Assessing physician preferences on future therapeutic options and diagnostic practices in non-alcoholic steatohepatitis

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Table of contents

Master Questionnaire - SCREENER

NASH Patient Perspectives and Preference – Quantitative PHYSICIAN Survey

V0.04 – 23/11/17

Length of interview: 15 minutes. Length of this screener: 3 minutes

Start fieldwork: TBD

End fieldwork: TBD

I. QUOTA CHECK BASED ON SAMPLE VARIABLES

Physician Sample	**Online – 15 min**			
	Canada	Germany	UK	US
Split between markets	**n=30**	**n=30**	**n=30**	**n=30**

II. PHYSICIAN SCREENER

Dear Doctor,

Thank you very much for agreeing to participate in this interview. Your input is highly appreciated and we are really looking forward to learning from you today.

First, we would like to ask you some questions to assess your eligibility to participate in an online survey lasting approximately 15 minutes. Our topic of interest today is **NASH (non-alcohol related steatohepatitis).**

S01 [S]

This survey is for research purposes only and we pursue no sales or marketing purposes. This research is sponsored by a pharmaceutical company and is being carried out within the BHBIA/ABPI guidelines and the code of conduct of the Market Research Society. Your individual responses will be kept confidential and anonymous and reported only in aggregate.

We are now being asked to pass on to our client details of adverse events that are mentioned during the course of market research interviews. Although this will be a market research interview and what you say will, of course, be treated in confidence, should you raise during the discussion an adverse event in a specific patient, we will need to report this even if it has already been reported by you directly to the company or the relevant regulatory authority. In such a situation you will be asked whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event. Everything else you say during the course of the interview will continue to remain confidential

Are you happy to proceed with the interview on this basis?

Please indicate your response by selecting the appropriate option below:

SCRIPTER: There is only one answer possible.

❑1	I would like to proceed and give permission for my contact details to be passed on to the drug safety department of the company if a side effect is mentioned by me during the survey
❑2	I would like to proceed but do not wish for my contact details to be passed on to the drug safety department of the company if a side effect is mentioned by me during the survey.
❑3	I don't want to proceed and wish to end the interview here.

SCRIPTER: all respondents with answer3 go to the end of the questionnaire (S01=3 – SCREENOUT)

S02 [S]
What is your primary medical specialty?

❑1	Hepatology
❑2	Gastroenterology
❑3	Internal Medicine with a sub-specialisation in hepatology
❑4	Other → **Terminate**

S03 [S]
Since completing medical training and residency, for how many years have you been in clinical practice?

❑1	<3 years → **Terminate**
❑2	3 – 35 years
❑3	35 years + → **Terminate**

S04 [S]
In the past 3 months, approximately how many patients have you personally seen and managed for any condition?

[WHOLE NUMBER] [ADD RANGE 0-6000]

Please enter #: ____ patients with any condition in 3 months

→ Terminate if <100 patients with any condition

S05 [S]
Out of these *[DISPLAY ANSWER FROM S04]* patients, approximately how many patients have you personally seen and managed for any **liver condition** in the past 3 months?

[WHOLE NUMBER] [ADD RANGE 0-6000]

Please enter #: ____ patients with a **liver condition** in the past 3 months

[THIS NUMBER SHOULD NOT BE HIGHER THAN S04]

→ Terminate if <40 patients with any liver condition

IMPORTANT: PLEASE TALLY S05. RESPONSES FOR ALL THOSE SCREENED, INCLUDING TERMINATES.

S06 [S]
Out of these *[DISPLAY ANSWER FROM S05]* patients, how many patients **with non-alcoholic steatohepatitis (NASH)** have you **personally seen** in the past 3 months?

Here, we are specifically referring to **Nonalcoholic steatohepatitis (NASH)**, a form of NAFLD which – in addition to fat in the liver – is defined by the histologic hallmarks of inflammation, cell damage, and fibrosis.

