Madrigal MGL-3196 NASH Phase III Study
Challenge Call

June 27, 2018

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Agenda

- Strategy and proposed study team

- Customer update and milestones

- Protocol overview

- RFP Specifications

- Country and Site Profile

- Recruitment rate

- Enrollment Models

- Recruitment Strategy

- "Data Story" for Site Identification

MGL-3196
A Phase 3, Multinational, Double-Blind, Randomized, Placebo Controlled Study of MGL-3196 in Patients With Non Alcoholic Steatohepatitis (NASH)

Customer Update

Date	Milestone
June 25	Received RFP and protocol synopsis from Madrigal
June 27	Confirmed country strategies with Steve Harrison
June 28	Challenge Call
July 3	F2F meeting with Summit in San Antonio, TX to discuss operational detail
July 8-9	Bid defense prep
July 10	Bid defense meeting

IQVIA Differentiators

- IQVIA-Summit Partnership Agreement

- Next Generation Healthcare Analytics

- Embedding NASH Recruitment Specialists to drive recruitment

- Established NASH sites and referral networks of metabolic disease sites

- Comparatively stronger relationship with Synexus

- NASH Center of Excellence: Extensive clinical and operational knowledge

- Strong KOL collaborations and ongoing NASH scientific community involvement

MGL-3196 Protocol

Primary Objective: The primary objective of this study is to determine the effect of the once-daily, oral administration of XX mg of MGL-3196 versus matching placebo on the resolution of NASH without worsening of fibrosis (via biopsy)

Patient Population: The population for this study is male and female patients ≥18 years of age with biopsy-proven NASH. The population will be comprised of patients who are diagnosed as high-risk fibrosis stage 1 (~10%), fibrosis stage 2 (~45%) and fibrosis stage 3 (~45%).

Screening: 6 Weeks

Patients required to have had a qualifying liver biopsy within 90 days of randomization

Treatment: 52 Weeks

• Baseline + 12 monthly visits

• Liver biopsy at Week 52

Follow up: 4 Weeks

Considerations

• FibroScan NOT included in protocol

  - Assumed by Madrigal/Summit to be standard pre-screening procedure of ALL sites and to be used to reduce SF

  - Assumed that all sites will have FibroScan – Madrigal will not purchase equipment

  - IQVIA will need to incorporate cost in "Patient Recruitment Fee"

• Stratification

• Exclusion criteria #3: Hypothyroidism

• Exclusion criteria #34: Serum AST <20 (reduce SF)

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Madrigal RFP Specifications

Subjects	
Screened	3,000
Enrolled (randomized)	**1,125**
Completed	900
Screen failures **(62.5%)**	1,875
Drop out **(20%)**	225

Timelines	
CRO Start	1-Jun-18
Final Protocol Available	15-Aug-18
First SIV	14-Oct-18
First Patient First Visit (Screened)	11-Nov-18
First Patient Randomized	**23-Dec-18**
Last Patient First Visit	**23-Jun-20**

Note: Timeline to be pushed out by 2 months in bid

18 Months Enrollment

Sites	
United States	50 (24 CIRB)
Western Europe France, Germany, Italy, Spain, UK	30
Synexus	–
Total	**80**

Steve Harrison's Assumptions

Summit's Assumptions	Sites	Patients
Summit (United States)	35	600
KOLs (United States)	10	50
IQVIA (Western Europe)	25	250
Total	70	900

- Startup of Summit's sites (activated) within 2 months
- Enrollment at 2-3 p/s/m
- Aim to enroll all patients within 12 months!!

IQVIA will submit a **Bid-to-Spec** strategy/budget with 80 sites and **Alternate** with 99 sites allowing Western Europe to enroll at a more realistic rate of **0.7 p/s/m** (compared to 0.95 p/s/m) – which is in alignment with Madrigal's request to "de-risk" the unsubstantiated strategy proposed by Steve Harrison

