CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

OBETICHOLIC ACID (OCALIVA)

(Intercept Pharmaceuticals Canada, Inc.)

Indication: For the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date:	August 2017
Report Length:	64 Pages

CADTH

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

Abbreviations

ALP	alkaline phosphatase
AST	aspartate aminotransferase
CDR	CADTH Common Drug Review
CI	confidence interval
ITT	intention-to-treat
ELF	enhanced liver fibrosis
IWRS	interactive Web response system
LSMD	least squares mean difference
MCID	minimal clinically important difference
NOC/c	notice of compliance with conditions
OCA	obeticholic acid
PBC	primary biliary cholangitis
SD	standard deviation
TE	transient elastography
UDCA	ursodeoxycholic acid
ULN	upper limit of normal

Drug	Ocaliva (obeticholic acid) 5 mg or 10 mg
Indication	For the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.
Reimbursement Request	As per indication
Manufacturer	Intercept Pharmaceuticals Canada, Inc.

Executive Summary

Introduction

Primary biliary cholangitis (PBC) occurs as a result of immune-mediated damage to bile ducts, with an associated inflammatory response leading to progressive fibrosis and loss of patency. This loss of patency leads, in turn, to hepatic accumulation of bile acids, resulting in liver damage with progressive fibrosis and, potentially, cirrhosis. PBC is more common in women than in men and is the most common reason for liver transplant among women.[1] Patients with PBC report fatigue and pruritus as key symptoms that negatively impact quality of life. Patients are also clearly affected by the potential progression to severe liver disease and associated complications such as decompensated liver disease, hepatocellular carcinoma, liver transplant, and death. Thirty per cent of persons can progress to advanced liver disease, decompensated disease, or death.[2]

PBC is a relatively uncommon disease and affects between 9,000 and 11,000 Canadians,[3] mostly women between the ages of 50 and 70 years, although some patients are diagnosed at an earlier age according to the clinical expert consulted for this review. A 2009 study focusing on the Calgary Health Region found an incidence of 30 cases per million for PBC and a prevalence that had risen from 100 cases per million in 1996 to 227 cases per million in 2002.[1]

There is currently only one approved therapy for PBC in Canada — ursodeoxycholic acid (UDCA) — and more than 80% of patients with PBC receive UDCA.[3] Those patients who respond to UDCA tend to have improved clinical outcomes (e.g., transplant-free survival); however, about 40% to 50% of patients treated with UDCA do not respond to therapy.[4,5] There are also a small number of patients who are unable to tolerate UDCA, approximately 10% according to the clinical expert. In their input to the CADTH Common Drug Review (CDR), patient groups described gastrointestinal symptoms (diarrhea), weight gain, alopecia, dizziness, and flu-like adverse effects while on UDCA, in addition to PBC-related symptoms such as pruritus and fatigue.

Obeticholic acid (OCA) is a farnesoid X receptor agonist. Farnesoid receptors are a novel pharmacological target, and stimulation of these receptors appears to have multiple effects; in PBC, the most notable is the reduction in hepatocellular concentration of bile acids. OCA is approved by Health Canada for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. In approving OCA, Health Canada issued a notice of compliance with conditions (NOC/c) pending results of trials to verify the clinical benefit of OCA. One of these trials, study 747-302, was designed to evaluate OCA, either in combination with UDCA or as monotherapy in patients with early, moderately advanced, and advanced PBC, with a primary composite of clinical end points (e.g., death, transplant). The other trial, study 747-401, was designed to enrol a population of PBC patients with moderate to severe hepatic impairment (Child–Pugh class B and C).[6] The recommended starting dose in the Health Canada–approved product monograph is 5 mg by mouth daily; however, patients may up-titrate to 10 mg daily after six months to improve response if an adequate reduction in alkaline phosphatase (ALP) or total bilirubin has not been achieved. Continuation of OCA in a patient with no improvement in biochemical markers of PBC (ALP and bilirubin)

after one year on the maximum effective dose (10 mg) should be assessed based on the clinical course of PBC and the potential risks and benefits of continued use.[7]