[WHOLE NUMBER] [ADD RANGE 0-6000]

Please enter #: ____ **non-alcoholic steatohepatitis (NASH)** patients in the past 3 months

[THIS NUMBER SHOULD NOT BE HIGHER THAN S05]

→ Terminate if <20 NASH patients

IMPORTANT: PLEASE TALLY S06. RESPONSES FOR ALL THOSE SCREENED, INCLUDING TERMINATES.

Thank you for your time. We are looking forward to your participation in this study!

END OF PHYSICIAN SCREENER

STANDARD SCREENED OUT TEXT:

Thank you very much for participating in the survey, but unfortunately you are not in the target group of this survey. We hope we will have the chance to include you in one of our surveys in the near future.

Understanding physicians' point of views on NASH

-- Qualitative Research Discussion Guide –

6.04.2017

Study Details:

- **30- minutes telephone interviews with 6 specialists per country treating NASH patients: Canada, Germany, UK**

Research Objectives:

- ✓ Overall perception of NASH versus NAFLD versus fatty liver?
- ✓ Get a better understanding of NASH diagnosis
- ✓ Elaborate which terminology is used with patients as well as what level of information / detail is shared with them
- ✓ Discuss and elaborate which symptoms are linked to NASH and considered to be a (potential) trigger for action
- ✓ Detailed understanding of role of biopsy (when? In what patients? Why? Future use?)
- ✓ How does the current NASH management look like?
- ✓ What are desirable treatment outcomes today and in the future?
- ✓ What do physicians know about treatments in development? How will this change management of NASH? Diagnosis? Treatment?
- ✓ Understand barriers for referring patients for market research and clinical trials

→ Discuss overall project with physicians and try to win them for patient recruitment

Introduction and welcome

Good morning / afternoon / evening, _____. My name is _____. I am calling on behalf of <<company name>>, a global medical marketing research and consulting firm.

Thank you very much for agreeing to participate in this telephone interview. Your input is highly appreciated and we are really looking forward to learning from you today.

Our topic of interest is **NASH, its diagnosis, management and potential future dynamics**.

Just as a brief introduction, let me remind you that I am an independent market researcher and my role in this discussion is to understand your thoughts and opinions.

Your participation is anonymous and all your answers will be treated confidentially, for the sole purpose of this market research. There is no intention to sell or to promote anything.

This research is sponsored by a pharmaceutical company. At all times, we will be adhering to the ABPI Code of Practice and the BHBIA guidelines. You have the right to withdraw from the interview at any time during the interview process and to withhold information as you see fit.

S1 We would also like to mention that the client will be able to listen to our conversation, but at the same time reassure you that all information that you share will be kept strictly confidential and no directly identifiable information will be shared with our client. You will stay anonymous at all times.

Are you happy to proceed on this basis?

Yes, I have read and agree to proceed ☐

_____

No ☐ → Note down and inform <<company>>

S2 This discussion is for market research purposes only. There will be no direct sales or promotions as a result of your participation. Your individual responses will be kept confidential and anonymous and reported only in aggregate.

Adverse events

'We are now being asked to pass on to our client details of adverse events that are mentioned during the course of market research interviews. Although this will be a market research interview and what you say will, of course, be treated in confidence, should you raise during the discussion an adverse event in a specific patient, we will need to report this even if it has already been reported by you directly to the company or the relevant regulatory authority. In such a situation you will be asked whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event. Everything else you say during the course of the interview will continue to remain confidential.'

Are you happy to proceed with this interview on this basis?

If yes, continue interview

If no, terminate interview

S3 I would like to record our discussion today. This is for analysis purposes only.

Are you happy to proceed on this basis?

Yes ☐

No ☐

Section 1: [approx. 10 min]

Objectives:

- ❖ Introduction
- ❖ Perception of NASH
- ❖ Understanding of NASH patients
- ❖ Definition of NASH versus NAFLD versus Fatty Liver

- ➢ After the long introduction we would like to get to know you better. Could you please **introduce yourself**?
  - o Specialty
  - o Working environment

- Number of patients
- Number of patients with liver disease, NASH, NAFLD

- If I was a **medical student** and asked you to summarize the **3-5 most important things** I should know about NASH, what would you say?

