probability of NO clinical decompensation over a median 4-year follow-up

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Ripoll et al, Gastroenterology 2007, 133(2), 481-488.
Figure modified from D'Amico et al, Journal of Hepatology 44 (2006) 217–231.

Cirrhotic Study Endpoints

Phase 2a: Histologically defined study endpoints not mandated but should be considered*

Improvement Portal Hypertension (HVPG <10 mmHg) and/or MELD

Phase 2b/3: Histologically defined study endpoints with NASH + Fibrosis required*

Improvement of Fibrosis by ≥1 stage(s), without worsening of NASH

Improvement Portal Hypertension (HVPG <10 mmHg) and/or MELD

Phase 3/4: Event-driven endpoints*

Event Free Survival
(Hepatic Decompensation, HCC, OLT, Liver-Related and/or All-Cause Mortality)

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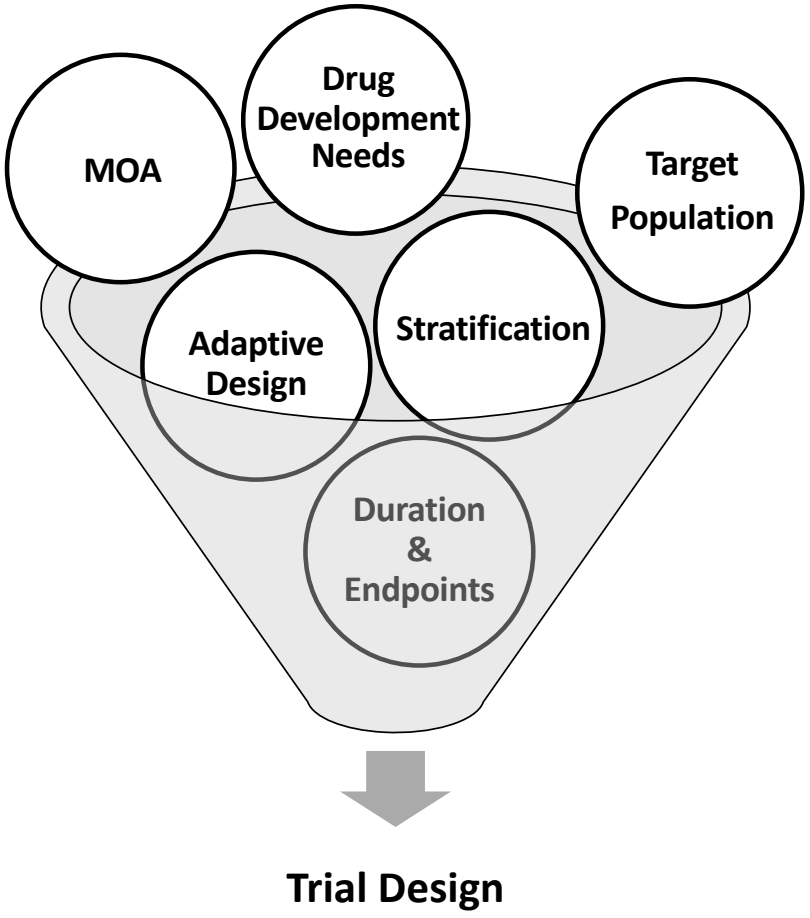
* No increase in Cardiovascular disease or other extra-hepatic events

Potential Trial Designs

Factors to Consider in NASH Trial Design

- **IMP Mechanism of Action (MoA)**
- **Target Population**
  - Pre-cirrhotic vs. Cirrhotic
- **Trial Purpose & Clinical Development Phase**
  - Safety data (DILI, lipid profiles re: CVD risk, etc)
  - Dose Ranging
  - Proof of Concept (Phase 2a (PoC))
  - Proof of Efficacy (Phase 2b, Phase 3/4)
- **Trial Design Factors**
  - Placebo Controlled vs. Open Label
  - Sample size
  - Stratification (T2DM, ethnicity)
  - Statistical analysis plan
  - Duration & Endpoints



