MRI-PDFF of Liver Tissue as a Diagnostic Enrichment Biomarker (DDTBMQ000082)

Administrative Information

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Drug Development Need

As of September 2018, there are 102 ongoing clinical investigations listed on www.clinicaltrials.gov in the United States alone which cite fatty liver disease as the condition under investigation.

Despite the high prevalence of steatosis, defined as a liver fat > 5%, recruitment for these trials is inefficient, as only a subset of participants with steatosis will have steatohepatitis. Non-alcoholic steatohepatitis (NASH), the more aggressive form of non-alcoholic fatty liver disease (NAFLD), may progress to cirrhosis and hepatocellular carcinoma (HCC). Since NASH is estimated to overtake hepatitis C virus infection as the leading cause of liver transplantation in the US in the coming decade, and there are no current FDA-approved therapies for this disease, the need to find appropriate therapeutic targets is now more urgent than ever before [1]. Prior to enrolment, a biopsy is required to confirm the presence of NASH. Clinical trials thus run the risk of failing to recruit sufficient numbers of histologically-eligible subjects to appropriately power the clinical trial to demonstrate that the compound under investigation significantly alters participant pathology. Furthermore, some participants who do not have NASH will have undergone an unnecessary, risky procedure.

The gold standard procedure for the assessment of the degree of fibrosis and the severity of disease activity (inflammation, ballooning and steatosis grade) is the liver biopsy. It is invasive, with a definite though small morbidity, and is often not acceptable to patients [2]. This results in poor recruitment rates and can be difficult to justify repeated examinations. The accuracy of liver biopsy for assessing fibrosis and inflammation has been questioned, as it assesses only 0.002% of the liver, and up to 30% of results can be false negatives [3]. It carries a significant risk of serious bleeding complications, which is further amplified as patients with severe liver disease

have abnormal coagulation [4, 5].

NASH patients are at risk of developing hepatocellular carcinoma. There is a definite death rate associated with biopsy of the non-tumour liver, which is likely to be higher in tumour biopsies given the increased vascularity of hepatocellular carcinoma (HCC). Furthermore, although the risk of tumour seeding is low (approximately 2%-3% [6]) this has the potential to rapidly transform the prognosis from curable to incurable. A recent review on the topic discusses the need and value of liver biopsy for clinical and research purposes in HCC patients, as well as the ethical considerations for when to biopsy [6].

Histology itself is imperfect: with a liver biopsy, there is significant intra- and inter-observer variability in histological interpretation [7]. This has led to several different grading and staging systems for liver characterisation, such as Knodell [8], Ishak [9], METAVIR [10], Scheuer [11], Brunt [12] and the NAFLD Activity Score [13]. Agreement between these classifications is limited, even when the same slides are assessed in comparative studies [14].

It is therefore vital that this procedure is performed only on potential participants where the outcome of the biopsy is expected to guide management, and should involve discussion between patient and clinician regarding risk versus benefit [15].

Drug development is not currently benefitting from the many advances in biomedical sciences. It would be more ethical if potential participants were screened prior to enrolment in order to limit unnecessary biopsies and refine the pool of participants towards the intended patient population, i.e. those more likely to have NASH.

Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) is a non-invasive, quantitative biomarker to assess liver fat content (steatosis), one of the components in the NAFLD Activity Score [13]. We provide results from independent test and validation datasets with MRI-PDFF and biopsy confirmed steatosis data to demonstrate the utility of the biomarker within the proposed Context of Use (COU).

In this submission we propose the use of MRI-PDFF as a rule-out diagnostic for the purpose of reducing unnecessary biopsy of potential participants that will ultimately not meet the enrolment criteria for clinical trials based on histopathology.