NASH Global Competitive Landscape

>60 phase II-III trials are targeting >13,500 patients in nearly 30 countries

Global competition by phase

Global competition by country
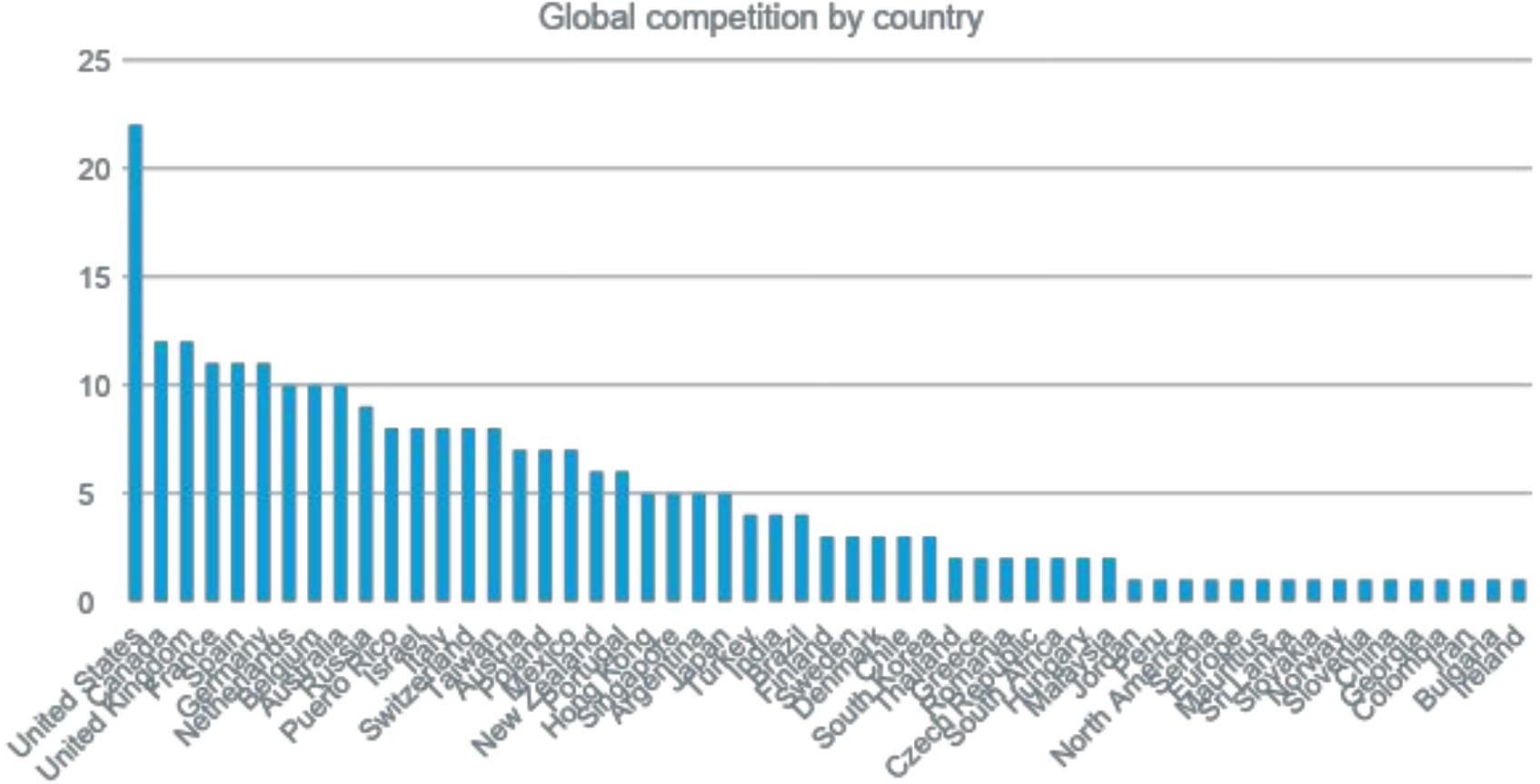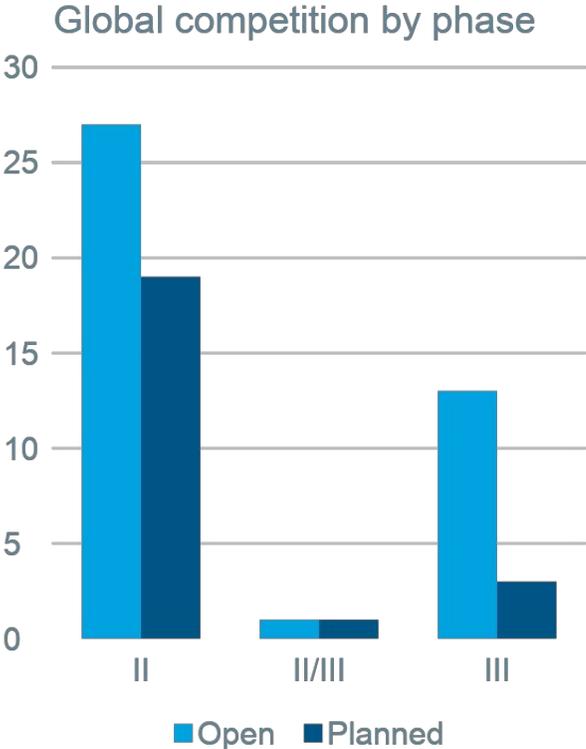
Source: Citeline, Jan 2018 (includes trials planned and recruiting)