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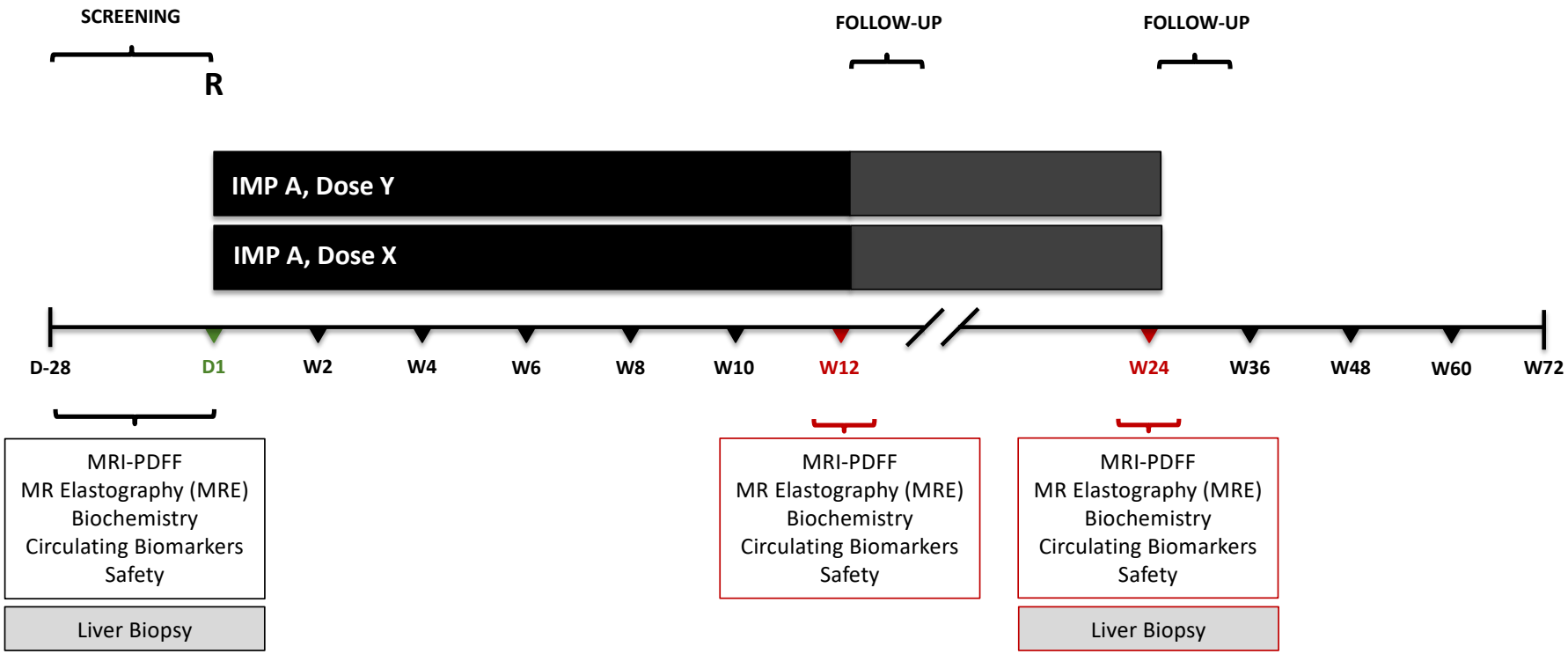
Phase 2a: Proof of Concept (PoC)



Histological data at Baseline and at End of Treatment not always necessary for Phase 2a (PoC) Studies

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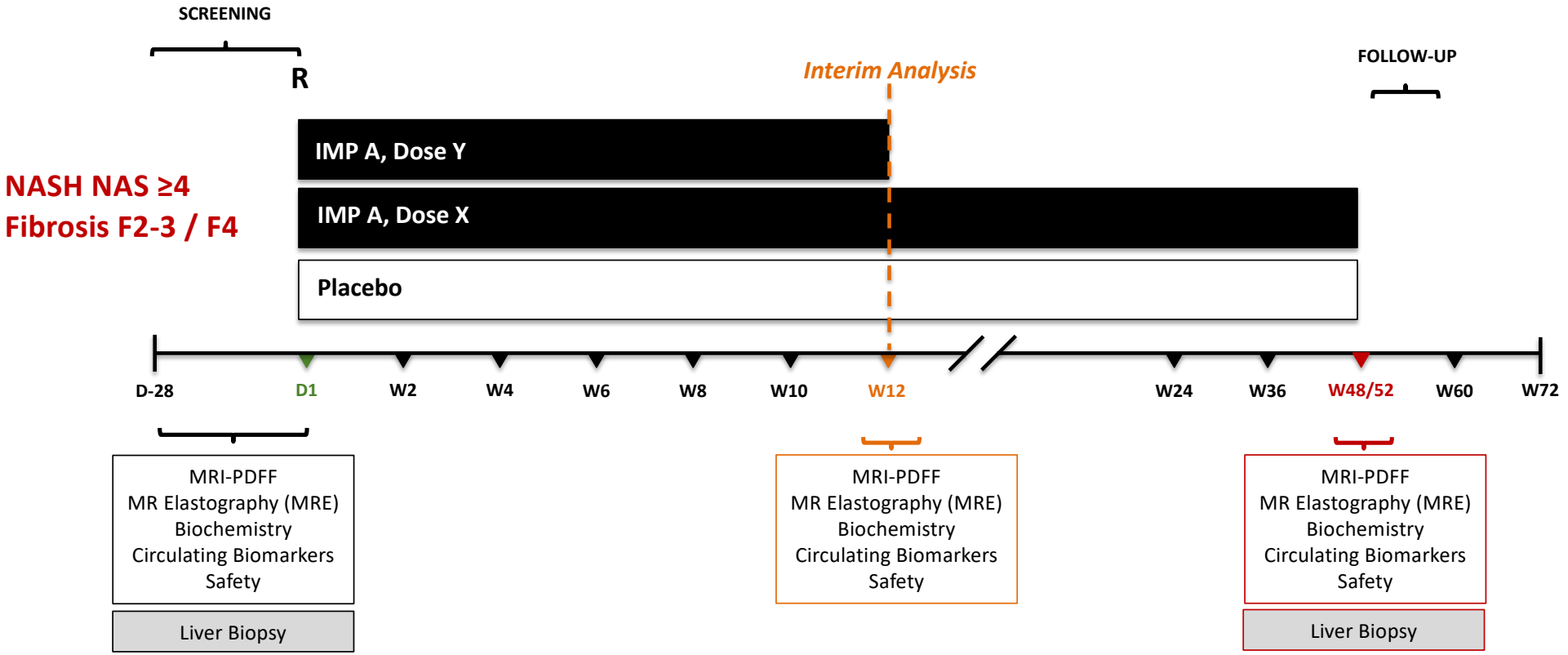
Phase 2b ± Adaptive Design Elements