Biomarker Information

Non-alcoholic fatty liver disease (NAFLD) is currently the most common cause of chronic liver disease worldwide. Furthermore, the progressive form of NAFLD, non-alcoholic steatohepatitis (NASH), is one of the leading indications for liver transplantation. In spite of the burden posed by fatty liver diseases, the United States Food and Drug administration has yet to approve any therapies for treatment of NASH. One of the major barriers for drug development remains the need for liver biopsy for selection of potentially eligible participants. Liver biopsy is expensive and invasive, carrying with it risks of abdominal pain, bleeding and death. As such, there is a major need for noninvasive enrichment biomarkers to reduce the number of unnecessary liver biopsies for enrolment into clinical trials. MRI-PDFF is a non-invasive, quantitative biomarker to assess liver fat content. Here we present that MRI-PDFF is an accurate quantitative imaging biomarker with high repeatability and reproducibility. We provide results from test and validation datasets with MRI-PDFF against liver histology to show optimal MRI-PDFF cutoffs to reduce the number of unnecessary biopsies prior to enrolment in clinical trials and identify those who are most likely to meet the criteria for enrolment in NASH clinical trials.

Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) of liver tissue is a magnetic resonance imaging-derived noninvasive, quantitative biomarker to assess liver fat content.

Hepatic steatosis is a common condition of the liver, characterized by accumulation of lipids in the liver. It affects over 20% of the general population and associates with disorders that result in diffuse liver fat deposition, such as NAFLD. Hepatic steatosis is the histological hallmark of NAFLD and is recognized as a key pathogenic process leading to the development of the more aggressive NAFLD subset, NASH. Despite the high prevalence of steatosis, defined as a liver fat > 5%, recruitment for these trials is inefficient, as only a subset of participants with NAFLD will have NASH. Prior to enrolment, a biopsy is required to confirm the presence of NASH. Clinical trials thus run the risk of failing to recruit sufficient numbers of histologically-eligible subjects to appropriately power the clinical trial to demonstrate that the compound under investigation significantly alters participant pathology. Furthermore, some participants who do not have NASH will have undergone an unnecessary, risky procedure. In this submission we propose the use of MRI-PDFF as a rule-out diagnostic for the purpose of reducing unnecessary biopsy of potential participants that will ultimately not meet the enrolment criteria for clinical trials based on histopathology. MRI-PDFF reflects the content of fat in the liver and is a reliable and standardised biomarker of hepatic steatosis.

Context of Use

Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) of liver tissue is a diagnostic enrichment biomarker that can be used, in conjunction with clinical risk factors, to identify patients who are more likely to have liver histopathologic findings appropriate for inclusion in non-alcoholic steatohepatitis (NASH) clinical trials.

Biomarker Measurement (Analytical)

The percentage of fat in the liver, or proton density fat fraction (PDFF), is being measured using MR: MRI-PDFF. This advanced MRI technique measures the fraction of mobile protons in the liver attributable to liver fat (the PDFF), which is a direct measure of liver fat content and is a fundamental tissue property. MRI-PDFF takes into account the confounders of most other MRI sequences that only measure signal fat-fraction (the fraction of the MRI signal that is attributable to liver fat), which as a result of confounders may not reflect true liver fat content. Both technical and biological factors exist as signal fat-fraction confounders, including T1 bias, T2 relaxation, T2* decay, noise bias, eddy currents, spectral complexity of the fat spectrum, and J-coupling. After correcting all confounding factors, the signal fat-fraction is equivalent to the PDFF.

Steatosis is characterized by abnormal and excessive accumulation of lipids within hepatocytes. It is an important feature of liver disease, and the histological hallmark of non-alcoholic fatty liver disease (NAFLD).

Ultrasound and computed tomography (CT) can be used to assess liver fat but have limited accuracy as well as other limitations [16]. Magnetic resonance imaging (MRI) techniques can decompose the liver signal into its fat and water signal components and thus assess liver fat more directly than CT- or ultrasound-based methods.