NASH Country Selection Criteria

- Estimated prevalence per 100k Diabetes
- Estimated prevalence per 100k NAFLD
- Estimated prevalence per 100k Obesity
- Investigator interest*
- Interest in NASH trials requiring liver biopsy*
- Median NAFLD patient volume*
- Median estimated enrollment*
- Access to MRI-PDFF* (not applicable for Madrigal)
- IQVIA NASH Network
- IQVIA top performing T2DM Endocrinology Sites
- IQVIA start-up timelines
- Competing NASH trials
- Completed NASH trials

*Results from IQVIA NASH Global Investigator Survey

IQVIA conducted a global feasibility study in 2018 selecting >20 countries for proactive development of our NASH Site Network

Tier 1 Countries

North America
United States
Canada
Western Europe
United Kingdom
Germany
Italy
France
Spain
Belgium
Sweden
Austria
Russia
Eastern Europe
Bulgaria
Poland
Czech Republic
Romania
Hungary
Asia Pacific
India
Singapore
Central/South America
Brazil
Colombia
Mexico
Argentina
Chile
EMEA
South Africa
Turkey
Israel

IQVIA™

The IQVIA Integrated NASH Network is Founded on Global Partnerships and Accelerated Recruitment
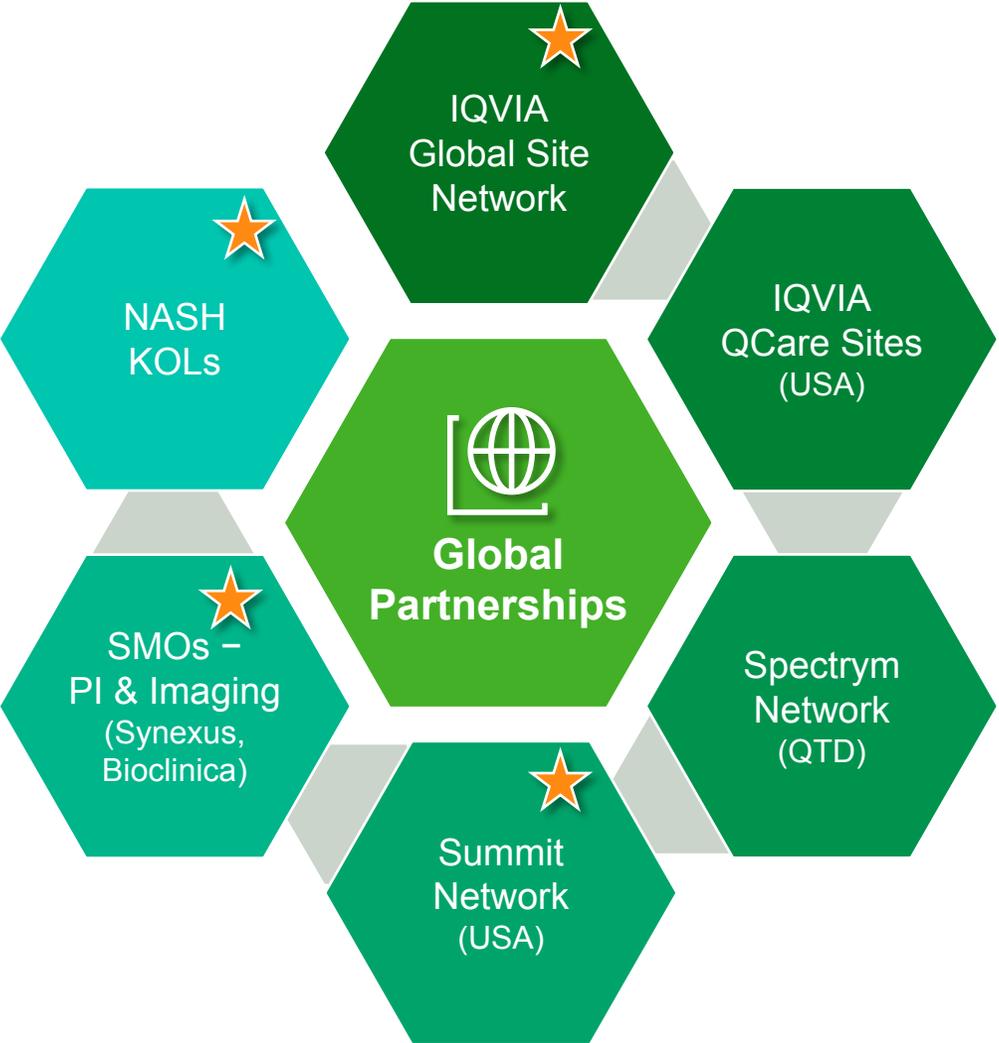
Accelerating Enrollment at IQVIA NASH Sites

