Errata to FDA Briefing Document
Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting
09/13/2024

This erratum contains corrections to FDA's Briefing Document for the September 13, 2024, Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting. The committee will discuss new drug application (NDA) 207999 Supplement 011, submitted by Intercept Pharmaceuticals, Inc. for obeticholic acid (OCA, or Ocaliva) to reduce the risk of death, liver transplant, and hepatic decompensation in adults with primary biliary cholangitis (PBC) without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension, either in combination with ursodeoxycholic acid (UDCA) with an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA.

1) **Page 1, treatment indication, line numbers 20-26**

Treatment of adult patients with primary biliary cholangitis (PBC) without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension, either in combination with ursodeoxycholic acid (UDCA) with an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA.

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

To reduce the risk of death, liver transplant, and hepatic decompensation in adults ~~*Treatment of* adult patients~~ with primary biliary cholangitis (PBC) without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension, either in combination with ursodeoxycholic acid (UDCA) with an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA.

2) **Section 1.1, page 9, second last paragraph**

Despite some study patients now being contraindicated for continuing in Trial 747-302 it reached study closure and achieved the target number of events based on an expanded definition of the primary composite endpoint.

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

Despite **55% of** ~~some~~ study patients now being contraindicated for continuing in Trial 747-302, it reached study closure and achieved the target number of events based on an expanded definition of the primary composite endpoint.

3) **Section 1.2, page 11, third last paragraph from bottom of page**

In this document, PBC subjects in Trial 747-302 who remained eligible for OCA are called the "USPI-Labeled Population."

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

In this document, PBC subjects in Trial 747-302 who ~~remained eligible for OCA~~ **were classified as eligible for OCA at baseline** are called the "USPI-Labeled Population."

4) Section 1.2, page 12, second paragraph

"The Applicant considered using three databases: (1) Global PBC; (2) UK-PBC; and (3) Komodo. However, a Clean Room Committee (CRC) reported the following: (a) the Global PBC was inadequate for use due to an "insufficient sample size"; (b) the UK-PBC database was also inadequate for use due to data deficiencies, i.e., "obvious problems with the data."

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

The Applicant considered using three databases: (1) Global PBC; (2) UK-PBC; and (3) Komodo **as potential sources of externals controls for Study 302**. However, a Clean Room Committee (CRC) reported the following: (a) the Global PBC was inadequate for use due to an "insufficient sample size"; (b) the UK-PBC database was also inadequate for use due to data deficiencies, i.e., ~~"obvious problems with the data."~~ "**suitability for the specific data requirements needed for the Study 302 external control analysis were not met**."

5) Section 4.1, page 23, first paragraph titled "Summary of Safety"

Subjects were not enrolled in Trial 747-301 if they had pruritus at baseline.

Revised text (additions in bolded and underlined font):

Subjects were not enrolled in Trial 747-301 if they had **"severe"** pruritus **or those requiring systemic treatment for pruritus (e.g., with bile acid sequestrants [BAS] or rifampicin)** at baseline.

6) Section 4.2.1.2, page 25, second paragraph

Hepatocellular carcinoma was removed as an efficacy endpoint in protocol version 4, submitted in September 2017.

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

Hepatocellular carcinoma was ~~removed as an~~ **redefined from a primary** efficacy endpoint **to a secondary efficacy endpoint** in protocol version 4, submitted in September 2017.

7) Section 4.2.1.4, page 27, third paragraph

Subjects who did not meet any of these criteria were adjudicated as USPI-labeled and with the current labeling would be considered the appropriate population for treatment.

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

Subjects who did not meet any of these criteria **at baseline** were ~~adjudicated~~ **determined** as USPI-labeled and with the current labeling would be considered the appropriate population for treatment.