Most magnetic resonance imaging (MRI) techniques measure the signal fat-fraction – the fraction of the liver MR signal attributable to liver fat. However, the signal fat-fraction may be confounded by numerous technical and biological factors and may not reliably reflect hepatic fat content. Several water-fat separation techniques exist, and each decomposes the liver signal in a different manner. By addressing the factors that confound the signal fat-

fraction, MRI-PDFF techniques measure the proton density fat-fraction – the fraction of the liver proton density attributable to liver fat – which is a fundamental tissue property and a direct measure of liver fat content.

Thus, MRI-PDFF is derived from the fat and water component images[1] acquired during an MR examination, and computed as the ratio $\frac{\text{fat}}{\text{fat+water}}$, expressed as a percentage (unit %).

MRI-PDFF reflects the content of fat in the liver and is a reliable and standardised biomarker of hepatic steatosis. Moreover, because MRI-PDFF is independent of acquisition parameters and agnostic to platform differences, it is a highly repeatable and reproducible biomarker [16].

Biomarker Measurement (Clinical)

As per the guidance document Qualification Process for Drug Development Tools, our COU statement contains a concise biomarker use statement and a comprehensive description of conditions for the biomarker to be used in the qualified setting, termed the conditions for qualified use. A decision tree diagram is shown to provide additional clarity on the proposed COU for MRI-PDFF.

Use Statement

Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) of liver tissue is a diagnostic enrichment biomarker that can be used, in conjunction with clinical risk factors, to identify participants who are more likely to have liver histopathologic findings appropriate for inclusion in non-alcoholic steatohepatitis (NASH) clinical trials.

Conditions for Qualified Use

General Considerations

- For use in clinical trials for agents which propose to alter (any combination of) the hepatic adiposity, fibrotic- or inflammatory status of liver tissue
- To be used in conjunction with clinical risk factors and/or other diagnostics
- To be used as a pre-screening strategy to select participants more likely to have histopathologic findings
- To be used as a safety consideration with the aim of reducing unnecessary biopsies
- Diagnosis of NASH to be confirmed via histopathology
- During pre-screening, potential participants will undergo an MR examination to determine whether further evaluation using biopsy is required
- During pre-screening, participants with an MRI-PDFF under the proposed cut-off will be excluded; participants meeting or exceeding the cut-off threshold will be evaluated further using biopsy to determine if the enrolment criteria of the clinical trial had been met

Population Considerations

- Participant population are adults aged 18 or above
- Participant population are those with clinical signs suggesting non-alcoholic fatty liver disease (NAFLD)

[1] With confounding factors that depend on the water-fat separation technique used adequately addressed.

- The desired participant population for inclusion in the clinical trial is at-risk participants that meet any of the following criteria:
    - histopathological findings of NAS≥4
    - Brunt steatosis ≥ 2
    - biopsy confirmed NASH

Data Acquisition Considerations

- Modality: Magnetic Resonance Imaging (MRI) at 1.5T or 3T
- Widely available on most MR manufacturers and models
- Routine MR safety screening applies
- Only for use in participants where MR is not contraindicated

Post Processing Considerations

- MRI-PDFF is computed as per the published literature [16]

Biomarker Interpretation

- MRI-PDFF of liver tissue is an estimate of the percentage of fat in the liver tissue
- MRI-PDFF values in the liver have been shown to correlate with steatosis [17]
- MRI-PDFF can be used as a rule-out diagnostic for the purpose of reducing unnecessary biopsy of potential participants that will ultimately not meet the enrolment criteria for clinical trials based on histopathology
- MRI-PDFF can discriminate between potential participants in an at-risk population, as necessitated by the study design of the clinical trial, based on using the histopathological criteria listed against each grouping as the ground truth reference. Refer to Table 1.

Table 1 - Histopathological criteria for distinguishing between different at-risk populations.