Data-Driven Site Selection
Identification of investigators and referral partners using claims and lab data to locate patients with NASH risk factors

Proactive Site Development
Establishing sites and embedding resources to build the recruitment pathway in advance of trials

NASH Recruitment Specialists (NRS)
Deployment of onsite resources to:
- Identify qualified patients via EMR queries and chart reviews utilizing predictive risk factors
- Populate the patient registry with patients pre-screened via FibroScan
- Develop referral networks and funnel qualified patients into the pre-screening process

Community-based Recruitment
Development of a direct-to-patient outreach model in appropriate countries to raise awareness for NASH risk factors, pre-qualify patients, and refer them to nearby sites for pre-screening

IQVIA's Assets Accelerate the Identification and Enrollment of Patients with NASH Risk Factors

0.4 p/s/m
Industry Recruitment Rate

+

Data-driven Site Selection

+

Proactive Site Development

+

NASH Recruitment Specialists

+

Community-based Recruitment

=

0.7 p/s/m
IQVIA NASH Sites in Europe
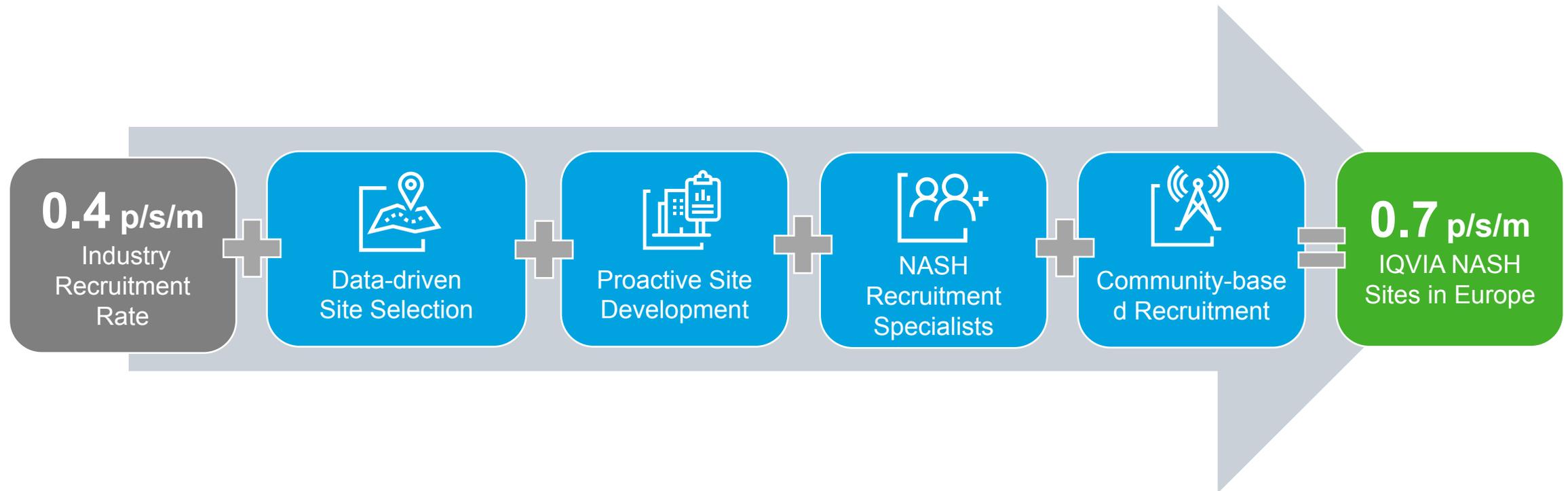
Bid-to-Spec Strategy