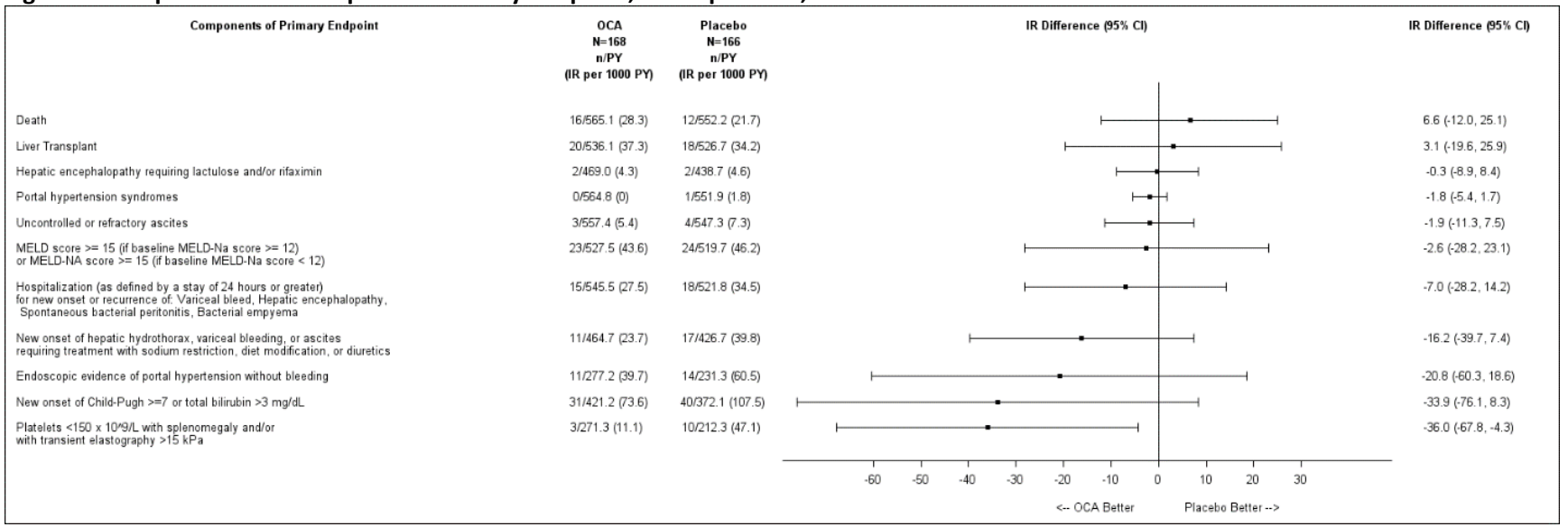
8) Section 4.2.3, page 36 (Figure 6) and Section 8.3.6, page 79 (Figure 11)

Revised text (additions in bolded and underlined font)

Patient-years are updated to include all on-study time at risk. See Revised Figure 6 below.

Revised Figure 6

Figure 6. Components of the Expanded Primary Endpoint, ITT Population, Trial 747-302



Source: Statistical reviewer analysis using Applicant submitted dataset adevt,xpt and adsl.xpt.

[1]According to the Applicant, if an expanded endpoint components trigger occurred after any positively adjudicated endpoint event, the trigger was not sent for adjudication. Thus, the expanded endpoint components may not be reliably captured in this analysis.

[2]The incidence rate (IR) is calculated by dividing the number of subjects who experienced the event by the total number of patient-years (PYs) of at-risk time and multiplying by 1000. At-risk time for a subject who experienced an event is time from randomization to the first event, and at-risk time for a subject who did not experience an event is time from randomization to end of study. Analysis of each component ignores the occurrence of other components and important intercurrent events (e.g., deaths)

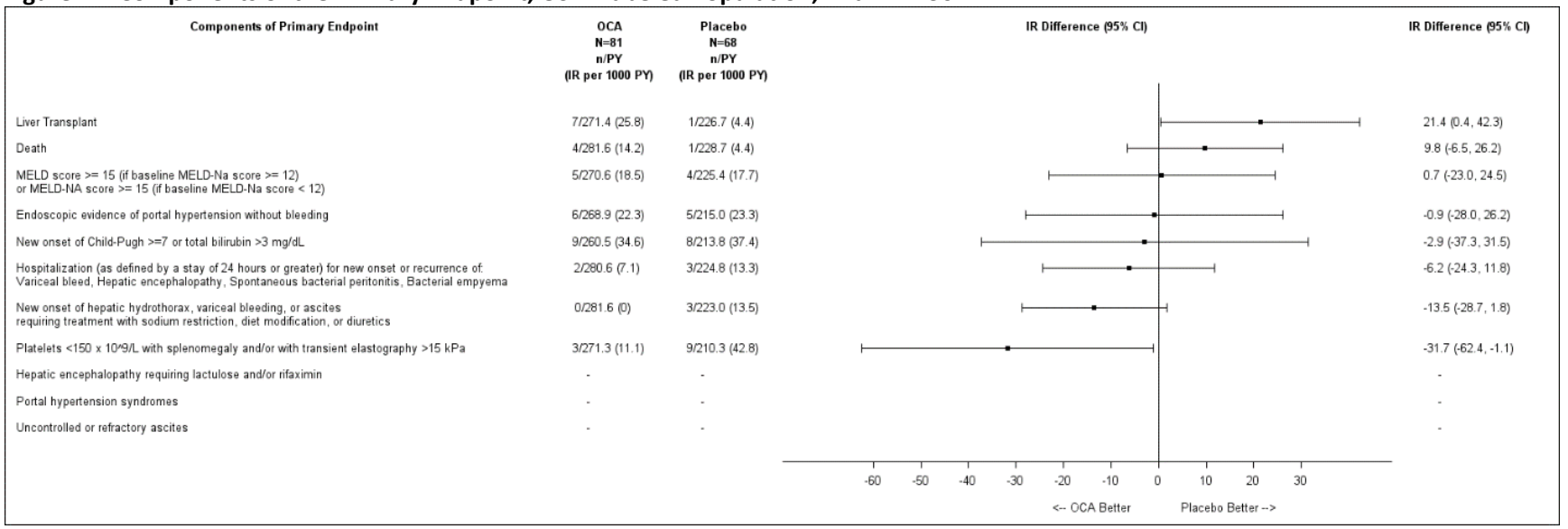
[3] IR difference is calculated by subtracting the IR of events in the placebo arm from the IR of events in the OCA arm