At present, histological data at Baseline and at End of Treatment is necessary for Phase 2b Studies

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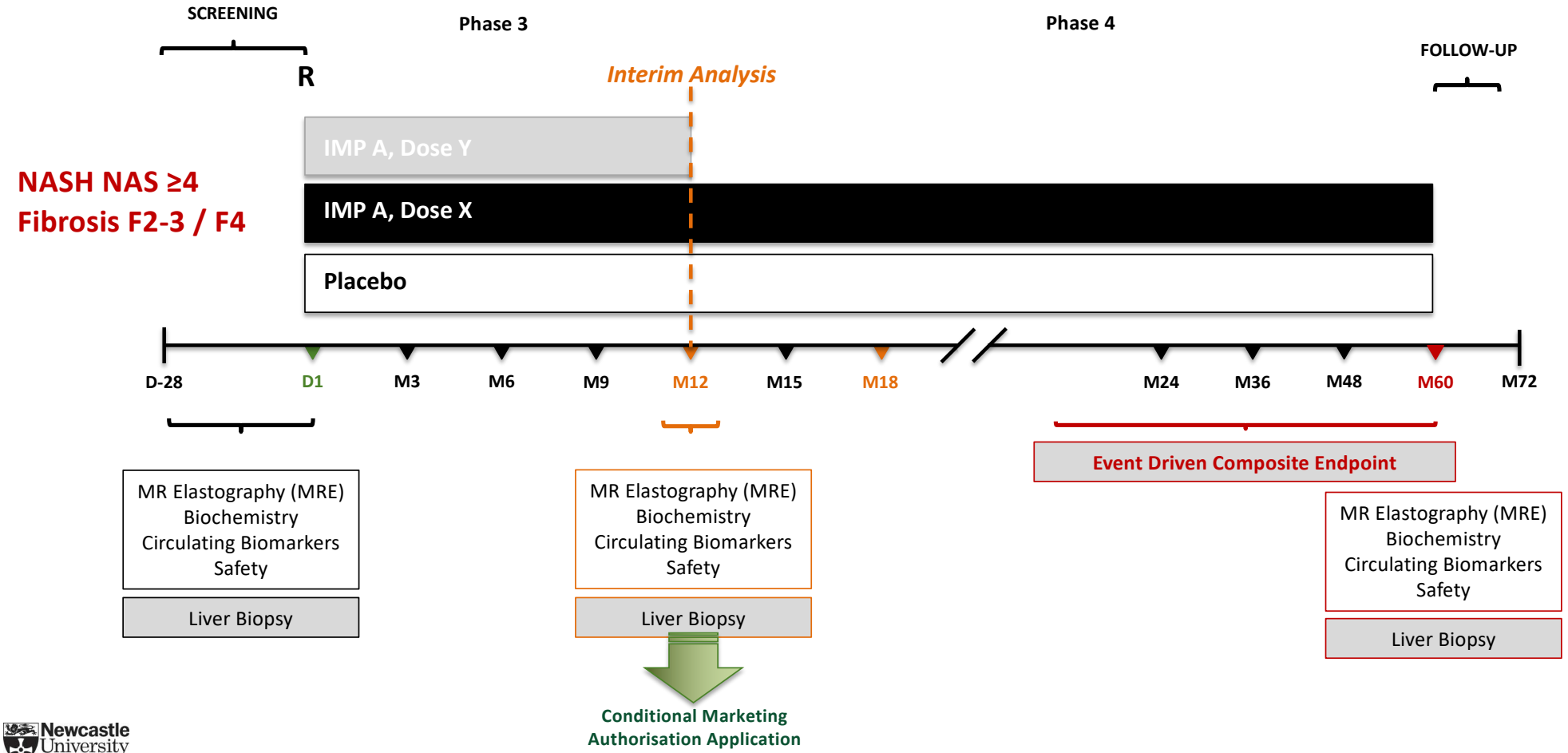
Phase 3/4 Study ± Adaptive Design Elements