18 Months Enrollment (Historical Startup Timelines)

Site Selection Visit Start	06-Aug-2018
First Patient Screened	11-Nov-2018
First Patient Randomized	**23-Dec-2018**
Last Patient Randomized	23-Jun-2020

	Country	Sites	Enroll Rate (p/s/m)	Average FPR to LPR (months)	Patients Screened	Patients Contributed	Patients Completed
Summit	**United States**	35	**1.50**	10.78	1600	600	480
KOLs	**United States**	10	**0.40**	13.07	149	56	45
IQVIA	**United Kingdom**	10	**0.95**	13.18	346	130	104
	France	5	**0.95**	13.08	171	64	51
	Germany	5	**0.95**	13.27	176	66	53
	Italy	5	**0.95**	13.01	171	64	51
	Spain	5	**0.95**	12.09	160	60	48
Synexus	**United Kingdom**	5	**1.00**	16.56	227	85	68
	6	80	1.10		3,000	1,125	900

Madrigal's Bid-to-Spec Strategy (assuming IQVIA's historical startup timelines) requires sites in Western Europe to recruit at 0.95 p/s/m to enroll all patients within 18 months which is an aggressive, unsubstantiated rate

Alternate Strategy

18 Months Enrollment (Startup of Summit Sites Within 2 Months)

	Country	Sites	Enroll Rate (p/s/m)	Average FPR to LPR (months)	Patients Screened	Patients Contributed	Patients Completed
Summit	United States	35	**1.50**	10.78	1600	600	480
KOLs	United States	10	**0.40**	10.61	123	46	37
IQVIA 35 Sites	United Kingdom	10	**0.70**	10.22	205	77	62
	France	5	**0.70**	10.45	101	38	30
	Germany	5	**0.70**	10.65	107	40	32
	Italy	5	**0.70**	10.38	101	38	30
	Spain	5	**0.70**	9.46	93	35	28
	Belgium	5	**0.70**	11.53	115	43	34
Synexus 19 Sites	Germany	4	**1.00**	10.88	120	45	36
	UK	7	**1.00**	10.70	208	78	62
	Poland	8	**1.00**	10.14	227	85	68
	8	99	1.02		3,000	1,125	900

IQVIA proposes an Alternate Strategy with sites in Western Europe enrolling at 0.70 p/s/m, the addition of 5 IQVIA sites in Belgium, and Synexus sites in Germany, UK, and Poland
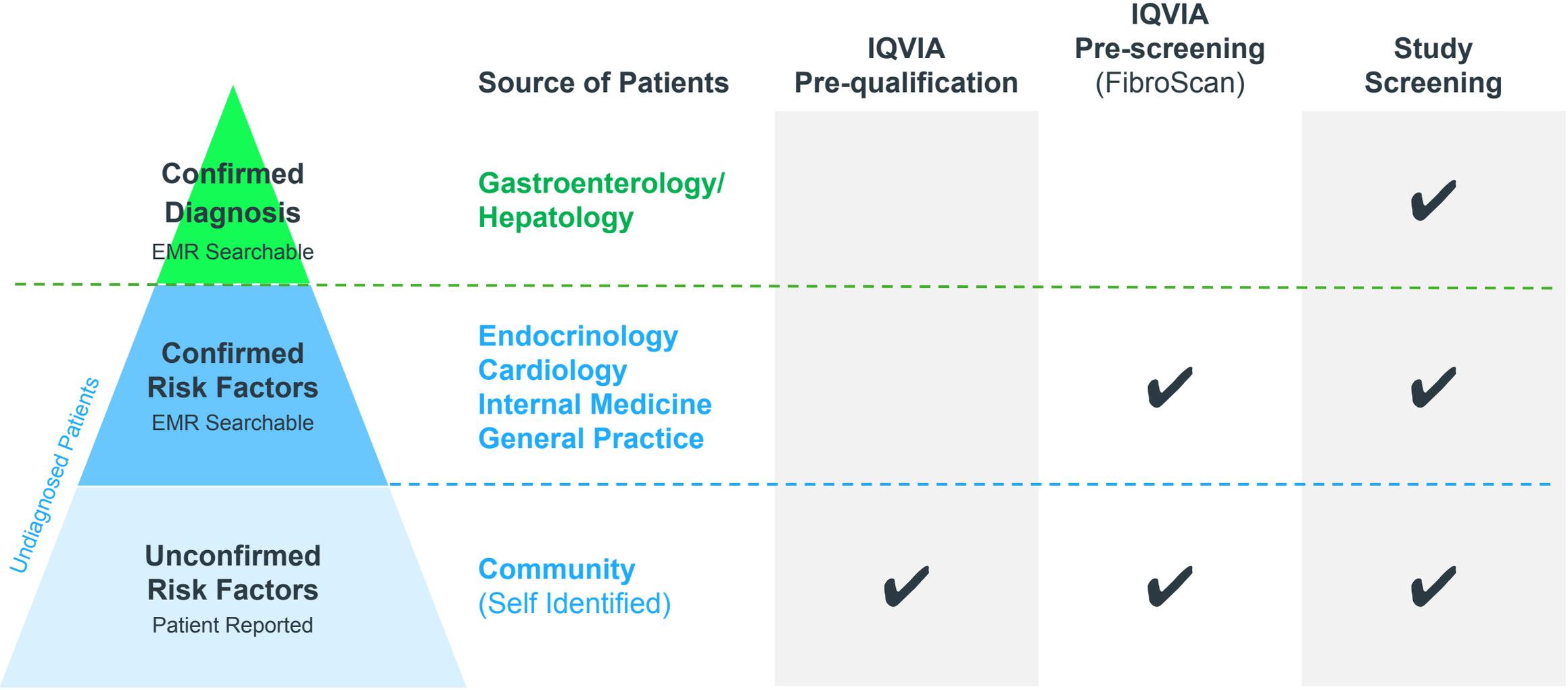
NASH Site Profile