The 95% confidence interval was calculated based on normal approximation and $\hat{\sigma}(IR) = \sqrt{n/PY^2}$

Abbreviations: OCA, obeticholic acid; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with event; PY, patient-year; IR, incidence rate

Revised Figure 11

Figure 11. Components of the Primary Endpoint, USPI-Labeled Population, Trial 747-302



Source: Statistical reviewer analysis using Applicant submitted dataset adevt,xpt

[1]According to the Applicant, if an expanded endpoint components trigger occurred after any positively adjudicated endpoint event, the trigger was not sent for adjudication. Thus, the expanded endpoint components may not be reliably captured in this analysis.

[2]The incidence rate (IR) is calculated by dividing the number of subjects who experienced the event by the total number of patient-years (PYs) of at-risk time and multiplying by 1000. At-risk time for a subject who experienced an event is time from randomization to the first event, and at-risk time for a subject who did not experience an event is time from randomization to end of study.

Analysis of each component ignores the occurrence of other components and important intercurrent events (e.g., deaths)

[3] IR difference is calculated by subtracting the IR of events in the placebo arm from the IR of events in the OCA arm

The 95% confidence interval was calculated based on normal approximation and $\hat{\sigma}(IR) = \sqrt{n/PY^2}$

Abbreviations: CI, confidence interval; IR, incidence rate; N, number of subjects in treatment arm; n, number of subjects with event; OCA, obeticholic acid; PY, patient-years

9) Section 4.2.4.2, Page 39, last paragraph

"At baseline, this subject had a baseline MELD score of 8.4, laboratory parameters within the normal ranges, and …."

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

"At baseline, this subject had a baseline MELD score of 8.4, laboratory parameters ~~within the normal ranges~~ **consistent with the subject's underlying disease**, and… "

10) Section 4.2.4.4.2, Page 43 (Table 9)

Error for IR values for the "Overall Safety Population", SAE of pruritus, Total OCA group
Replace IR = .04 with correct value of IR = 0.421

11) Section 4.2.4.4.2, Page 43 (Table 9)

Error for IR values for "Overall Safety Population", Pruritus requiring treatment, Total Placebo group. Replace IR = 46.5 with correct value of IR = 14.825

12) Section 4.3.3, Page 51 (Table 13)

Table 13: Baseline Demographics and Clinical Characteristics, Patients Treated With Obeticholic Acid (OCA) and Control Periods Before and After Statistical Weighting, Study 747-405

		Non-OCA-treated	
	OCA-treated N=403 n (%)	Before Weighting N=11,246 n (%)	After Weighting N=405.37 n (%)
<=1.2 mg/dL	360 (89.3)	10,159 (90.3)	363.9 (89.8)
>1.2 mg/dL	43 (10.7)	1,087 (9.7)	41.47 10.2)

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

Table 13. Baseline Demographics and Clinical Characteristics, Patients Treated With Obeticholic Acid (OCA) and Control Periods Before and After Statistical Weighting, Study 747-405

Parameter	Treated With OCA N=403		Not Treated With OCA			
			Unweighted N=11,246		Weighted N=405.37	
	n	%	n	%	n	%
~~Total bilirubin (TB)~~						
~~≤1.2 mg/dL~~	~~329~~	~~81.6~~	~~9,434~~	~~83.9~~	~~332.66~~	~~82.1~~
~~>1.2 mg/dL~~	~~74~~	~~18.4~~	~~1,812~~	~~16.1~~	~~72.70~~	~~17.9~~
Total bilirubin (TB)						
≤1.2 mg/dL	**360**	**89.3**	**10,159**	**90.3**	**363.90**	**89.8**
>1.2 mg/dL	**43**	**10.7**	**1,087**	**9.7**	**41.47**	**10.2**

13) Section 83.8.1, page 84 (Table 32)

Revised text (deletions in strikethrough font and additions in bolded font noted)

1. One OCA-treated subject who had myocardial infarction **one year prior to death. At the time of death, the subject continued to have ongoing liver disease.**

2. One placebo-treated subject was hospitalized with hepatic encephalopathy **five months prior to event of death. At the time of subject's death, the liver disease was ongoing.**

Footnote: The AEs leading to death are not from adae.xpt dataset but were noted in the subject narratives.

