Errata to FDA Briefing Document
Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting
05/19/2023

This erratum contains corrections to FDA's Briefing Document for the May 19, 2023, Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting. The committee will discuss new drug application (NDA) 212833, submitted by Intercept Pharmaceuticals, Inc. for obeticholic acid (OCA) 25 mg oral tablets for the proposed treatment of pre-cirrhotic liver fibrosis due to nonalcoholic steatohepatitis.

1) Section 2.2.1, Page 12

   "The AE profile from FLINT and D8602001 were consistent with the observed dose dependent increase in pruritus and drug-induced liver-injury (DILI) in subjects with primary biliary cholangitis (PBC) treated with doses ranging between 5 mg and 10 mg."

   Revised text (deletions in strikethrough font and additions in bolded and underlined font):

   "The AE profile from FLINT and D8602001 were consistent with the observed ~~dose dependent increase in pruritus, and~~ drug-induced liver-injury (DILI) **and dose-dependent pruritus. Dose dependent DILI and pruritus were observed** in subjects with primary biliary cholangitis (PBC) treated with OCA doses ranging between 5 mg**,** ~~and~~ 10 mg, **25 mg, and 50 mg**."

2) Section 3.2.3.1, Page 31
   "However, rapid progression and irreversible injury was observed in three OCA 25 mg treated subjects in three phase 2 trials (747-209, FLINT, and D8602001)."

   Revised text (deletions in strikethrough font and additions in bolded and underlined font):

   "However, rapid progression and irreversible **liver** injury **due to DILI** was observed in ~~three~~ two OCA ~~25 mg~~ treated subjects in ~~three~~ phase 2 trial~~s~~ (747-209~~, FLINT, and D8602001~~)." **In the phase 2 trial (Trial 747-209), these two subjects (Refer to Appendix, subject 16 and 33) died after rapid and irreversible progression of liver failure. Both subjects had compensated cirrhosis (Child-Turcotte-Pugh (CP)-A status) at baseline.**

   Subject 33 died soon after development of severe cholestatic DILI (total bilirubin 18.1 mg/dL). OCA 25 mg was discontinued after the development of severe cholestatic DILI, and the subject died 17 days after OCA discontinuation. Role of DILI in death (fatal outcome): contributory role

   Subject 16 was started on OCA 10 mg. On Day 140 the subject developed acute on chronic liver failure (ACLF) with development of hepatic encephalopathy (HE), ascites

requiring paracentesis, coagulopathy, and upper GI bleeding. On day 145 the subject developed a second event of HE. OCA 10 mg was discontinued on Day 153. The subject died on day 304 (151 days after discontinuing OCA and developing acute-on-chronic liver failure (ACLF). Role of DILI in death (fatal outcome): contributory role cannot be ruled out

DILI was observed across the entire NASH drug development program, including in FLINT and D8602001 trials. However, no deaths, liver decompensation, or liver transplant events were observed in either the FLINT trial or the D8602001 trial."

3) Section 3.2.3.1.2, page 34

"One subject with cirrhosis died of acute on chronic liver failure (Table 12, #10, Subject 2)."

Revised text (deletions in strikethrough font and addition bolded and underlined font):
*"One subject with cirrhosis died of acute on chronic liver failure (Table 12, #**4**~~10~~, Subject 2).*

4) Section 3.2.3.1.2, Page 35, Table 12
"Table 12: Twelve Subjects on OCA With Moderate to Severe Liver Injury Assessed as at Least Possible DILI by FDA or the HSAC"

Revised text (additions in bolded and underlined font):
The subject described in row #5 (Subject 5) was dosed with OCA 10 mg and not OCA 25 mg.

5) *Section 3.3.2, page 53*
"A 60-year-old female (Subject) developed "bridging fibrosis with cirrhotic nodule formation" on biopsy by Day 470 on OCA, but OCA was neither dose reduced to 10 mg per protocol nor discontinued."

Revised text (addition in bolded and underlined font):

"A 60-year-old female (Subject **2**) developed "bridging fibrosis with cirrhotic nodule formation" on biopsy by Day 470 on OCA, but OCA was neither dose reduced to 10 mg per protocol nor discontinued."

6) Page 59, Benefit Risk Effects, Table 22
"Dysglycemia
Cumulative incidence difference (%) for clinically important deterioration in glycemic control at month 36
Diabetes 4.6 (0.2, 9.1)
Pre-diabetes 11.7 (0.6, 22.8)
Normoglycemia 9.9 (-0.5, 20.2)

-Deterioration of glycemic control occurred in a high incidence of subjects treated with placebo (86%, 56%, and 79% of diabetic, prediabetic, and normoglycemic subjects at 36 months, respectively)"

Revised text (deletions in strikethrough font and additions in bolded and underlined font):
"Dysglycemia
Cumulative incidence difference (%) for clinically important deterioration in glycemic control at 36-month
Diabetes 4.6 (0.2, 9.1)
Pre-diabetes **8.5 (-2.9, 20.0)** ~~11.7 (0.6, 22.8)~~
Normoglycemia **6.8 (-2.9, 16.6)** ~~9.9 (0.5, 20.2)~~

-Deterioration of glycemic control occurred in a high incidence of subjects treated with placebo (**84%,** ~~86%~~ **35%,** ~~56%,~~ and 79% of diabetic, prediabetic, and normoglycemic subjects at 36 months, respectively)."

7) Appendix 6.1, Page 63, Table 23
The cause of death for the Patient ID #16 in the Table is listed as preferred term: Progression of decompensated liver disease (verbatim: End stage liver disease).

Revised text (deletions in strikethrough font and additions in bolded and underlined font):

The cause of death for the Patient ID #16 in the Table ~~is listed as preferred term: Progression of decompensated liver disease (verbatim: End stage liver disease~~ **should not contain either preferred term or verbatim term. These terms were not provided by the Applicant.**