- Thinking about the **different severity stages of NASH**. How do you personally distinguish between those / define severity in NASH?

- Imagine I am a NASH patient who is not yet that knowledgeable about NASH, what would you **tell me about the disease**? What are the things that you think are essential for me to know? What else?
  - What terminology would you use to talk about NASH?
  - In the dialogue, how would you approach severity / Metavir score with me?

- Before we dig deeper into our key topic for today, can you quickly help me to understand the **differences between NASH, NAFLD and fatty liver**?
  - From a **medical point of view**, how would you **define** each?
  - Are there any **medical implications** of differentiating the three? How? Why?
  - What is the **terminology** you are using **with patients**? Why is that?

ONLY ASK, IF ENOUGH TIME LEFT

- We know all patients are different, but if I'd ask you to describe a **typical NASH patient** to me, how would this patient look like?
  - Age
  - Gender
  - Symptoms
  - Comorbidities
  - Living situation
  - Cause for NASH
  - Level of education towards NASH
  - …

- Thinking about NASH patients who suffer from mentioned range of comorbidities, what is your primary focus when managing the patient? Comorbidities vs. NASH? If not priority, why not and when does NASH come in?

- Do you think NASH patients take their disease seriously? Why? Why not?

- On the other hand, how seriously do you take NASH? Why?

Section 2: [approx. 10 min]

Objectives:

- Understanding medical journey
- Deep-dive on symptoms related to NASH
- Role of biopsy
- Patient-physician dialogue

- Please tell me a little bit more about the **medical patient journey** of a typical NASH patient.
  - What **triggers** the **diagnosis**?
    i. Which symptoms and/or test results?
    ii. Who notices that something is wrong?
    iii. What percentage is an incidental diagnosis versus diagnosis because of NASH symptoms / complaints?
  - **Who** diagnoses NASH?

i. Referral behavior?
ii. Who is usually the primary medical point of contact?
iii. What specialties are involved? Role of GP versus specialist?

- **What tests** are usually performed to confirm NASH?
  - Who decides what tests are performed?
  - Do patients have a say in this as well?
    i. Do you (always) communicate results to the patient?
    ii. Are the test results monitored / Is the test repeated over time?

VERY IMPORTANT QUESTION:

- Let's talk about **liver biopsy** in more detail. **When** do you perform or refer a patient for a liver biopsy for NASH?
  - In which **patients**? Under which **circumstances**?
    i. Severity / Suspicion of cirrhosis? Clinical Trial setting? Insurance status? Guidelines?
  - What is the **benefit** of performing a biopsy? What are potential **drawbacks**?
  - What, if at all, are the **medical implications** of a biopsy?
  - Would you **re-do a biopsy** over time for a specific patient? Why? When? How?

- How long does it typically take to confirm a diagnosis of NASH? In other words, how long is the time period from a first visit to a physician (based on symptoms or incidental findings) until a confirmed (or suspected) diagnosis of NASH?

VERY IMPORTANT QUESTION:

- Now, I would like to talk a little bit more about **symptoms in NASH**. What, if at all, are typical symptoms that you see in your NASH patients?
  - What symptoms do you probe on (during diagnosis or monitoring)? What else?
  - Do you have the feeling that **patients notice** their NASH symptoms? Why? Why not?
  - Can you **always clearly link** the symptoms to NASH? Which ones? Which ones can't you clearly link to NASH?
  - Do NASH symptoms **worsen over time / with severity** stage? How?
  - *In case, physicians do not see many symptoms:* What does this mean for your disease management that patients are not experiencing any symptoms?
  - Do symptoms typically worsen as the disease progresses *(e*.g. from steatosis to fibrosis to cirrhosis). How tight is the association between symptoms and disease stage?
  - Which other aspects, such as physical examination do you take into account during the conversation?