Results and Interpretation

Included Studies

One manufacturer-sponsored, multi-centre, double-blind randomized controlled trial met the inclusion criteria for this CDR review. Study 747-301 (POISE) included adult patients with PBC who either had failed to achieve targets (either ALP or bilirubin) on UDCA or had not tolerated UDCA. These patients were randomized in a 1:1:1 manner to OCA 10 mg daily or placebo or a dose titration starting at 5 mg and increasing to 10 mg daily for those with an inadequate response. Of the two OCA interventions, the latter group reflects the Health Canada–approved recommended dose for OCA, as patients are not currently recommended to start on 10 mg daily of OCA therapy. Patients remained on therapy for 12 months. The study was designed to test the superiority of each of the OCA interventions to placebo, although the primary analysis tested the superiority of the OCA 10 mg intervention to placebo and the key secondary analysis tested the superiority of the OCA titration group to placebo. The primary outcome was a composite outcome that reflected the proportion of patients reaching targets for both ALP and bilirubin after 12 months of therapy.

Key critical appraisal issues of the POISE trial that may have affected internal validity included the potential for unblinding, with a higher proportion of OCA-treated patients than placebo patients experiencing pruritus, the lack of accounting for multiplicity in most of the secondary outcomes, and a numerically higher rate of withdrawals in the OCA-treated group versus placebo (10% versus 4%). Issues with blinding are less likely to affect the primary outcome, which relies on objective measures such as biomarkers. Issues that may have affected external validity included the lack of data for key clinical outcomes, the exclusion of patients with advanced liver disease, and the lack of an established minimal clinically important difference (MCID) for the primary outcome.

Efficacy

A larger proportion of OCA-treated patients achieved the composite outcome of ALP less than 1.67 times the upper limit of normal (ULN) and total bilirubin at ULN or lower, and decrease in ALP of 15% or more from baseline at 12 months compared with placebo (46% versus 10% of participants), and this difference was statistically significant (odds ratio 9.1; 95% confidence interval, 3.6 to 23.2; $P < 0.0001$). Among other secondary outcomes, OCA also reduced ALP (least squares mean difference [LSMD] −28.2% reduction; standard error 3.4; $P < 0.0001$) and bilirubin (LSMD −18.3% reduction; standard error 6.3; $P = 0.0039$) versus placebo. There was one death in the study, in a patient receiving OCA titration; otherwise, there were no events for other clinical outcomes such as morbidity, cirrhosis, and transplant. The lack of clinical outcomes and subsequent reliance on a surrogate outcome is a limitation of the efficacy results in POISE. The key surrogates used, ALP and bilirubin, appear to be accepted surrogate biomarkers in PBC, and any elevation above the ULN is considered likely to be clinically relevant (see Appendix 4). The lack of clinical events or of statistically significant changes in fibrosis likely reflect the relatively short follow-up of this study. The long-term open-label study extension (summarized in Appendix 5) did not provide any additional insight regarding the impact of OCA on clinical outcomes; however, it is an ongoing study, with only 21 months of follow-up at this writing. There were no statistically significant differences between OCA and placebo for any of the subscales of the PBC-40, a disease-specific health-related quality-of-life instrument. In their input to CDR, patient groups described quality of life as being a key issue in PBC.

A limitation of the overall study data is that only a small number (less than 10) of patients per group were not on UDCA; therefore, it cannot be ascertained whether patients not on UDCA will benefit from OCA. The majority of patients who will take OCA will likely combine it with UDCA; however, OCA is also indicated as a monotherapy in patients who cannot tolerate UDCA. One of the phase II studies that was not included in the systematic review (summarized in Appendix 6) compared OCA monotherapy with placebo and found statistically significant differences for the same primary composite outcome versus placebo. However, this study used OCA 10 mg daily as a starting dose, and this is not the recommended starting dose in the Health Canada–approved product monograph.

Harms

Pruritus was the main adverse effect associated with the use of OCA, and a notable harm in this review. Interpretation of this finding is challenging, given that pruritus is also a major symptom of PBC, and nearly 60% of study participants in POISE had pruritus at

baseline. The extent to which pruritus became a tolerability issue was dose-dependent, as only 1% of participants in the OCA titration group withdrew because of pruritus, while 10% of patients in the OCA 10 mg group withdrew because of pruritus. There were no statistically significant differences between OCA titration and placebo on a pruritus visual analogue scale or a five-dimension symptom scale after 12 months. Overall, 16% of patients in the OCA titration group had a serious adverse event versus 4% of patients in the placebo group. There was no pattern of specific serious adverse events that were more frequent with OCA therapy, and none of the serious adverse events were attributable to OCA. Although hepatic-related adverse events were more common at higher OCA doses (25 mg and 50 mg daily) in the phase II dose-finding studies, there was no signal of elevated risk of hepatic-related adverse events in POISE in either the OCA titration or the OCA 10 mg groups.