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LITMUS (Liver Investigation: Testing Marker Utility in Steatohepatitis)

FACTS & FIGURES

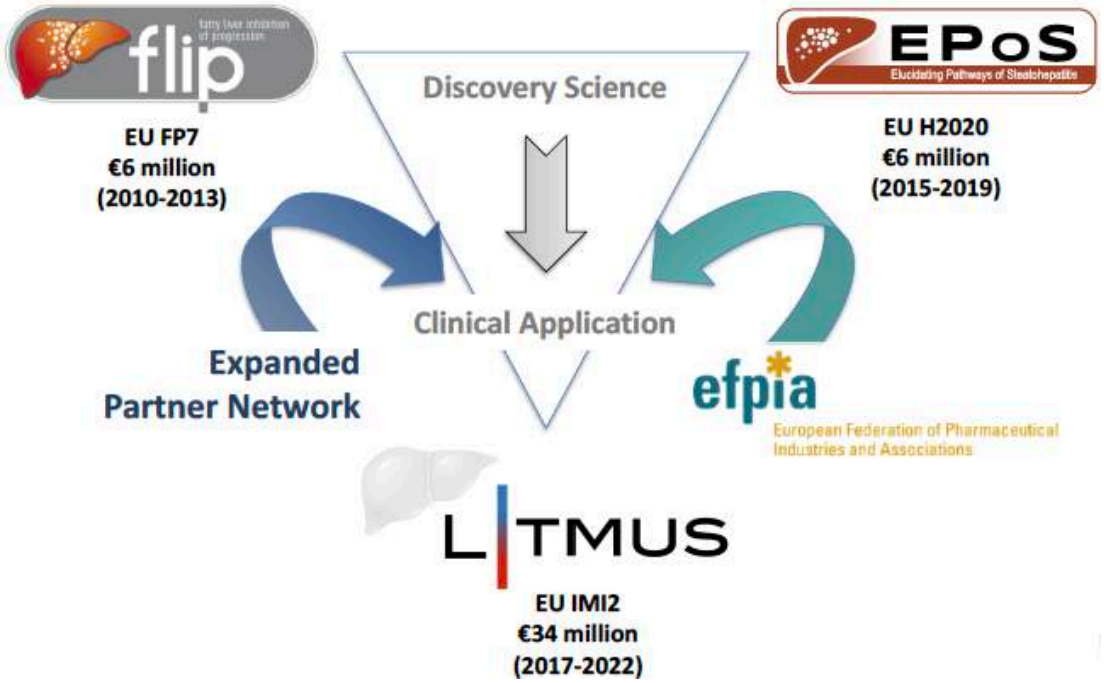
Start Date	01/11/2017
End Date	31/10/2022
Contributions	**€**
IMI Funding	15 797 881
EFPIA in kind	15 571 213
Other	1 103 310
Total Cost	32 472 404

PROJECT LINKS

Project website:
www.litmus-project.eu

Twitter:
@LITMUS_IMI

Coordinator: Prof Quentin M. Anstee



The overarching objectives of LITMUS are to develop, robustly validate and advance towards regulatory qualification biomarkers that diagnose, risk stratify and monitor NASH activity/fibrosis stage for use in clinical trials.

Conclusions

- **NAFLD is highly prevalent, largely asymptomatic disease characterised by substantial inter-patient variability in disease severity and outcome.**
- A number of promising compounds to treat NAFLD are entering Phase 2/3 clinical trials.
- **Drug-development for NAFLD/NASH is challenging however there is a clear consensus in the field regarding trial design, endpoints and needs for further research.**
- **There is an urgent need for more sensitive and specific, independently validated and qualified non-invasive biomarkers for use in NAFLD trials.**

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