Errata to the FDA Briefing Document

Oncologic Drugs Advisory Committee (ODAC) Meeting

October 10, 2018

BLA 761088

CT-P10, a proposed biosimilar to US-Rituxan (rituximab)

Applicant: Celltrion, Inc.

Errata to the FDA Briefing Document

ODAC Meeting

Page	Original	Corrected
Page 6	The Applicant is seeking licensure of CT-P10 for the following proposed indications:	The Applicant is seeking licensure of CT-P10 for the following **US-licensed Rituxan** indications:
Page 10	"Upon rituximab binding to CD20-expressing cells, macrophages recognize the bound rituximab through FcγRs (e.g., FcγIIa), ultimately triggering phagocytosis."	"Upon rituximab binding to CD20-expressing cells, macrophages recognize the bound rituximab through FcγRs (e.g., **FcγRIIa**), ultimately triggering phagocytosis."
Page 11, Figure 1	"FcγIIa" "FcγIIIa"	"**FcγRIIa**" "**FcγRIIIa**".
Page 16	"Of the 15 CT-P10 drug product lots tested, 12 (80%) are within the QR (9.74 - 10.76 mg/mL) defined by the variability in protein concentration observed in US-licensed Rituxan."	"Of the 15 CT-P10 drug product lots tested, 12 (80%) are within the QR (9.74 **- 10.75** mg/mL) defined by the variability in protein concentration observed in US-licensed Rituxan."
Page 23	"To elucidate the difference observed in the IEC-HPLC profiles, the Applicant performed a peak characterization study using one lot of each drug product to determine the constituents with in the acidic, main and basic peaks."	"To elucidate the difference observed in the IEC-HPLC profiles, the Applicant performed a peak characterization study using one lot of each drug product to determine the constituents **within** the acidic, main and basic peaks."
Page 24	"HC Asn55 is located within the complementarity determining region (CDR), however the assessment of the purified peaks shows no significant increase of CD20 binding for the fractionated peaks 1 and 2 compared to the unfractionated antibody."	"HC Asn55 is located within the complementarity determining region (CDR), however the assessment of the purified peaks shows no significant **change** of CD20 binding for the fractionated peaks 1 and 2 compared to the unfractionated antibody."
	"Studies have shown that N-glycan sialylation in antibodies may impact FcγR binding and decrease effector function [30, 31]."	"Studies have shown that N-glycan sialylation in antibodies may impact FcγR binding and decrease effector function [**39, 40**]." **Added the following references (on page 66):**

		39. Scallon, B.J., et al., Higher levels of sialylated Fc glycans in immunoglobulin G molecules can adversely impact functionality. Mol Immunol, 2007. 44(7): p. 1524-34. 40. Li, T., et al., Modulating IgG effector function by Fc glycan engineering. Proc Natl Acad Sci U S A, 2017. 114(13): p. 3485-3490.
	"Slightly lower level of N-glycan sialylation is observed in the CT-P10 lots compared to the US-licensed Rituxan and EU-approved MabThera lots (Table 3)."	"**The CT-P10 lot contains a slightly lower level of N-glycan sialylation in the acidic peaks** compared to the US-licensed Rituxan and EU-approved MabThera lots (Table 3)."
Page 25	"A slight difference in the level of N- and C-terminal variants may contribute, in part, to the difference seen in the basic peaks. Numerous publications have shown that the C-terminal lysine is cleaved…"	"A slight difference in the level**s** of N- and C-terminal variants may contribute, in part, to the difference seen in the basic peaks. **N-terminal sequence variants are commonly observed in monoclonal antibody products and are not expected to affect the higher order structure of the antibody or antigen binding [30].** Numerous publications have shown that the C-terminal lysine is cleaved…"
	"CT-P10 lots are mostly within the QRs established by the analyzed US-licensed Rituxan lots, except for 2-3 CT-P10 lots which were just outside of US-Rituxan QRs for Met 365 and Met388 residues."	"CT-P10 lots are mostly within the QRs established by the analyzed US-licensed Rituxan lots, except for 2-3 CT-P10 lots which were just outside of US-Rituxan QRs for **Asn**365 and **Asn**388 residues."
Page 37, Figure 20	"FcγRn" in the title of the figure (located on upper right corner)	"**FcRn**"
Page 41-42	AUC_{0-t}	AUC_{0-last}
Page 42	"The PK of CT-P10 was also compared to that ofUS-Rituxan in a randomized, double-blind, 2-arm, parallel-group study conducted in patients with advanced follicular lymphoma (AFL) (Study CT-P10 3.3). CT-P10 (n = 59) or US-Rituxan (n = 62) was administered as weekly 375 mg/m2 IV infusions with concomitant drugs every 3 weeks up to 8 cycles to patients with AFL."	"The PK of CT-P10 was also compared to that ofUS-Rituxan in a randomized, double-blind, 2-arm, parallel-group study conducted in patients with advanced follicular lymphoma (AFL) (Study CT-P10 3.3). CT-P10 (n = 59) or US-Rituxan (n = 62) was administered ~~as weekly~~ 375 mg/m2 IV infusions with concomitant drugs every 3 weeks up to 8 cycles to patients with AFL."