At-Risk Population		Histopathological Criteria
Target Population	Off-Target Population	
NAS≥4	NAS<4	NAFLD Activity Score (NAS) CRN and fibrosis staging system [13]
Brunt steatosis ≥ 2	Brunt steatosis < 2	Brunt steatosis staging [13]
NASH	Simple Steatosis	NASH diagnosis based on the Brunt system [12] or FLIP algorithm [18]

- Two MRI-PDFF cut-offs are proposed: 7% is optimised for sensitivity; and 12% is optimised for specificity.
- An MRI-PDFF cut-off of 7% (optimised for sensitivity) is proposed with performance metrics derived from independent training and validation datasets. Refer to Table 2, Table 3 and Table 4.

Table 2 – Diagnostic performance using an MRI-PDFF cut-off of 7% to discriminate NAS≥4 participants in an at-risk population.

Classification Criteria

Diagnostic performance metrics using an MRI-PDFF cut-off of 7% to discriminate between: NAS<4 and NAS≥4		
Metric	Training Dataset	Validation Dataset
Classification Function		
Sensitivity	0.83	0.97
Specificity	0.70	0.47
Predictive Value		
NPV	0.68	0.94
PPV	0.84	0.60
Enrichment Analysis		
Enrichment %	27%	33%

Table 3 - Diagnostic performance using an MRI-PDFF cut-off of 7% to discriminate participants with Brunt steatosis ≥ 2 in an at-risk population.

Classification Criteria		
Diagnostic performance metrics using an MRI-PDFF cut-off of 7% to discriminate between: Brunt steatosis ≥ 2 and Brunt steatosis < 2		
Metric	Training Dataset	Validation Dataset
Classification Function		
Sensitivity	0.86	0.97
Specificity	0.72	0.55
Predictive Value		
NPV	0.74	0.94
PPV	0.84	0.71
Enrichment Analysis		
Enrichment %	32%	33%

Table 4 - Diagnostic performance using an MRI-PDFF of 7% to discriminate simple steatosis and NASH participants in an at-risk population.

Classification Criteria		
Diagnostic performance metrics using an MRI-PDFF cut-off of 7% to discriminate between: simple steatosis and NASH		
Metric	Training Dataset	Validation Dataset
Classification Function		
Sensitivity	0.73	0.94
Specificity	0.48	0.49
Predictive Value		

NPV	0.52	0.89
PPV	0.71	0.65
	Enrichment Analysis	
Enrichment %	12%	29%

- An MRI-PDFF cut-off of 12% (optimised for specificity) is proposed with the following performance metrics derived from independent training and validation datasets. Refer to Table 5, Table 6 and Table 7.

Table 5 – Diagnostic performance using an MRI-PDFF cut-off of 12% to discriminate NAS≥4 participants in an at-risk population.

Classification Criteria		
Diagnostic performance metrics using an MRI-PDFF cut-off of 12% to discriminate between: NAS<4 and NAS≥4		
Metric	Training Dataset	Validation Dataset
	Classification Function	
Sensitivity	0.61	0.77
Specificity	0.93	0.86
	Predictive Value	
NPV	0.55	0.82
PPV	0.94	0.82
	Enrichment Analysis	
Enrichment %	43%	82%