- I'd like to read out a list of potential **symptoms or physical or mental signs.** Please tell me which ones you are observing as well and in your opinion could be clearly linked to NASH or other comorbidities?
  //If not mentioned spontaneously, please probe on://
  - Fatigue (please specify what kind of fatigue, what can they not do anymore?)
  - Pain (please specify where patients experience pain)
    - If yes, how do you measure pain (if at all) acute and over time?
  - Abdominal discomfort, GI symptoms, bloating, pressure, tightness, gas, fullness
  - Muscle cramps
  - Overweight
  - Itch (please specify where patients experience itch and how severe it is)
  - Sleeping problems
  - Weight loss / loss of appetite
  - Nausea
  - Weakness / feeling lethargic
  - Flu like symptoms, please explain…
  - Dermatological (skin) related problems (psoriasis, atopic dermatitis)
  - Jaundice, yellowing of skin and eyes

- Clammy palms, red palms, sweaty skin
- Spider like blood vessels, enlarged blood vessels just beneath the skin
- Fluid build-up, swelling of legs (edema) and/or abdomen (ascites)
- Depression and anxiety
- Stress, difficulty concentrating

- Which of the symptoms we have just discussed would you approach first? Why?
- …and which of the symptoms do you believe is most worrying to patients? Why do you say so?

- In the long-term, **who is usually monitoring** NASH patients?
  - Frequency?
  - What is done during monitoring?
    i. Which topics are discussed?
    ii. Which tests are performed?

- Taking into account everything we have discussed so far, in your opinion, how are patients **ADLs and QoL impacted** by NASH? Why?

Section 3: [approx. 5 min]

Objectives:

❖ Current management
❖ Future Outlook
❖ Ideal treatment outcome

In this section of the interview I would like to talk about the current disease management and a future outlook with you.

- **What are you currently doing to manage** NASH patients?
  //If not mentioned spontaneously, probe on://

  - Prescription medication
  - Non-prescription products
  - Recommended lifestyle modifications, which ones?//what is exactly communicated to the patients (level of detail)?

  //For each management approach, probe on://

  - What are the treatment objectives for each approach?
  - What goals do you communicate to your patients?

- What is your opinion on drug treatment versus lifestyle changes for the management of NASH?

- In general, we know that currently there is **no medical drug treatment** available to treat NASH. How do you **communicate this to your patients, if at all**?
  - If there were drugs available, would this influence your conversation with the patients (about their need to manage NASH, and maybe about the need for a biopsy?)

- To what extent do **other comorbidities impact your NASH management**? Please explain.

- What would you say are the biggest **unmet needs** when it comes to the management of NASH?

  //In case not mentioned spontaneously, please probe on://

  - Education/information needs
  - Treatment needs
  - Needs with regard to daily life

- If there was a **new medication available** to treat NASH, what would you **expect** the treatment to achieve? Please think of 3 or more **ideal outcomes** of a treatment and rank them in order of importance to you (1st, 2nd, 3rd).

  //In case not mentioned spontaneously, please probe on://

  - What medical parameters / measure would be important?
  - What symptom-related improvement should be seen?
  - What would be important for patients?

Section 4: [approx. 4 min]

Objectives:

❖ Understand barriers for referring patient for clinical trials and market research studies

- A number of pharmaceutical companies are running clinical trials in NASH and there have been reports in the literature of slow recruitment and challenges in **identifying biopsy-confirmed F2 and F3 NASH patients for clinical trials.** Do you have an explanation for this?

- Do you generally refer patients for clinical trials of NASH drugs?
  i. If yes: Why do you refer patients for clinical trials?
  ii. If no: What are the barriers for referring patients for clinical trials?
    - How could these barriers be overcome in order to win more patients for clinical trials of NASH drugs?