<table>
<tr><td></td><td>“The Cmax and Ctrough were compared in patients with low tumor burden follicular lymphoma (LTBFL) in Study CT-P10 3.4 administered CT-P10 (n = 130) or US-Rituxan (n = I28) as monotherapy. These patients received weekly 375 mg/m2 IV infusions for 4 weeks (induction period) and every 8 weeks thereafter, up to a maximum 6 cycles (maintenance period).”</td><td>“The Cmax and Ctrough were compared in patients with low tumor burden follicular lymphoma (LTBFL) in Study CT-P10 3.4 administered CT-P10 (n = 130) or US-Rituxan (n = I28) as monotherapy. These patients received weekly 375 mg/m2 IV infusions for 4 weeks (induction period) and every 8 weeks thereafter, up to a maximum 13 cycles (maintenance period).”</td></tr>
<tr><td>Page 42, Table 8</td><td><table><tr><th></th><th>CT-P10 vs. US-Rituxan*</th></tr><tr><td>Primary parameter</td><td></td></tr><tr><td>$AUC_{0\text{-}14d}$ (h*mcg/mL)</td><td>98.9 (90.8 - 108)</td></tr><tr><td>$AUC_{0\text{-}last}$ (h*mcg/mL)</td><td>98.5 (88.7 - 110)</td></tr><tr><td>$AUC_{0\text{-}inf}$ (h*mcg/mL)</td><td>97.1 (87.9 - 104)</td></tr><tr><td>Secondary parameter</td><td></td></tr><tr><td>C_{max} (mcg/mL)</td><td>96.7 (90.3 - 104)</td></tr></table></td><td>Delete two rows in table<table><tr><th></th><th>CT-P10 vs. US-Rituxan*</th></tr><tr><td>$AUC_{0\text{-}14d}$ (h*mcg/mL)</td><td>98.9 (90.8 - 108)</td></tr><tr><td>$AUC_{0\text{-}last}$ (h*mcg/mL)</td><td>98.5 (88.7 - 110)</td></tr><tr><td>$AUC_{0\text{-}\infty}$ (h*mcg/mL)</td><td>97.1 (87.9 - 104)</td></tr><tr><td>C_{max} (mcg/mL)</td><td>96.7 (90.3 - 104)</td></tr></table></td></tr>
<tr><td>Page 45</td><td>“Up to 8 treatment cycles of -10 or US-Rituxan were administered after which patients were evaluated for disease response.”</td><td>“Up to 8 treatment cycles of CT-10 or US-Rituxan were administered after which patients were evaluated for disease response.”</td></tr>
<tr><td>Page 47</td><td>“OS defined as the interval between randomization and death from any”</td><td>“OS defined as the interval between randomization and death from any cause.”</td></tr>
<tr><td>Page 48</td><td>“The Kaplan-Meier curves of the duration of response are shown in Figure 23. The median duration of response was not estimable (NE) in the CT-P10 arm (95% CI, 28.3, NE) vs. 28.6 months in the US-Rituxan arm (95% CI, NE, NE). The Kaplan-Meier curves do not show significant differences with respect to duration of response.”
“The Kaplan-Meier curves of the duration of response are shown in the following figure. The median duration of response was not estimable (NE) in the CT-P10 arm (95% CI, 28.3, NE) vs. 28.6 months in the US-Rituxan arm (95% CI, NE, NE).”</td><td>Delete the statement “The Kaplan-Meier curves of the duration of response are shown in the following figure. The median duration of response was not estimable (NE) in the CT-P10 arm (95% CI, 28.3, NE) vs. 28.6 months in the US-Rituxan arm (95% CI, NE, NE).</td></tr>
</table>

Page 49	"The median PFS 31.2 months in the CT-P10 arm (95% CI, NE, NE) vs. 31.1 months in the US-Rituxan arm (95% CI, NE, NE)."	"The median PFS 31.2 months in the CT-P10 arm (95% CI, NE, NE) vs. 31.1 months in the US-Rituxan arm (95% CI, 31.1, NE)."
Page 52	"Randomization was stratified by region (Asia Pacific vs. Europe vs. North America and other), Ann Arbor stage (II vs. III vs. IV), and age (≤ 60 vs.< 60 years)."	"Randomization was stratified by region (Asia Pacific vs. Europe vs. North America and other), Ann Arbor stage (II vs. III vs. IV), and age (≥ 60 vs.< 60 years)."
Page 57	"In study CT-P10 3.3, the estimated ORR difference was 5.7% (90% CI, 14.7%) at MC3 (i.e. Up to 7 months)."	"In study CT-P10 3.3, the estimated ORR difference was 5.7% (90% CI, -1.7%, 14.7%) during the core study period or induction period."
Page 59, Table 16	"Subjects With at Least One TEAE: 94 (72.3), 90 (70.3)"	"Subjects With at Least One TEAE: **92 (70.8)**, **86 (67.2)**"
	"Subjects With at Least One SAE: 7(5.4)"	"Subjects With at Least One SAE: **6(4.6)**"
Page 59-60, Table 17	"Asthenia 5(5.7), 7(10.0)"; "Hypertension 5(7.1), 3(4.3)"	"Asthenia **4**(5.7), 7(10.0)"; "Hypertension 5(7.1), **2(2.9)**"
Page 60, Table 18	"Diarrhea 8(6.2), 12(9.3)"; "Neutropenia 3(2.3), 3(2.3)"	"Asthenia **4**(5.7), 7(10.0)"; "Diarrhea 8(6.2), **6(4.7)**"; "Neutropenia **1(0.8)**, 3(2.3)"
Page 61	"Among the patients with TEAE of neutropenia, 18 in the CT-P10 treatment group and 7 in the US-Rituxan group had bone marrow involvement at baseline."	"Diarrhea 8(6.2), **6(4.7)**"; "Among the patients with TEAE of neutropenia **during the Core Study Period, 19** in the CT-P10 treatment group and 7 in the US-Rituxan group had bone marrow involvement at baseline."
Page 61, Table 19	"Cardiac disorders: 4(3.1), 7(5.5)"	"Cardiac disorders: 4(**5.7**), 7(**10.0**)"