Inadequate Evidence, and Safety Concerns for Accelerated Approval for NDA# 212833 (Obeticholic Acid; Intercept Pharmaceuticals) for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis.

Testimony before the Food and Drug Administration's Gastrointestinal Drugs Advisory Committee

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I'm Michael Abrams from Public Citizen's Health Research Group. I have no financial conflicts of interest on this matter.

Nonalcoholic steatohepatitis with fibrosis (here after: NASH) impacts millions of persons in the US each year and marks liver disease that, over many years, can lead to transplantation or death.[1] There are presently no FDA-approved pharmacologic treatments for this illness. Diet- and exercise-induced weight loss, and bariatric surgery both treat NASH; however, the former is difficult to sustain and the latter carries substantial risks.

There are currently several pharmaceutical inventions in development for NASH,[2] today you are discussing obeticholic acid (OCA), a synthetic form of a liver bile acid that is slightly different than the native substance it aims to mimic.[3]

A single randomized placebo-controlled trial (747-303) was initiated in 2015 to test daily 10 or 25 mg doses of OCA versus placebo as a treatment for NASH.[4] That trial has since randomized 931 subjects (into three nearly equal groups) and followed them 18 months for interim analyses that evaluated two pre-specified surrogate outcomes for the explicit purpose of seeking accelerated approval.

Those analyses, plus supplemental analyses with more statistical models and subjects,[5] have demonstrated only one small therapeutic effect: an improvement in fibrosis (and no worsening of

[1] Food and Drug Administration. FDA Briefing Document for NDA# 212833. Drug name: Obeticholic Acid. Applicant: Intercept Pharmaceuticals. Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting. May 19, 2023. https://www.fda.gov/media/168215/download. Accessed May 18, 2023. PDF p. 8.
[2] Lee KC, Wu PS, Lin HC. Pathogenesis and treatment of non-alcoholic steatohepatitis and its fibrosis. *Clin Mol Hepatol*. 2023;29(1):77-98.
[3] Food and Drug Administration. FDA Briefing Document for NDA# 212833. Drug name: Obeticholic Acid. Applicant: Intercept Pharmaceuticals. Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting. May 19, 2023. https://www.fda.gov/media/168215/download. Accessed May 18, 2023. PDF p. 10.
[4] *Ibid*. PDF pp. 16-18.
[5] *Ibid.* PDF p. 20.

NASH) that was observed in 23% of the 25 mg patients and 12% of the placebo patients.[6] No differences with placebo were seen with the 10 mg OCA dose, and neither dose demonstrated efficacy in *resolving* NASH (and no worsening of fibrosis), the other pre-specified outcome. These findings were generally similar with the addition of more subjects and alternative histological grading.

Equally important, hundreds of observations from the post-hoc interim 18-month randomized trial demonstrated many adverse effects of obeticholic acid. Focusing hereafter on the 25 mg dose, serious adverse events occurred in 10.2% of subjects taking the drug versus 7.5% of those on placebo.[7] Treatment interruption due to pruritus occurred in 20% versus 2% of subjects, respectively.[8] "Probable" or "possible" drug-induced liver disease was identified in 32.1% versus 7.4%, respectively, requiring liver transplantation in at least one case where OCA was used.[9] Gall bladder disease,[10] 'bad' cholesterol (LDL-C) increases,[11] worse blood sugar control,[12] and more cancer[13] and kidney injury[14] all were evident with OCA use versus placebo.

Moreover, if OCA were to be approved to treat NASH it would plausibly dramatically increase the need for liver biopsies and other assays,[15] and the use of other drugs such as statins and corticosteroids, which have their own adverse effects.[16]

Accordingly, the FDA's summary review has concluded that the *clinical efficacy* of OCA remains unknown, and that wider use of this drug will require "unrealistic metabolic monitoring," and expose patients to numerous drug-induced and other iatrogenic risks. FDA further concludes that the existing data thus "cannot justify OCA use in NASH subjects with stage 2 or 3 fibrosis."[17]

We agree with that assessment, and thus we encourage you to vote today against approval of obeticholic acid as a treatment for NASH.

[6] *Ibid*. PDF p. 26.
[7] *Ibid*. PDF p. 29.
[8] *Ibid*. PDF p. 30.
[9] *Ibid*. PDF pp. 34, 36.
[10] *Ibid*. PDF pp. 41.
[11] *Ibid*. PDF pp. 41-42, 44.
[12] *Ibid*. PDF p. 46-47.
[13] *Ibid.* PDF p. 49.
[14] *Ibid.* PDF p. 50.
[15] *Ibid.* PDF p. 51.
[16] *Ibid.* PDF pp. 53-54.
[17] *Ibid.* PDF p. 54.