Errata to the FDA Briefing Document
GIDAC Advisory Committee Meeting
April 7, 2016

1. Page 11-12

Original text:

The pre-specified primary analysis was a responder analysis, and the definition of the response was a composite of three criteria:

- a reduction of ALP below 1.67×ULN at Month 12 **and**
- a reduction of ALP ≥ 15% at Month 12 **and**
- a reduction of total bilirubin to < ULN at Month 12

Revised text:

The pre-specified primary analysis was a responder analysis at Month 12, and the definition of the response was a composite of three criteria:

- ALP < 1.67 x ULN and
- Total bilirubin within normal limits, and
- ALP decrease of ≥ 15%

2. Page 15

Original text:

Specifically, we recommend a starting dose of 5 mg 2 times a week, and then up titration to 3 times a week based on tolerability and biochemical response.

Revised text:

Specifically, we recommend a starting dose of 5 mg once a week, and then up titration to 5 mg twice a week, and then 10 mg twice a week, based on tolerability and biochemical response.

3. Page 61:

Original table:

Pruritus	**Placebo (n=38)**	**OCA 10mg (n=38)**	**OCA 25mg (n=48)**	**OCA 50mg (n=41)**
Mild	16 (84%)	8 (44%)	21 (50%)	12 (36%)
Moderate	5 (26%)	8 (44%)	19 (45%)	21 (64%)
Severe	0 (0%)	6 (33%)	9 (21%0	15 (45%)
Total	**19 (50%)**	**18 (47%)**	**41 (85%)**	**33 (80%)**

Table 19: Pruritus safety population - N=165

Revised table:

Table 19: Summary of Pruritus TEAEs and Severity

Summary by MedDRA Preferred Term (Safety Population: N=165)				
	Placebo (n=38)	**OCA 10mg (n=38)**	**OCA 25mg (n=48)**	**OCA 50mg (n=41)**
Subjects with TEAE of Pruritus	19 (50%)	18 (47%)	41 (85%)	33 (80%)
Subjects with TEAE of Pruritus	0	0	1 (2%)	0
Summary of Pruritus TEAEs by Severity (Subjects with at least 1 TEAE of Pruritus: N=112)				
	Placebo (n=19)	**OCA 10mg (n=18)**	**OCA 25mg (n=42)**	**OCA 50mg (n=33)**
Mild	16 (84%)	8 (44%)	21 (50%)	12 (36%)
Moderate	5 (26%)	8 (44%)	19 (45%)	21 (64%)
Severe	0 (0%)	6 (33%)	9 (21%)	15 (45%)

4. Page 71:

Original text:

Primary Endpoint

ALP and TB composite response criteria at Month 12; a patient was designated as a responder if **all three** of the following conditions were met:

• 12-Month value of ALP < 1.67×ULN

• ALP reduction from baseline at Month 12 ≥ 15%

• 12-Month value of TB < ULN

Revised text:

Primary Endpoint

Proportion of patients meeting ALP and TB composite response criteria at Month 12; a patient was designated as a responder if **all three** of the following conditions were met:

- ALP < 1.67x ULN and
- total bilirubin ≤ ULN, and
- ALP decrease of ≥ 15% from baseline

5. Page 90:

Original table:

Table 28: TB Summary at Month 12 (ITT)

Time Point/Statistics	10 mg OCA (N = 73)	OCA Titration (N = 70)	Placebo (N = 73)
Baseline TB Concentration (µmol/L)			
n	73	70	73
Mean (SD)	11.3 (6.69)	10.3 (5.51)	11.8 (7.38)
Median	9.2	9.1	9.2
Min, Max	2, 34	2, 36	2, 39
Month 12 TB Concentration (µmol/L)			
n	63	64	70
Mean (SD)	9.6 (4.68)	9.9 (4.82)	13.2 (8.69)
Median	7.9	8.2	9.8
Min, Max	2, 25	4, 28	4, 45
Absolute Change from Baseline to Month 12 (µmol/L)			
n	63	64	70
Mean (SD)	-1.2 (4.36)	-0.62 (3.33)	1.4 (4.13)
Median	-0.46	-0.34	1.3
Min, Max	-18, 7	-9, 7	-7, 20
Percentage Change from Baseline to Month 12 (%)			