Potential Place in Therapy[1]

Before the approval of OCA, there was only one approved therapy for PBC, UDCA, which has been shown to increase overall and transplant-free survival.[8,9] Approximately 40% to 50% of patients experience an inadequate response to UDCA, as defined by biochemical measures (i.e., ALP, bilirubin),[4,5] and an additional 10% of individuals with PBC cannot tolerate UDCA. In patients who have a suboptimal response, there is a poorer prognosis, and there are currently no other therapies available. These are two important unmet medical needs in the therapy of PBC.

OCA is a farnesoid X receptor agonist affecting biliary homeostasis; it has been shown to decrease inflammation and has antifibrotic activity.[10,11] In the phase III POISE study,[12] the addition of OCA to UDCA resulted in a biochemical response in 46% of patients (versus 10% of patients in the placebo group) who had a prior suboptimal response or intolerance to UDCA. The POISE study's primary end point (i.e., composite of the proportion of participants achieving an ALP of less than 1.67 times ULN, total bilirubin at ULN or lower, and a decrease in ALP of 15% or more from baseline at month 12) is a validated outcome and has previously been shown to be predictive of the natural history of PBC. In clinical practice, OCA would be added to UDCA in patients who did not respond adequately to UDCA (defined as ALP of less than 1.67 times ULN after one year) or would be used as stand-alone therapy in patients who could not tolerate UDCA. The criterion for initiating OCA is the ALP level and is independent of fibrosis. Not surprisingly, given that the phase III study was of short duration, there was no improvement in fibrosis regression or mortality seen.

Overall, OCA is well tolerated, although there is a signal of increased pruritus, which is dose-dependent. Thus, OCA is to be titrated up from 5 mg to 10 mg daily at six months, depending on the patient's biochemical response to the drug. In the majority of patients, pruritus was manageable and did improve to some degree.[12] Prescribers should ensure that patients are adequately informed of the risks of pruritus at the 10 mg dose and that a management strategy for pruritus is available.

According to the clinical expert consulted for this review, OCA is a welcome and important addition to the therapy of PBC, as there has been a significant unmet medical need. PBC can result in decompensated liver disease and increased mortality if not treated adequately.

Conclusions

One manufacturer-sponsored, double-blind randomized controlled trial met the inclusion criteria for this CDR review. The POISE study randomized 216 patients with PBC in a 1:1:1 manner to OCA titration (initiated at 5 mg daily, inadequate responders increased to 10 mg daily after six months), OCA 10 mg daily, or placebo. The primary analysis compared the OCA 10 mg dose with placebo; however, according to the Health Canada–approved product monograph, this dose is not approved as an initial starting dose in Canada. Therefore, the focus of this review was on comparisons between OCA titration and placebo. The OCA titration group was superior to placebo for the primary composite outcome consisting of combined reductions in ALP and bilirubin after 12 months of therapy (secondary efficacy analysis), and was also superior to placebo for ALP and bilirubin reductions separately. There were no statistically significant differences in any health-related quality-of-life subscales on the PBC-40, including itch and fatigue, versus placebo. Pruritus was the most common adverse event in the OCA titration group but it is also a common symptom of PBC, which complicates the interpretation of the benefit of OCA for symptoms of PBC. Serious adverse events were numerically more common in the OCA titration than the placebo group; however, there was no specific pattern of serious adverse events attributable to OCA.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Table 1: Summary of Results