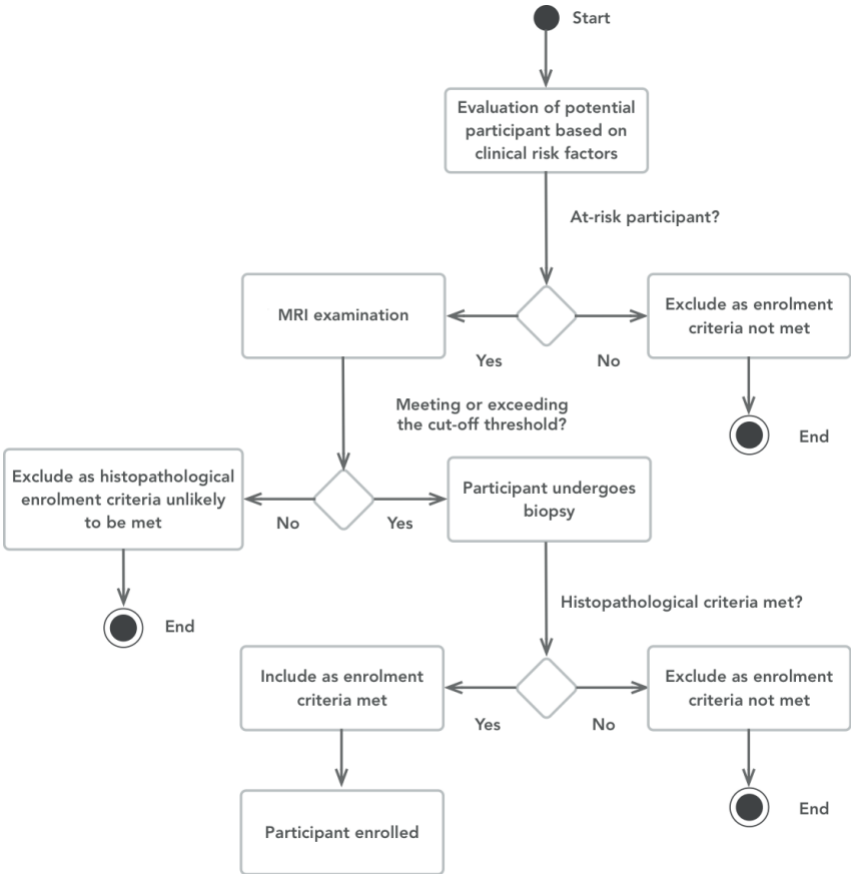
Table 6 - Diagnostic performance using an MRI-PDFF cut-off of 12% to discriminate participants with Brunt steatosis ≥ 2 in an at-risk population.

Classification Criteria		
Diagnostic performance metrics using an MRI-PDFF cut-off of 12% to discriminate between: Brunt steatosis ≥ 2 and Brunt steatosis < 2		
Metric	Training Dataset	Validation Dataset
	Classification Function	
Sensitivity	0.63	0.72
Specificity	0.94	0.92
	Predictive Value	
NPV	0.59	0.74
PPV	0.95	0.91
	Enrichment Analysis	
Enrichment %	48%	71%

Table 7 - Diagnostic performance using an MRI-PDFF of 12% to discriminate simple steatosis and NASH participants in an at-risk population.

Classification Criteria		
Diagnostic performance metrics using an MRI-PDFF cut-off of 12% to discriminate between: simple steatosis and NASH		
Metric	Training Dataset	Validation Dataset
Classification Function		
Sensitivity	0.50	0.69
Specificity	0.70	0.85
Predictive Value		
NPV	0.45	0.73
PPV	0.74	0.82
Enrichment Analysis		
Enrichment %	17%	63%

As per the guidance document Qualification Process for Drug Development Tools, we include a decision tree diagram to provide additional clarity to the proposed COU for MRI-PDFF. The application of MRI-PDFF in the proposed COU is depicted below and includes the actions that would be taken based on the interpretation of results:



Additional Considerations for Radiographic Biomarkers

How has the method for image acquisition, analysis, and integration of the data been optimized?

At imaging sites: (i) Standardized acquisition protocols (optimised to address the factors that confound the accurate quantification of hepatic fat content) are used and documented in acquisition manuals; (ii) Phantoms are used to activate and quality control check new imaging sites prior to any acquisition of participant data; and (iii) MRI technicians at imaging sites are trained on how to acquire the data on participants.

At analysis site: (i) Quality Control (QC) checks are performed on the data at the analysis site, for example to detect whether acquisition parameters had been altered; (ii) Operators analysing data are trained and assessed prior to analysing participant data; and (iii) Data is read centrally.

Extensive performance testing had been performed as part of the 510(k) review of the regulated diagnostic. As part of the evaluation, comparisons between different MRI vendors, models and field strengths were conducted and performance assessed against predefined acceptance criteria.