- We are conducting market research with patients in order to identify their needs and preferences with regards to the management of NASH. Again we are struggling to find **biopsy-confirmed F2 and F3 NASH patients** that are willing to participate.
  - Would you be interested to support our recruitment process for this study and are we allowed to reach out to you again? Of course, you are allowed to refuse at any time.
    i. If no: What are the barriers for you to help us to find the right patients for our market research?
      - How could we overcome these barriers in order to win more patients for this market research?
    ii. If yes: How many patients that are F2 or F3 and that are diagnosed by biopsy could you potentially refer?
      - What next steps would you recommend for our collaboration?

Section 5: [approx. 1min]

Objectives:

❖ Wrap-up and closing

- As we are now coming to the end of our discussion, I was wondering if you feel that there were any other aspects regarding NASH or our initiative in particular that we did not touch on yet, that you would like to feedback on? Please elaborate.

Thank you very much for your time and your willingness to share your opinions.

I think it was a very interesting discussion for all of us and it is highly appreciated.

Table S1. Relative importance of 11 product attributes – ranked by each country.

Item	Label	Total (N=121)	Canada (n=31)	Germany (n=30)	UK (n=30)	US (n=30)	Heps (n=30)	Gastros (n=85)	Internal Medicine (n=6)
1	Impact on liver status (ranging from liver status is stabilized, e.g. no regression of fibrosis and no worsening of inflammation [no worsening of NASH] to liver status is better, e.g. regression of fibrosis from F3 to F2 or F1 and reduction of inflammation [resolution of NASH])	1	1	1	2	1	1	1	Data not shown (sample size too low)
2	Progression of cirrhosis (ranging from slows down progression to cirrhosis to no progression to cirrhosis)	2	2	2	1	2	2	2	
3	Impact on weight (ranging from no impact to weight loss by at least 5%)	7	6	5	9	8	7	7	
4	Impact on fatigue and stomach pain (ranging from no impact to reduction of both)	6	7	6	5	6	8	5	
5	Impact on blood sugar / diabetes medication (ranging from lowering blood sugar (HbA1c) to making current diabetes medication less effective	3	3	3	3	3	3	3	
6	Impact on cholesterol (ranging from increasing the level of LDL cholesterol in the blood to having no interaction with cholesterol-lowering medication)	4	4	4	4	4	4	4	

Item	Label	Total (N=121)	Canada (n=31)	Germany (n=30)	UK (n=30)	US (n=30)	Heps (n=30)	Gastros (n=85)	Internal Medicine (n=6)
7	Impact on patients' frequency of visits to their doctor for their liver condition (ranging from more visits to same number of visits)	5	5	8	6	5	5	6	
8	Possibility to cause diarrhea (ranging from mild to not at all)	9	9	9	8	11	9	9	
9	Possibility to cause nausea (ranging from occasional to not at all)	10	10	11	11	9	9	11	
10	Possibility to cause headache (ranging from occasional to not at all)	11	11	10	10	10	11	10	
11	Possibility to cause itching (ranging from moderate to not at all	8	8	7	7	7	6	8	

Table S2. Physician participant sub-specialisms.

	Total	Country				Place of practice		
	----------	USA ----------	Canada ----------	Germany ----------	UK ----------	Hospital specialized in liver conditions ----------	Hospital NOT specialized in liver conditions ----------	Office [Ex-UK] ----------
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)
Total	121	30	31	30	30	60	31	30
Hepatology	30	3	14	8	5	20	6	4
	25%	10%	45%	27%	17%	33%	19%	13%
			BE			H		
Gastroenterology	85	27	12	22	24	39	22	24
	70%	90%	39%	73%	80%	65%	71%	80%
		C		C	C			
Internal Medicine with a sub-specialization in hepatology	6	-	5	-	1	1	3	2
	5%	-	16%	-	3%	2%	10%	7%
Other	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-

Comparison Groups: BCDE/FGH

T-Test for Means, Z-Test for Percentages
Uppercase letters indicate significance at the 95% level.