Composite Primary Outcome	OCA Titration[a]	OCA 10 mg	Placebo
Patients with ALP < 1.67 × ULN, total bilirubin ≤ ULN, and ALP decrease ≥ 15% from baseline to month 12, n (%) — ITT population	32/70 (46%)	34/73 (47%)	7 (10%)
Odds ratio (OCA/placebo) [95% CI]	9.1 [3.6 to 23.2] *P* < 0.0001[b]	9.4 [3.7 to 23.9] *P* < 0.0001[b]	N/A
Subgroup: UDCA use			
No	2/5 (40)	1/6 (17)	NR
	P = 0.0833[c]	*P* = 0.3173[c]	–
Yes	30/65 (46)	33/67 (49)	NR
	P < 0.0001[c]	*P* < 0.0001[c]	–
ALP Change From Baseline			
Mean (SE) baseline ALP, U/L	325.9 (13.9)	316.3 (12.2)	327.5 (13.5)
LS mean (SE) change at 12 months (ITT population), U/L	−112.5 (14.4) N = 64	−129.9 (14.6) N = 62	−14.4 (14.7) N = 70
LS mean (SE) % change at 12 months	−33.0 (3.7)	−39.1 (3.8)	−4.8 (3.8)
LSMD % (SE) vs. placebo	−28.2 (3.4)	−34.4 (3.4)	N/A
P value	*P* < 0.0001[d]	*P* < 0.0001[d]	–
Decrease ALP ≥ 10% at 12 months, n (%)	55 (79)	60 (82)	29 (40)
CMH *P* value[b]	*P* < 0.0001	*P* < 0.0001	–
Decrease ALP ≥ 15% at 12 months, n (%)	54 (77)	56 (77)	21 (29)
CMH *P* value[b]	*P* < 0.0001	*P* < 0.0001	–
Decrease ALP ≥ 20% at 12 months, n (%)	49 (70)	53 (73)	17 (23)
CMH *P* value[b]	*P* < 0.0001	*P* < 0.0001	–
Decrease ALP ≥ 40% at 12 months, n (%)	21 (30)	25 (34)	1 (1)
CMH *P* value[b]	*P* < 0.0001	*P* < 0.0001	–
ALP ≤ ULN at 12 months, n (%)	1 (1)	5 (7)	0
CMH *P* value[b]	*P* = 0.3063	*P* = 0.0221	–
Total Bilirubin			
Mean (SE) baseline bilirubin, µmol/L	10.3 (0.7)	11.3 (0.8)	11.8 (0.9)
LS mean (SE) change at 12 months, µmol/L	−0.4 (0.7) N = 64	−1.0 (0.7) N = 62	1.9 (0.7) N = 70
P value[d]	*P* = 0.0004	*P* < 0.0001	–
LS mean (SE) % change at 12 months	1.2 (6.7)	−0.2 (6.9)	19.5 (6.8)
LSMD (SE) vs. placebo	−18.3 (6.3)	−19.8 (6.3)	N/A

Composite Primary Outcome	OCA Titration[a]	OCA 10 mg	Placebo
P value[d]	*P* = 0.0039	*P* = 0.0020	–
Mortality			
Deaths	1	0	0
Cause	Heart failure	–	–
Symptoms — PBC-40 score			
General Symptoms			
Baseline mean (SD)	13.8 (5.3)	12.9 (4.6)	13.6 (5.3)
Mean (SD) change from base to month 12	0.0 (3.7) N = 62	0.7 (3.5) N = 64	0.3 (2.9) N = 68
LSMD [95% CI] vs. placebo	−0.33 [−1.43 to 0.76] *P* = 0.5498[d]	0.22 [−0.87 to 1.31] *P* = 0.6920[d]	N/A
Itch			
Baseline mean (SD)	4.1 (3.6)	3.8 (3.3)	4.3 (3.7)
Mean (SD) change from base to month 12	0.9 (3.3)	1.1 (2.8)	0.2 (2.7)
LSMD [95% CI] vs. placebo	0.46 [−0.42 to 1.35] *P* = 0.3041[d]	0.62 [−0.25 to 1.50] *P* = 0.1617[d]	N/A
Fatigue			
Baseline mean (SD)	25.9 (10.8)	24.7 (9.4)	26.2 (11.2)
Mean (SD) change from base to month 12	−0.6 (5.9)	0.0 (7.3)	−2.1 (6.0)
LSMD [95% CI] vs. placebo	1.64 [−0.51 to 3.79] *P* = 0.1332[d]	1.92 [−0.21 to 4.06] *P* = 0.0766[d]	N/A
Cognitive Function			
Baseline mean (SD)	11.4 (5.4)	11.5 (5.3)	11.6 (6.0)
Mean (SD) change from base to month 12	0.1 (3.2)	0.5 (3.9)	0.3 (3.5)
LSMD [95% CI] vs. placebo	−0.16 [−1.35 to 1.03] *P* = 0.7928[d]	0.27 [−0.91 to 1.44] *P* = 0.6566[d]	N/A
Social			
Baseline mean (SD)	19.7 (8.6)	19.5 (7.7)	21.0 (8.8)
Mean (SD) change from base to month 12	0.1 (5.6)	0.5 (6.8)	−1.4 (6.2)
LSMD [95% CI] vs. placebo	1.22 [−0.86 to 3.30] *P* = 0.2494[d]	1.60 [−0.46 to 3.66] *P* = 0.1265[d]	N/A
Emotional			
Baseline mean (SD)	6.4 (2.9)	7.1 (2.7)	6.8 (3.3)
Mean (SD) change from base to month 12	−0.1 (2.1)	−0.2 (2.3)	−0.5 (2.1)
LSMD [95% CI] vs. placebo	0.34 [−0.36 to 1.04] *P* = 0.3366[d]	0.44 [−0.25 to 1.13] *P* = 0.2138[d]	N/A
Morbidity	NR	NR	NR
Transplant	NR	NR	NR
Cirrhosis	NR	NR	NR