- Performance evaluation to demonstrate that the MRI-PDFF biomarker, as measured by two devices commercially available and cleared by the FDA, yields equivalent results
- Performance evaluation using phantoms to demonstrate accuracy of MRI-PDFF
- Performance evaluation using phantoms to demonstrate repeatability of MRI-PDFF
- Performance evaluation using phantoms to demonstrate reproducibility of MRI-PDFF
- Performance evaluation using volunteers across a range of liver fat values to demonstrate repeatability of MRI-PDFF
- Performance evaluation using volunteers across a range of liver fat values to demonstrate reproducibility of MRI-PDFF

Does data currently exist to support the proposed cutoff point(s), if imaging results are not reported as a continuous variable?

Yes

Provide the name and version of the software package to be used for image acquisition and analysis (limited to 500 characters).

LiverMultiScan. However, there are numerous 510(k) cleared devices on the market that can quantify liver fat using MRI-PDFF:

- K143020, manufactured by Mirada Medical Ltd (LiverMultiScan 1)
- K172685, manufactured by Perspectum Diagnostics Ltd (LiverMultiScan 2)
- K103411, manufactured by GE Medical Systems (IDEAL-IQ)
- K133526, manufactured by Philips Medical Systems (mDIXON Quant)
- K141977, manufactured by Siemens Medical Solutions (LiverLab)

Supporting Information

The performance of MRI-PDFF quantified from raw MR data was explored in a sample of n=110 biopsy confirmed NAFLD participants. This training dataset was pooled from two similar UK-based cohorts into participants with liver disease. We have used our training dataset to determine optimal MRI-PDFF cut-offs for identifying participants based on different selection criteria. The optimal cut-off for discriminating individuals was determined using the following cut-offs: NAS≥4, Brunt steatosis ≥2, and NASH diagnosis by histopathology. We have conducted enrichment analyses for the different histopathological reference criteria. Details of the analyses are available. From this we propose two MRI-PDFF cut-offs to maximise sponsor flexibility based on trial design considerations: (1) a cut-off of 7% is proposed for use within the COU as it is optimised for sensitivity; (2) a cut-off of 12% is proposed for use within the COU as it is optimised for specificity. Finally, we have validated these cut-offs in an equivalent US based cohort.

Full study protocols and analysis are available.

In addition, MRI-PDFF is widely used in clinical trials for NASH compounds, but has not been formally qualified within this context. A summary of clinical trials is presented below.

Table 8: Clinical Trials with PD involvement

Sponsor	Therapy Class	Population	Phase	Primary Endpoint	Patient No.	Further information	Expected read-out
Galectin	Anti-fibrotic	NASH, Advanced Fibrotic (biopsy)	Ph II	Change in cT1 (LMS)	1 site; n= 30	NASH-FX study	Completed YE 2016
Tobira (Allergan)	Anti-inflammatory	NASH (biopsy) / Pre-diabetic / T2D	Ph II	Change in insulin sensitivity	1 site; n= 30	ORION	Completed YE 2016
Intercept	Metabolic	NASH, F2/3 (biopsy)	Ph III	Histology: change in liver fibrosis / NASH resolution	15 sites; n ≈ 150	Mid Tier, sub-study	2024
Novartis	Metabolic	NASH (biopsy) + ↑ALT / T2D + ↑BMI + ↑ALT	Ph II	Safety & Tolerability; improvement in ALT	3 sites; n ≈ 20	Tier 1, sub-study	YE 2018
Novartis	Metabolic	NASH (biopsy) + ↑ALT / T2D + ↑BMI + ↑ALT ; MRI PDFF ≥10%	Ph IIb	Safety & Tolerability; improvement in ALT/AST); change in hepatic fat (MRI-PDFF)	2 sites; n = 14	Tier 1, sub-study	YE 2018
Madrigal	Metabolic	NASH (biopsy); MRI PDFF ≥10%	Ph II	Change in hepatic fat (MRI-PDFF)	2-3 sites; n ≈ 80	MGL-3196	YE 2017
NGM Bio	Metabolic	NASH (biopsy); MRI PDFF ≥8%	Ph II OLE	Change in hepatic fat (MRI-PDFF)	1-2 sites; n=30	NGM282	YE 2017