14) Section 8.3.9, Page 88, first paragraph

One subject had one quantifiable PK sample at screening and four subjects had quantifiable PK samples in the follow-up phase. The reason for OCA exposure in subjects in Study 747-302 treated with OCA in the placebo arm was not fully documented.

Revised text (additions in bolded font):

One subject **(out of 40 subjects)** had one quantifiable PK sample at screening and four subjects **(out of 40 subjects)** had quantifiable PK samples in the follow-up phase. **Of these four subjects' with quantifiable PK samples in the follow-up phase, three subjects had documented commercial OCA use.** The reason for OCA exposure in subjects in Study 747-302 treated with OCA in the placebo arm was not fully documented.

15) Section 8.3.8.4 page 86 – 87 (Table 34 and Table 35)

Tables 34 and 35 revised to include AEs that began after initiation of investigational product. Calculations censor both the patient counts and patient time.

Revised Table 34: Overview of Adverse Events, Safety Population, Trial 747-302- Overall

Event Category	Total-OCA PY=564.2 N=168 n/py (EAIR)	Total-Placebo PY=551.4 N=166 n/py (EAIR)	EAIR Difference (95% CI)
SAE	67/433.5 (15.5)	75/416.7 (18.0)	-2.5 (-8.2, 3.0)
SAEs with fatal outcome	15/563.2 (2.7)	11/550.5 (2.0)	0.7 (-1.2, 2.6)
Life-threatening SAEs	4/559.3 (0.7)	2/542.6 (0.4)	0.3 (-0.7, 1.5)
SAEs requiring hospitalization	66/434.7 (15.2)	70/427.9 (16.4)	-1.2 (-6.6, 4.2)
SAEs resulting in substantial disruption of normal life functions	7/559.2 (1.3)	3/541.7 (0.6)	0.7 (-0.5, 2.1)
Other	26/529.3 (4.9)	25/515.8 (4.8)	0.1 (-2.7, 2.8)
AE leading to permanent discontinuation of study drug	63/466.1 (13.5)	48/480.2 (10.0)	3.5 (-0.9, 8.0)
AE leading to dose modification of study drug	82/321.7 (25.5)	61/432.3 (14.1)	11.4 (5.0, 18.3) *
AE leading to interruption of study drug	48/425.9 (11.3)	44/472.5 (9.3)	2.0 (-2.3, 6.3)
AE leading to reduction of study drug	44/433.2 (10.2)	23/503.3 (4.6)	5.6 (2.2, 9.4) *
AE leading to dose delay of study drug	0/564.2 (0)	0/551.4 (0)	0.0 (-0.7, 0.7)
Any AE	162/45.7 (354.8)	160/67.2 (238.1)	116.7 (52.4, 185.0) *
Severe and worse	93/357.7 (26.0)	84/395 (21.3)	4.7 (-2.2, 11.9)
Moderate	53/397.6 (13.3)	55/413.6 (13.3)	0.0 (-5.1, 5.2)
Mild	16/519.1 (3.1)	21/499.7 (4.2)	-1.1 (-3.7, 1.3)

Source: adae.xpt, adsl.xpt; Software: R

Treatment-emergent adverse events (TEAE) are defined as any event starting on or after the first dose of the investigational product till the end of study, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product till the end of study (on-study TEAE).

Study duration is up to 2398 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Severity as assessed by the investigator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Total person-year at risk (py) is calculated as the total time until the initial occurrence of the event for subjects who experienced an event or, the end of follow-up (which is end of the study) for subjects who did not, among subjects at risk at the beginning of the study.