Composite Primary Outcome	OCA Titration[a]	OCA 10 mg	Placebo
Markers of Fibrosis			
ELF score, mean (SE) baseline	9.76 (0.13)	9.81 (0.14)	10.03 (0.15)
LS mean (SE) change at 12 months	0.24 (0.12) N = 55	0.20 (0.12) N = 63	0.33 (0.13) N = 64
P value[d]	*P* = 0.4718	*P* = 0.2324	–
Hepatic stiffness (FibroScan), mean (SE) baseline	10.70 (1.46) N = 35	11.35 (1.45) N = 32	12.70 (1.71) N = 39
LS mean (SE) change at 12 months	1.28 (1.34) N = 32	0.46 (1.39) N = 26	1.82 (1.35) N = 34
P value[d]	*P* = 0.6818	*P* = 0.3267	–

ALP = alkaline phosphatase; ANCOVA = analysis of covariance; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; ELF = enhanced liver fibrosis; ITT = intention-to-treat; LS = least squares; MD = mean difference; N/A = not applicable; NR = not reported; OCA = obeticholic acid; PBC-40 = primary biliary cholangitis 40-item questionnaire; SD = standard deviation; SE = standard error; UDCA = ursodeoxycholic acid; ULN = upper limit of normal; U/L = units per litre; vs. = versus.

[a] Dose titration to 10 mg daily occurred at 6 months for inadequate responders; remaining patients stayed at the 5 mg dose.

[b] *P* values obtained using CMH test stratified by randomization strata factor.

[c] Subgroup *P* values based on LS mean (SE) difference between OCA treatment and placebo and were obtained using CMH general association test stratified by randomization strata factor.

[d] *P* values for comparing OCA treatments with placebo were obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Source: Clinical study report for POISE.[13]

Introduction

Disease Prevalence and Incidence

Primary biliary cholangitis (PBC) occurs as a result of immune-mediated damage to bile ducts, with an associated inflammatory response leading to progressive fibrosis and loss of patency. This loss of patency leads, in turn, to hepatic accumulation of bile acids, resulting in liver damage with progressive fibrosis and potentially cirrhosis. PBC is more common in women than in men and is the most common reason for liver transplant among women.[1] Patients with PBC report fatigue and pruritus as key symptoms that negatively impact quality of life. Patients are also clearly affected by the potential progression to severe liver disease and associated complications such as decompensated liver disease, hepatocellular carcinoma, liver transplant, and death. Thirty per cent of patients can progress to advanced liver disease, decompensated disease, or death.[2]

PBC affects between 9,000 and 11,000 Canadians,[3] mostly women between the ages of 50 and 70, although some are diagnosed at an earlier age, according to the clinical expert consulted for this review. A 2009 study focusing on the Calgary Health Region found an incidence of 30 cases per million for PBC, and a prevalence that had risen from 100 cases per million in 1996 to 227 cases per million in 2002.[1]

Standards of Therapy

There is currently only one approved therapy for PBC in Canada — ursodeoxycholic acid (UDCA) — and more than 80% of patients with PBC receive UDCA.[3] Those patients who respond to UDCA tend to have improved clinical outcomes (e.g., transplant-free survival); however, about 40% to 50% of patients treated with UDCA do not respond to therapy.[4,5] There are also a small number of patients who are unable to tolerate UDCA, with the most common reason being gastrointestinal symptoms. According to the clinical expert, it is difficult to predict which patients will be unable to tolerate UDCA. In their input to the CADTH Common Drug Review (CDR), patients also reported weight gain, alopecia, dizziness, and flu-like adverse effects while on UDCA, in addition to PBC-related symptoms such as pruritus and fatigue.

