July 13, 2020

The Honorable Dr. Stephen M. Hahn
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Joseph G. Toerner, MD, MPH
Acting Director, Division of Hepatology and Nutrition
Office of Immunology and Inflammation
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Suite 4177
Silver Spring, MD 20993

Dear Commissioner Hahn and Dr. Toerner:

The Fatty Liver Foundation (FLF) is a leading, non-profit, grassroots patient advocacy organization dedicated to improving the identification, diagnosis, treatment, and support of Americans with fatty liver, non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) through awareness, screening, education, and patient outreach. We are writing to express our concerns about the FDA's process for receiving patient input in the Agency's priority review of Intercept Pharmaceuticals' New Drug Application (NDA) for obeticholic acid (OCA) as a designated breakthrough therapy for the treatment of liver fibrosis due to NASH.

We applaud recent actions taken by the Agency in granting an accelerated approval pathway for the review of drugs that are intended to treat patients with liver fibrosis due to NASH through the breakthrough therapy designation process. Our patient community is very aware of the fact that there are no therapies or treatments for NASH. We are grateful for the efforts made by the Agency to issue guidance to assist industry sponsors in the clinical development of drugs for the treatment of noncirrhotic NASH patients with liver fibrosis.

We have watched with keen interest and we have been greatly encouraged in recent years as the Agency has moved under section 505(n)(1) of the FDA Modernization Act of 1997 to consider patients to be appropriate members of the panels of experts called for by the Act. We see inclusion of patients in the Advisory Committee (AdCom) membership as a very valuable and forward-looking improvement over policies of the past. This is in keeping with the society wide movement to promote patient engagement and wellness as a necessary element for improving public health.

NASH patients and our advocate community noted FDA's initial announcement on convening a much-anticipated AdCom meeting related to the NDA for OCA with April 22, 2020 as the tentatively scheduled meeting date. The Agency subsequently decided to postpone this AdCom until June 9, 2020 as the new tentatively scheduled meeting date due to the COVID-19 public health emergency.

Our patient community was anxious to have an opportunity add our voice to the record and we were dismayed when the Agency issued a Complete Response Letter (CRL) on June 26, 2020, without holding the Adcom. We understand that the Agency suggested that the applicant could submit additional post-interim analysis of efficacy and safety in order to address uncertainty related to the predicted benefit of OCA. We note that the OCA application was based on surrogate histopathologic endpoints which had driven the design of the Phase III trial. It is our understanding that at issue is whether benefits and risks analyses support accelerated approval for treatment of liver fibrosis due to NASH. As a primary channel for the voice of the patient we have an opportunity to bring perspective about things that are of value to our community and we feel it is important for the FDA to understand our perspective as you weigh the merits of candidates like OCA.

We are anxious to understand what risk factors prompted the CRL, but it is important that FDA weigh benefits appropriately. Absent new data, the results of the Phase III trial demonstrated that OCA met the design endpoint which most importantly was a one stage reduction in fibrosis. As patients, we wish to be on record as stating that a reduction in NASH staging is of great value to us. There are numerous studies about fibrosis but for reference you might consider "Fibrosis Stage not NASH Predicts Mortality"[1]. It is well documented that a reduction in fibrosis reduces mortality so the OCA results are of great interest to us.

I have included in the attachments a table which shows the hazard ratio. It compares the risk of dying from this fibrotic disease compared to a person without the condition. In this case it shows that the hazard ratio for a stage 4 fibrosis is nearly 11. That compares to a hazard ratio for stage 3 fibrosis of under 4. The value to the patient community of a one stage reduction of fibrosis is hard to overstate. Since the phase 3 data of OCA indicated that, as a minimum measure, some patients did see a one stage reduction the possibility of OCA being available to us is highly important.

As patients, and advocates, we believe that people living with NASH are entitled to information about new therapies that is sufficient for us, with our physicians, to make necessary risk and benefit analyses regarding our treatment. We are anxious to learn what concerns prompted the CRL, but wish to express the view that for a disease with no treatment alternatives, such as NASH, the FDA's proper role should be to assure that we and our physicians have the information which would allow us to judge the risk benefit for ourselves. Fibrosis stage improvement is crucial to our health and we seek to have our voices be considered in the deliberations about drugs under consideration.