Bird Rock Bio	Metabolic	Pre-diabetic / T2D; MRI PDFF ≥10%	Ph IB	Safety & Tolerability	6-10 sites; n= 84	BRB-018-001	YE 2017
Biotie	Anti-inflammatory	PSC	Ph II	Alk-Phos	2-3 sites; n ≈ 40	BUTEO	H1 2018
Axcella	Metabolic	Metabolic Liver Disease (NASH cohort)	Ph IIa	Change in cT1 (LMS)	15 sites; n = 105	BioTech	H2 2018
CymaBay	PPAR agonist	NASH; NAS ≥ 4 (biopsy)	Ph II	Change in MRI-PDFF	15 sites; n = 175	MDX-8025	H2 2019
Gemphire	PPAR agonist	Paedatric NASH; NASH-CRN (biopsy)	Ph II	Change in MRI-PDFF (HepaFat Scan)	3 sites; N = 40	Mid Tier	H2 2018
Inventiva	PPAR agonist	NASH; SAF Activity 3/4 , <4 Fibrosis (biopsy)	Ph II	Change in SAF (at least 2 points)	1 site; n = 70	Mid Tier, sub study	H1 2018
Novo Nordisk	GLP-1 analogue	NASH; F2/3 NASH-CRN (biopsy)	Ph II	NASH resolution	4 sites; n = 50	Tier 1, sub study	H2 2019
Second Genome	Anti-inflammatory	F1-3 NASH ≥8% MRI-PDFF, MRE 2.5-4.6kPa	Ph IIa	Safety/tolerability, and MRI measured inflammation/fibrosis	10 sites; n=100-160	BioTech	H2 2020
HighTide	TBD	TBD	TBD	TBD	TBD	TBD	TBD
NorthSea Therapeutics	Metabolic	F1-3 NASH, NAS ≥4	Ph IIb	Efficacy	~30 sites; n = ~200	BioTech	H2 2021
Enyo Pharma	Metabolic	F2-3 NASH Fibroscan ≥6.9 kPa, ≥10% MRI-PDFF	Ph IIa	Safety and Efficacy	~35 sites; n = 160	BioTech	H1 2021
Harokopio University		Confirmed NAFLD/NASH	Early Ph 1	Improvement in cT1 and MRI -PDFF	N = 52	MAST4HEALTH	Dec 2019

Table 9: Clinical trials with no PD involvement

Sponsor	Population	Phase	Primary Endpoint	Patient No.	Further information	Expected read-out	Clinical Trials identifier
Novartis	NASH (biopsy) + ↑ALT / T2D + ↑BMI + ↑ALT	Ph II	Safety and Efficacy	34 sites N = 192	LMB763	YE 2019	NCT02913105
Novartis	NASH (biopsy) F1, F2, F3 and ↑ALT OR ↑ALT AND ↑BMI	Ph II	Efficacy	N = 110	LIK066	Oct 2019	NCT03205150