IQVIA's NASH sites will be pre-qualified and have stated an interest in the Madrigal study via a blinded survey

Site Selection Criteria

- NAFLD and risk factor patient volume

- NASH experienced KOLs

- Interest in NASH trials requiring liver biopsy

- Established referral partners (e.g., endocrinologists, GPs)

- Estimated enrollment

- Willingness to work with a NASH Recruitment Specialist in advance of activation to:

    - Search EMR

    - Establish referral network, and/or

    - Pre-screen patients via FibroScan (unit may be provided)

- Competing NASH trials

Patients will enter the NASH Registry Via Different Pathways Depending on their Stage of Diagnosis

Building the Patient Funnel

Site Selection	Deployment of NASH Recruitment Specialist	Preparation for Pre-screening	Start of Pre-screening Activity (Per IQVIA protocol)	Site Activation & Start of Study Screening (Labs & Biopsy)

Preparation for Pre-screening
- Pre-screening protocol training
- Echosens FibroScan Training
- Identification of patients with risk factors for NASH

Patients from the community with self-reported risk factors

Patients identified with risk factors via EMR search (site/referral partner)

Community Awareness

Promotional tools/advertising directs patients to **ClinicalResearch.com** to completed a questionnaire

Initial Patient Contact

[Resource] contacts pre-identified patients, educates them about NASH, and offers a screening opportunity via imaging (FibroScan)

Pre-screening Visit

[Resource] consents patients for pre-screening, conducts FibroScan, and enters patient into **IQVIA NASH Patient Database**