n	63	64	70
Mean (SD)	-1.1 (36.19)	1.3 (34.71)	17.0 (41.54)
Median	-5.1	-5.0	12.4
Min, Max	-51, 194	-51, 125	-43, 211
Baseline TB Concentration (×ULN)			
n	73	70	73
Mean (SD)	0.558 (0.3162)	0.514 (0.2490)	0.598 (0.3733)
Median	0.473	0.456	0.478
Min, Max	0.08, 1.78	0.11, 1.43	0.12, 2.03
Month 12 TB Concentration (×ULN)			
n	63	64	70
Mean (SD)	0.479 (0.2332)	0.496 (0.2221)	0.660 (0.4097)
Median	0.407	0.416	0.496
Min, Max	0.12, 1.28	0.22, 1.12	0.23, 1.96
TB ≤ 1.0×ULN at Month 12 – n (%)	**68 (93.2%)**	**68 (97.1%)**	**60 (82.2%)**
TB ≥ 1.0×ULN at Baseline – n (%)	7 (9.6%)	4 (5.7%)	7 (9.6%)
TB < 1.0×ULN at Month 12 – n (%) [1]	**5 (71.4%)**	**2 (50.0%)**	**1 (14.3%)**

Revised table:

Table 28: TB Summary at Month 12 (ITT)

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Min, Max	-51, 194	-51, 125	-43, 211
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Median	0.473	0.456	0.478
Min, Max	0.08, 1.78	0.11, 1.43	0.12, 2.03
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n	63	64	70
Mean (SD)	0.479 (0.2332)	0.496 (0.2221)	0.660 (0.4097)
Median	0.407	0.416	0.496
Min, Max	0.12, 1.28	0.22, 1.12	0.23, 1.96
TB ≤ 1.0×ULN at Month 12 – n (%)	**60 (82.2%)**	**62 (88.6%)**	**57 (78.1%)**
TB > 1.0×ULN at Baseline – n (%)	7 (9.6%)	4 (5.7%)	7 (9.6%)
TB ≤ 1.0×ULN at Month 12 – n (%) [1]	**5 (71.4%)**	**2 (50.0%)**	**1 (14.3%)**

6. Page 107:

Original table:

Table 1: Subjects with Adverse Events Leading to Study Discontinuation: Safety Population (N = 216)

Patient ID**	Preferred Term	Time to Onset[1]	Duration (days) of AE	Severity	Outcomes
PLACEBO					
1	Headache	43	29	Mild	Resolved
	Abdominal distension	66	6	Moderate	
	Nausea	66	6	Moderate	
	Vomiting	66	6	Moderate	
2	Rash	2	34	Moderate	Resolved
3	Consent withdrawn				Unknown
OCA TITRATION					
4	Hallucination	7	2	Moderate	Resolved

[1] For adverse events that start on or after the first dose of study drug, the time to onset of the adverse event is calculated as the start date - date of first dose of investigational product + 1. For adverse events that occur prior to the first dose of study drug, the time to onset is calculated as the start date – first dose of study drug.

5	Pruritus	221	32	Severe	Resolved
6	Cardiac failure	257	37	Severe	Fatal/patient died
7	Consent withdrawn				Unknown
8	Pruritus	47	27	Severe	Resolved
9	Pruritus	82	38	Severe	Resolved
10	Pruritus	9	153	Severe	Resolved
OCA 10 mg					
11	Pruritus	6	11	Severe	mild pruritus Ongoing
12	Pruritus	86	40	Severe	Resolved
13	Pruritus	11	9	Severe	Resolved
14	Contusion	67	6	Mild	Resolved
15	Pruritus	52	18	Severe	Resolved
	Withdrew consent				Unknown

Revised table:

Patient ID**	**Preferred Term**	**Time to Onset [2]**	**Duration (days) of AE**	**Severity**	**Outcomes**
PLACEBO					
1	Headache	43	29	Mild	Resolved
	Abdominal	66	6	Moderate	

[2] For adverse events that start on or after the first dose of study drug, the time to onset of the adverse event is calculated as the start date - date of first dose of investigational product + 1. For adverse events that occur prior to the first dose of study drug, the time to onset is calculated as the start date – first dose of study drug.

