ERRATA FOR ADVISORY COMMITTEE BRIEFING DOCUMENT
GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

Meeting Date: 07 April 2016

NEW DRUG APPLICATION FOR OBETICHOLIC ACID (OCA)

for the Treatment of Primary Biliary Cirrhosis (PBC)

(New Drug Application [NDA] 207999)

Sponsor:

Intercept Pharmaceuticals, Inc.
4760 Eastgate Mall
San Diego, CA 92121

USA

ADVISORY COMMITTEE BRIEFING MATERIALS
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These errata provide minor clarification to information contained within the briefing document to support the upcoming Advisory Committee meeting. The errata is intended to provide transparency of these minor clarifications. None of these changes affect the conclusions within the document

Final: 3 April 2016

General:

Patients with persistently elevated alkaline phosphatase (ALP): the statement in the briefing document that 70% of PBC patients treated with, or intolerant to, UDCA continue to have abnormally elevated ALP is based on data from the Global PBC Study Group (Lammers 2014), which shows that after a year of follow-up 2639 out of 3710 patients (ie, 71%) had ALP values greater than the upper limit of normal.

Evaluation of UDCA response criteria: there are a number of previous publications evaluating the unmet need in PBC that have defined UDCA response criteria according to several different ALP cut-off values of at least 1.5x ULN in order to identify patients at risk of progression to adverse outcomes. Based on this collective set of publications a 40% UDCA non-response rate has generally been cited, most closely approximating an ALP cut-off value of 1.67x ULN (Kumagi 2010) that informed the Phase 3 study endpoint. The briefing document includes a statement that "*up to 50% of patients with PBC have a suboptimal response*" based on a lower ALP cut-off value of 1.5x ULN, shown to differentiate risk patients with earlier stage disease (Corpechot 2011).

Statistical analyses and secondary endpoints: adjustments for multiplicity were conducted for the primary endpoint and key secondary endpoint. Other secondary endpoints were exploratory, so the statistical analyses are descriptive and the p-values nominal.

Specific:

Page 13: The statement "*The risk of adverse outcomes associated with inadequate or no response to UDCA (as determined primarily by ALP and, in more advanced disease, bilirubin as well) is substantial*" should be modified to state "*Data from the Global PBC study group supports that patients who have elevated ALP and/or total bilirubin after one year of treatment with UDCA have an increased risk of death or liver transplant."*

Page 14: The statement "*Activation of FXR regulates bile acid homeostasis enterohepatically, as well as inflammation and fibrosis in response to liver injury*" is based primarily on previously published nonclinical data and is supported by data from the clinical studies of OCA.
The statement "*Mean total bilirubin levels increased in the placebo group and were maintained in the OCA treatment groups, suggestive of a slowing of disease progression with OCA*" is speculative. While total bilirubin (TB) levels even within the normal range predict risk of adverse clinical outcomes and therefore stabilization of TB within normal limits is clinically important, the Phase 3 trial was not designed to test the effect on disease progression. Please note that for the patients with normal TB at entry, TB levels remained within normal limits. In the small subset of patients with abnormally elevated TB at entry, OCA treatment resulted in 7 of 11 (63%) normalizing compared to 1 of 7 (14%) in the placebo group.

Page 18: Please note that the graphic should reflect that serum bilirubin, albumin and platelets do not change in the majority of patients with PBC until cirrhosis is present. However, subsets of patients without cirrhosis may develop (i) severe ductopenic cholestasis, presenting with hyperbilirubinemia and jaundice, or (ii) pre-sinusoidal portal hypertension, hypersplenism and thrombocytopenia.

Page 24: The statement "*In fact, doubling of bilirubin was the regulatory endpoint used to support initial approval of UDCA in the US*" should be modified to "*In fact, doubling of bilirubin was the principal component of the composite clinical endpoint used to support regulatory approval of UDCA in the US*".

Page 29: With reference to the statement that *"Long-term safety data has been collected out to over 5 years in the open-label LTSE studies,"* there are a total of 14 patients (11 on OCA monotherapy) with exposure of 5 years.

Page 52: The statement "*Demographics and baseline characteristics were typical of a PBC population and included a high risk population of advanced or cirrhotic patients*" should be modified to *"Demographics were typical of the PBC population, inclusive of a proportionately smaller high risk group of patients with either a biochemical profile of moderately advanced disease (abnormal TB or albumin) or clinical evidence of cirrhosis"*.

Page 63: The statement that *"transient elastography (Fibroscan®) is one of the best current surrogate markers of liver fibrosis in PBC (Corpechot 2012)"* should be qualified. Transient elastography (TE) non-invasively measures shear wave velocity as an assessment of "liver stiffness" expressed in kilopascals (kPa), but the Fibroscan device has not been approved for diagnosis or staging of liver fibrosis. In studies to date it has only shown accuracy in detecting cirrhosis vs. not cirrhosis, but has not been shown to be accurate in detecting changes in liver fibrosis from stage to stage. The Corpechot paper reported results for 150 UDCA-treated patients with PBC followed for up to 5 years (average of 3 years), and appeared to demonstrate good correlation of a >2.1 kPa annual increase with risk of adverse outcomes (ie, 8.4-fold greater risk of progression to hepatic decompensation, liver transplant or death, $p<0.0001$). However, the use of TE as a non-invasive means to identify and monitor patients with PBC who may be at potentially greater risk of progression to adverse outcomes requires further study.

Page 72: The statement "*In summary, the pivotal study demonstrated clinically meaningful improvement in the primary composite endpoint shown to be associated with clinical benefit*" should be modified to **"***In summary, in the pivotal study OCA treatment demonstrated achievement of the primary composite endpoint, the components of which – ALP and total bilirubin – have been shown to be predictive of adverse clinical outcomes***"**.