Drug regulation is more than minimizing risks. Given the high prevalence of NASH, the associated co-morbidities, and the growing burden of end-stage liver disease, we believe that it is important to focus on maximizing public health gains by licensing therapies that will slow the progress of, halt, or reverse liver fibrosis due to NASH. OCA is the first of what we hope will be a variety of alternatives for our treatment, but we are concerned that this action on OCA will discourage other research since it appears to be unclear whether reaching agreed endpoints is being given sufficient valuation in this very complex drug development field.

To assist you in understanding the patient view, we did a brief survey of patients within our community about their understanding and views of OCA and fibrosis staging and I have attached a report of our results. Key points: of 239 responses 52% were aware that FDA was considering OCA for approval but 95% were aware that there are no treatments. When asked if a reduction of one stage of fibrosis would be of value 96% said yes. Perhaps the most telling response was that when asked if a drug would be of value to them if all it did was stop the progression of fibrosis 99% said yes.

From our position as a key part of the patient voice, we are seeking to understand the process which led to the cancellation of the AdCom, what information informed that process, and we ask that we be heard in an appropriate forum.

1. Hagström H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. *J Hepatol*. 2017;67(6):1265-1273. doi:10.1016/j.jhep.2017.07.027

Please contact me via email at wayne@fattyliverfoundation.org to set up a virtual meeting in the coming weeks to further discuss these issues. We look forward to working with you to resolve these issues.

Sincerely,

Wayne Eskridge

Wayne Eskridge
CEO and Co-Founder
Fatty Liver Foundation

Financial Disclosures: The Fatty Liver Foundation is a 501(c)(3) charitable foundation. Intercept Pharmaceuticals, the applicant sponsoring OCA, along with multiple other donors, has provided educational grants in support of our patient programs.

cc: Dr. Lara Dimick-Santos, MD, Medical Reviewer, Liver Products Specialist, OII/DHN, FDA
Dr. Julie Beitz, MD, Director, Office of Immunology and Inflammation, CDER, FDA
Dr. Robert Temple, MD, Deputy Center Director for Clinical Science, CDER, FDA
Dr. Peter Stein, MD, Director, Office of New Drugs, CDER, FDA
Dr. Patrizia Cavazzoni, MD, Deputy Center Director for Operations, CDER, FDA
Dr. Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, FDA

Fibrosis, not NASH predicts survival

N=619 biopsy-proven NAFLD, FU 12.6 yrs.

Feature	HR (95% CI)
Fibrosis stage 1	1.88 (1.28-2.77)
Fibrosis stage 2	2.89 (1.93-4.33)
Fibrosis stage 3	3.76 (2.40-5.89)
Fibrosis stage 4	10.9 (6.06-19.62)
Age	1.07 (1.05-1.08)
Diabetes	1.61 (1.13-2.30)
Current smoking	2.62 (1.67-4.10)
Statin use	0.32 (0.14-0.70)

https://www.ncbi.nlm.nih.gov/pubmed/28803953

The Fatty Liver Foundation has a question for liver disease patients. The FDA has delayed a decision on Intercept's NASH drug obeticholic acid (OCA) We would like to know what you think of that.

239

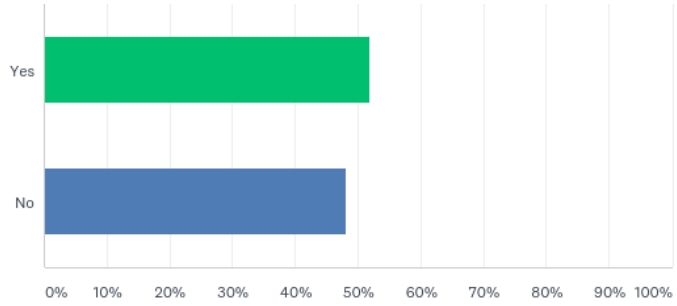
Total Responses

Date Created: Monday, July 13, 2020

Complete Responses: 239

Q1: Were you aware the FDA was considering OCA for approval for NASH?