	distension				
	Nausea	66	6	Moderate	
	Vomiting	66	6	Moderate	
2	Rash	2	34	Moderate	Resolved
3	Consent withdrawn				Unknown
OCA TITRATION					
4	Hallucination	7	2	Moderate	Resolved
5	Pruritus	221	32	Severe	Resolved
6	Diarrhea	288	82	Moderate	Resolved
7	Interstitial lung disease	218	10	Moderate	Resolved
8	Cardiac failure	257	37	Severe	Fatal/patient died
9	Consent withdrawn				Unknown
OCA 10 mg					
10	Pruritus	47	27	Severe	Resolved
11	Pruritus	82	38	Severe	Resolved
12	Pruritus	9	153	Severe	Resolved
13	Pruritus	6	11	Severe	Ongoing mild pruritus
14	Pruritus	86	40	Severe	Resolved
15	Pruritus	11	9	Severe	Resolved
16	Contusion	67	6	Mild	Resolved
17	Pruritus	52	18	Severe	Resolved
18	Withdrew				Unknown

	consent				

7. Page 116:

Original text:

A total of 4 cardiovascular SAEs were reported in 3 subjects: 1 subject in the placebo group experienced sick sinus syndrome and 1 subject in the OCA titration group had 2 SAEs of cardiac failure, 1 of which was fatal.

Revised text:

A total of 4 cardiovascular SAEs were reported in 2 subjects; 1 subject in the placebo group experienced sick sinus syndrome and chest pain and 1 subject in the OCA titration group had 2 SAEs of cardiac failure, 1 of which was fatal.

8. Page 162:

Original table:

Table 5: Statistical comparison of AUC0-t and Cmax of OCA and its conjugates in hepatic impairment (747-103)

		OCA		**Glyco-OCA**		**Tauro-OCA**		**Total OCA**	
Comparison	Param-eters	GMR*	90% CI	GMR	90% CI	GMR	90% CI	GMR	90% CI
Mild vs Normal	AUC	1.38	72.8 - 261	1.27	64.7 - 250	7.09	29.6 – 170	1.13	56.5 – 225
	Cmax	1.35	79.8 - 228	1.43	79.5 - 256	8.72	40.4 – 188	1.49	86.3 – 256
Moderate vs Normal	AUC	2.41	127 - 456	3.33	169 – 654	6.86	286 – 1640	4.20	211 – 838
	Cmax	1.91	113 - 323	3.73	208 - 670	5.63	261 – 1220	3.76	218 – 647
Severe vs Normal	AUC	7.03	372 - 1330	11.40	579 - 2240	36.80	1540 – 8830	17.30	867 – 3440
	Cmax	4.70	278 - 796	8.12	452 - 1460	21.40	991 - 4630	9.75	566 - 1680

*GMR= Geometric mean ratio

Revised table:

Table 5: Statistical comparison of AUC0-t and Cmax of OCA and its conjugates in hepatic impairment (747-103)

		OCA		**Glyco-OCA**		**Tauro-OCA**		**Total OCA**	
Comparison	Param-eters	GMR*	90% CI	GMR	90% CI	GMR	90% CI	GMR	90% CI
Mild vs Normal	AUC	1.38	0.73 – 2.61	1.27	0.65 – 2.50	0.71	0.30 – 1.70	1.13	0.57 – 2.25
	Cmax	1.35	0.80 – 2.28	1.43	0.80 – 2.56	0.87	0.40 – 1.88	1.49	0.86 – 2.56
Moderate vs Normal	AUC	2.41	1.27 – 4.56	3.33	1.69 – 6.54	6.86	2.86 – 16.43	4.20	2.11 – 8.38
	Cmax	1.91	1.13 – 3.23	3.73	2.08 – 6.70	5.63	2.61 – 12.17	3.76	2.18 – 6.47
Severe vs Normal	AUC	7.03	3.72 – 13.30	11.38	5.79 – 22.36	36.84	15.37 – 88.30	17.28	8.67 – 34.44
	Cmax	4.70	2.78 – 7.96	8.12	4.52 – 14.58	21.42	9.91 – 46.27	9.75	5.66 – 16.80

*GMR= Geometric mean ratio