Medical Review

Investigator reviews pre-screening results, assesses eligibility for study screening, and determines level of medical follow up with patient
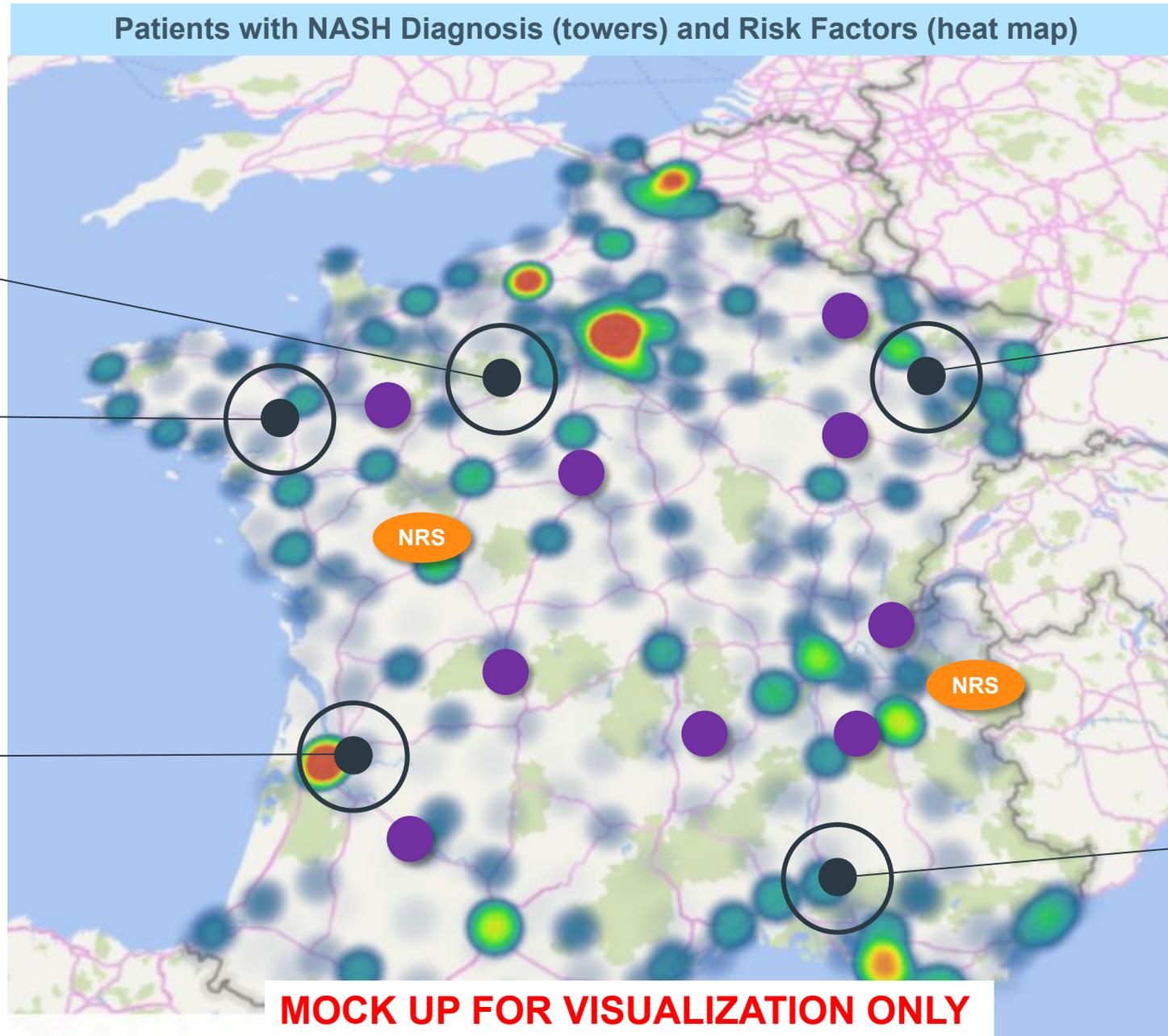
France

Patients with NASH Diagnosis (towers) and Risk Factors (heat map)

NRS — NASH Recruitment Specialist

● IQVIA Diabetes Investigator (Potential Referral Partner

Site Name
Investigator Name
City

Site Name
Investigator Name
City

Site Name
Investigator Name
City

Site Name
Investigator Name
City

Site Name
Investigator Name
City

MOCK UP FOR VISUALIZATION ONLY

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Risk Mitigation

Challenge	Solution
Site Selection – Willingness to utilize IQVIA model, including pre-screening via FibroScan and CTEs	Pre-qualify sites based on this expectation
Site Start-Up – Start up 35 Summit sites within the United States in 2 months	RACI already agreed and being refined for Madrigal project
Recruitment – IQVIA recruitment model not yet proven and dependent upon site agreement to "do things differently"	Share long-term value proposition with sites; Deploy well-trained CTEs to customize the IQVIA model to site practice and drive recruitment
Recruitment – Ensuring and sustaining enrollment at 0.7 p/s/m	Proactively identify, consent, and pre-screen at-risk patients in advance of site activation; house information in "IQVIA NASH Patient Database" for immediate follow up (pending navigation of privacy issues)
Retention – Retain patients through week 52 to collect biopsy for primary endpoint	Site training/tools to educate patients about study commitments (i.e., two biopsies) during consent; provide "Biopsy Prep Kit" to prepare patients and provide comfort

Thank you!