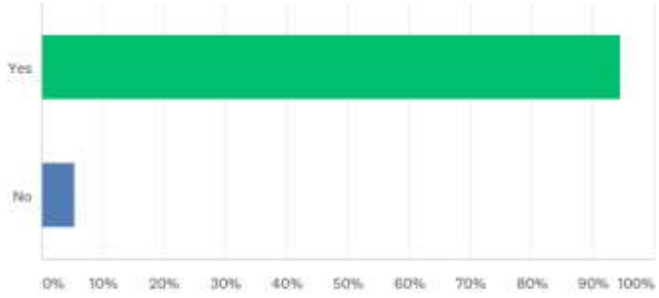
Answered: 239 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	51.88%	124
No	48.12%	115
TOTAL		239

Q2: Are you aware that there are no drug treatments for NASH?

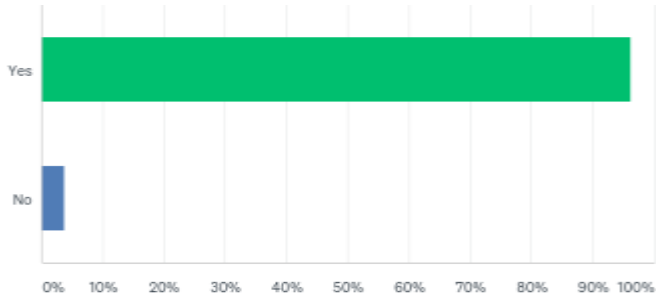
Answered: 239 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	94.56%	226
No	5.44%	13
TOTAL		239

Q3: To be approved as a NASH therapy the FDA required a one stage reduction in fibrosis. Do you feel that fibrosis reduction of one stage would be of value?

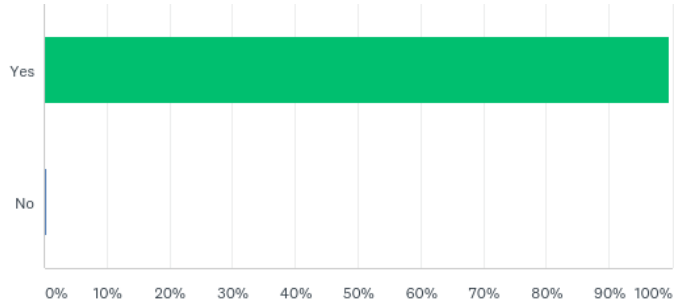
Answered: 238 Skipped: 1



ANSWER CHOICES	RESPONSES	
Yes	96.22%	229
No	3.78%	9
TOTAL		238

Q4: If all a drug therapy did was to stop the progression of fibrosis would that be of value?

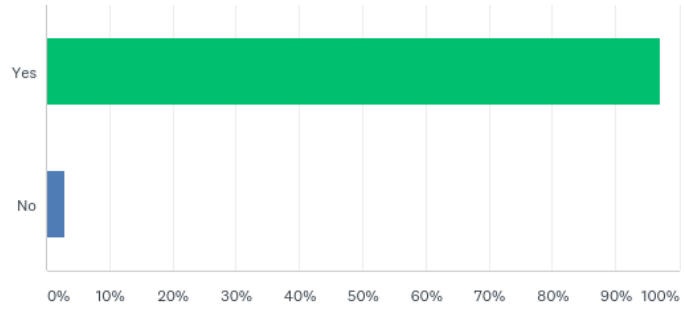
Answered: 239 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	99.58%	238
No	0.42%	1
TOTAL		239

Q5: Suppose a drug treatment only worked for less than half of the patients, would it still be useful to have it available?

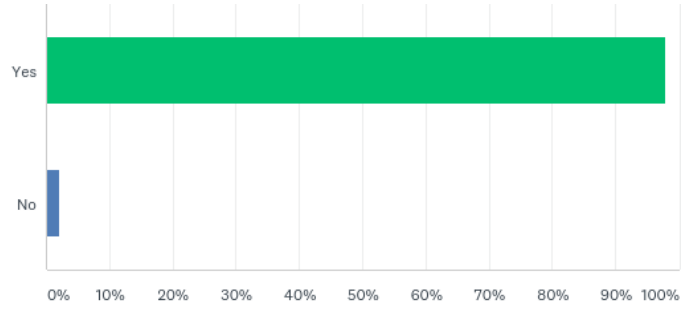
Answered: 238 Skipped: 1



ANSWER CHOICES	RESPONSES	
Yes	97.06%	231
No	2.94%	7
Total Respondents: 238		

Q6: Would you support asking the FDA to reconsider?

Answered: 238 Skipped: 1



ANSWER CHOICES	RESPONSES	
Yes	97.90%	233
No	2.10%	5
TOTAL		238