Total person-year (PY) is calculated as the total time until the end of follow-up (which is end of the study), among subjects at risk at the beginning of the study.

$$\frac{\text{Number of subjects who have experienced at least one event}}{\text{Total person years at risk}} \times 100$$

Risk Based - Exposure Adjusted Incidence Rate (EAIR) is calculated as the

Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incident rate (per 100 person-years); N, number of patients in treatment arm; n, number of patients with at least one event; OCA, obeticholic acid; PY, total person-years; py, total person-years (at risk); SAE, serious adverse event

Revised Table 35: Overview of Adverse Events, Safety Population, Trial 747-302

	USPI-Labeled			USPI-Contraindicated		
Event Category	**OCA PY=281.5 N=81 n/py (EAIR)**	**Placebo PY=228.5 N=68 n/py (EAIR)**	**EAIR Difference (95% CI)**	**OCA PY=282.8 N=87 n/py (EAIR)**	**Placebo PY=322.9 N=98 n/py (EAIR)**	**EAIR Difference (95% CI)**
SAE	22/239.4 (9.2)	20/197.4 (10.1)	-0.9 (-7.3, 5.0)	45/194 (23.2)	55/219.2 (25.1)	-1.9 (-11.5, 7.8)
SAEs with fatal outcome	4/281.4 (1.4)	1/228.5 (0.4)	1.0 (-1.2, 3.3)	11/281.8 (3.9)	10/321.9 (3.1)	0.8 (-2.3, 4.2)
Life-threatening SAEs	1/281.3 (0.4)	0/228.5 (0)	0.4 (-1.3, 2.0)	3/278 (1.1)	2/314.1 (0.6)	0.4 (-1.4, 2.6)
SAEs requiring hospitalization	21/240.6 (8.7)	19/197.7 (9.6)	-0.9 (-7.1, 4.9)	45/194 (23.2)	51/230.2 (22.2)	1.0 (-8.1, 10.5)
SAEs resulting in substantial disruption of normal life functions	3/281.2 (1.1)	0/228.5 (0)	1.1 (-0.6, 3.1)	4/278 (1.4)	3/313.2 (1.0)	0.5 (-1.6, 2.8)
Other	7/271.6 (2.6)	5/223.3 (2.2)	0.3 (-2.9, 3.4)	19/257.7 (7.4)	20/292.5 (6.8)	0.5 (-4.0, 5.3)
AE leading to permanent discontinuation of study drug	27/232.8 (11.6)	21/201.8 (10.4)	1.2 (-5.4, 7.6)	36/233.3 (15.4)	27/278.4 (9.7)	5.7 (-0.4, 12.4)
AE leading to dose modification of study drug	34/178.5 (19.0)	23/185.6 (12.4)	6.7 (-1.5, 15.3)	48/143.1 (33.5)	38/246.7 (15.4)	18.1 (8.2, 29.9) *
AE leading to interruption of study drug	21/217.7 (9.6)	17/203.1 (8.4)	1.3 (-4.7, 7.3)	27/208.1 (13.0)	27/269.4 (10.0)	3.0 (-3.1, 9.6)
AE leading to reduction of study drug	19/228.3 (8.3)	7/208.4 (3.4)	5.0 (0.4, 10.0) *	25/204.9 (12.2)	16/294.8 (5.4)	6.8 (1.7, 13.0) *
AE leading to dose delay of study drug	0/281.5 (0)	0/228.5 (0)	0.0 (-1.7, 1.4)	0/282.8 (0)	0/322.9 (0)	0.0 (-1.2, 1.4)
Any AE	76/29.9 (254.1)	63/45 (140.1)	114.0 (49.9, 185.0) *	86/15.7 (546.2)	97/22.2 (436.1)	110.1 (-31.1, 260.6)
Severe and worse	40/184 (21.7)	25/178.7 (14.0)	7.7 (-1.0, 16.9)	53/173.8 (30.5)	59/216.3 (27.3)	3.2 (-7.5, 14.4)
Moderate	26/194.9 (13.3)	24/164.4 (14.6)	-1.3 (-9.5, 6.6)	27/202.8 (13.3)	31/249.2 (12.4)	0.9 (-5.8, 8.0)
Mild	10/252.8 (4.0)	14/197.8 (7.1)	-3.1 (-8.3, 1.2)	6/266.3 (2.3)	7/301.9 (2.3)	-0.1 (-2.8, 2.8)

Source: adae.xpt, adsl.xpt; Software: R

Treatment-emergent adverse events (TEAE) are defined as any event starting on or after the first dose of the investigational product till the end of study, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product till the end of study (on-study TEAE).

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Total person-year (PY) is calculated as the total time until the end of follow-up (which is end of the study), among subjects at risk at the beginning of the study.

Risk Based - Exposure Adjusted Incidence Rate (EAIR) is calculated as the

$$\frac{\text{Number of subjects who have experienced at least one event}}{\text{Total person years at risk}} \times 100$$

Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incident rate (per 100 person-years); N, number of patients in treatment arm; n, number of patients with at least one event; OCA, obeticholic acid; PY, total person-years; py, total person-years (at risk); SAE, serious adverse event