	AND HbA1c 10% ≥ 6.5%						
Novartis	NASH (biopsy) F1, F2, F3 and ↑ALT OR ↑ALT AND ↑BMI AND T2DM AND ↑ALT MRI-PDFF ≥ 10%	Ph II	Safety, Tolerability and Efficacy	N = 345	FLIGHT-FXR	April 2020	NCT02855164
Erasme University Hospital	NASH (biopsy) SAF Activity ≥ 3 SAF steatosis ≥ 1 SAF fibrosis < 4 BMI ≥24 and ≥40 kg/m2	N/A	Safety	N = 12	Device (DMR Revita)	YE 2019	NCT03536650
NGM Bio	NASH (biopsy)	Ph II	Change in hepatic fat (MRI-PDFF)	n=250	NGM282	YE 2019	NCT02443116
NHS Tayside	NASH (biopsy) NAS ≥ 3	N/A – proof of concept	Improvement in insulin resistance (fsOGTT)	N = 20		Jan 2019	NCT03490370
Mayo clinic	NASH (biopsy/MRE proven) ≥ F1	Ph II	Change in Liver Fat Fraction (LFF)	N = 100		YE 2019	NCT02605616
Can-Fite BioPharma	NAFLD (liver triglyceride concentration ≥ 10% by NMRS) ≥ F4	Ph II	Safety and efficacy	N = 60	CF102	YE 2018	NCT02927314
Indiana University School of Medicine	HIV + NASH (biopsy)	Ph II	Proof of concept. Efficacy	N = 56	Vitamin E	YE 2025	NCT03669133
Lifespan	NASH (biopsy) NAS ≥ 4 ≥ 1 in each of steatosis, ballooning & inflammation	Ph I	Change in hepatic fat (MRI-PDFF)	N = 5	Fecal Microbiota Transplantation (FMT)	June 2018	NCT02469272
Changi General Hospital	BMI >27.5 kg/m2 NASH (LFT, U/S or biopsy)	Ph III	Safety and efficacy	N = 36	Liraglutide and Bariatric Surgery	Year end 2018	NCT02654665

Children's Hospital Medical Center, Cincinnati	NASH (biopsy) NAS ≥ 3	N/A	Efficacy	N = 70	weight loss surgery (WLS) vs. comprehensive lifestyle intervention (CLI)	June 2020	NCT02412540
Milton S. Hershey Medical Center	NASH (biopsy)	N/A	Efficacy	N = 42	NASHFit	Dec 2021	NCT03518294
Zydus Discovery DMCC	NAFLD or NASH (U/S, CT, MRI-PDFF or biopsy) ≥ 30% variance in LFTs	Ph II	Efficacy	N = 104	EVIDENCES II	July 2020	NCT03061721
Zydus Discovery DMCC	6 months post liver transplant. NAFLD (MRI-PDFF) ≥ 20% variance in LFTs	Ph IIa	Safety, tolerability and efficacy	N = 15	EVIDENCES VIII	July 2020	NCT03639623
Kowa Company, Ltd.	MRI-PDFF ≥ 10% ≥ 2.5 kPa MRE ↑ALT	Ph II	Efficacy (Change in hepatic fat MRI-PDFF) and safety	N = 100	K-877	May 2020	NCT03350165
Translational Research Institute for Metabolism and Diabetes, Florida	NASH (biopsy) MRI-PDFF ≥ 10% ≥ 2.7 kPa MRE	N/A	Efficacy: Change in hepatic fat MRI-PDFF & change in liver stiffness	N = 35	BARI	Dec 2019	NCT03294850
Pfizer	MRI-PDFF ≥ 6% CAP 260dB/m	Ph I	Efficacy (Change in hepatic fat MRI-PDFF) Tolerability and Efficacy	N = 45	PF-06865571	Feb 2019	NCT03513588
Pfizer	NASH (biopsy or presumed) MRI-PDFF ≥ 8% NAFLD	Ph IIa	Evaluate dose response effect on liver fat (MRI-PDFF)	N = 286	PF-05221304	March 2019	NCT03248882
Akcea Therapeutics	MRI-PDFF ≥ 10%, 27- 40 kg/m2, inclusive T2DM – HcA1c ≥ 7 to ≥ 10 Plasma TA >200 mg/dL at screening and	Ph II	Safety and efficacy	N = 144	ISIS 703802 AKCEA-ANGPTL3-LRx	May 2019	NCT03371355

	≥150 mg d/L at qulaification						
Elif Oral	Lipodistrophy MRI-PDFF ≥ 10%,	Ph I Ph II	Safety and efficacy	N = 8	Gemcabene	March 2020	NCT03508687

Previous Qualification Interactions and Other Approvals

None

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