Drug

Obeticholic acid (OCA) is a farnesoid X receptor agonist. Farnesoid receptors are a novel pharmacological target, and stimulation of these receptors appears to have multiple effects; in PBC, the most notable is the reduction in hepatocellular concentration of bile acids. Health Canada has approved OCA for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. Health Canada issued a notice of compliance with conditions (NOC/c) pending results of trials to verify the clinical benefit of OCA. One of these trials, study 747-302, was designed to evaluate OCA with a primary composite of clinical end points (e.g., death, transplant), either in combination with UDCA or as monotherapy in patients with early, moderately advanced, and advanced PBC. The other trial, study 747-401, was designed to enrol a population of PBC patients with moderate to severe hepatic impairment (Child–Pugh class B and C).[6]

The recommended starting dose of OCA is 5 mg by mouth daily; however, participants may up-titrate to 10 mg daily after six months to improve response if an adequate reduction in serum alkaline phosphatase (ALP) or total bilirubin has not been achieved. Continuation of OCA in a patient with no improvement in these biochemical markers of PBC (ALP and bilirubin) after one year on the maximum effective dose (10 mg) should be assessed on the basis of the clinical course of PBC and the potential risks and benefits of continued use.[7]

Indication under review
For the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.
Reimbursement criteria requested by sponsor
As per indication

Table 2: Key Characteristics of Obeticholic Acid and Ursodeoxycholic Acid

	Obeticholic Acid	Ursodeoxycholic Acid
Mechanism of Action	Farnesoid X receptor agonist Decreases intracellular hepatocyte concentration of bile acids	Multiple mechanisms: • Cytoprotective: inhibits apoptosis, reduces bile acid cytotoxicity • Improves renal excretion of bile acids • Modulates bile duct flow to preserve integrity of bile ducts
Indication[a]	Indicated for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA	Indicated for the management of cholestatic liver diseases, such as primary biliary cirrhosis
Route of Administration	Oral	Oral
Recommended Dose	Initial: 5 mg once daily (30 minutes before breakfast) May titrate to 10 mg daily after six months	13 to 15 mg/kg per day in 2 to 4 divided doses
Serious Side Effects or Safety Issues	Hepatic-related AE (10 mg dose)	–

AE = adverse event; PBC = primary biliary cholangitis; UDCA = ursodeoxycholic acid.

[a] Approved Health Canada indication.

Source: Health Canada–approved product monograph for OCA,[7] and Health Canada–approved product monograph for ursodeoxycholic acid.[14]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of OCA 5 mg or 10 mg for the treatment of adults with PBC.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adult patients with PBC Subgroups: Patients with inadequate response to UDCA Patients intolerant to UDCA
Intervention	Obeticholic acid 5 mg or 10 mg by mouth daily as monotherapy or in combination with UDCA
Comparators	UDCA Placebo
Outcomes	**Outcomes:** Mortality[a] Liver transplantation[a] Cirrhosis[a] Health-related quality of life[a] Symptoms (e.g., fatigue, pruritus) [a] Morbidity (e.g., osteoporosis, diabetes mellitus, liver cancer) [a] Liver enzymes (e.g., ALP) Markers of liver function (e.g., bilirubin) Other liver assessments (e.g., fibrosis) **Harms outcomes:** AEs SAEs WDAEs Notable harms: pruritus, reduction in HDL cholesterol, hepatic-related AEs
Study Design	Published and unpublished phase III RCTs

AE = adverse event; ALP = alkaline phosphatase; HDL = high-density lipoprotein; PBC = primary biliary cholangitis; RCT = randomized controlled trial; SAE = serious adverse event; UDCA = ursodeoxycholic acid; WDAE = withdrawal due to adverse event.

[a] Outcomes identified as important in Patient Input Summary (Appendix 1).

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was obeticholic acid (Ocaliva).

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on January 27, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on May 17, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in 0.

Results

Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 4 and described in the following section. A list of excluded studies is presented in 0.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

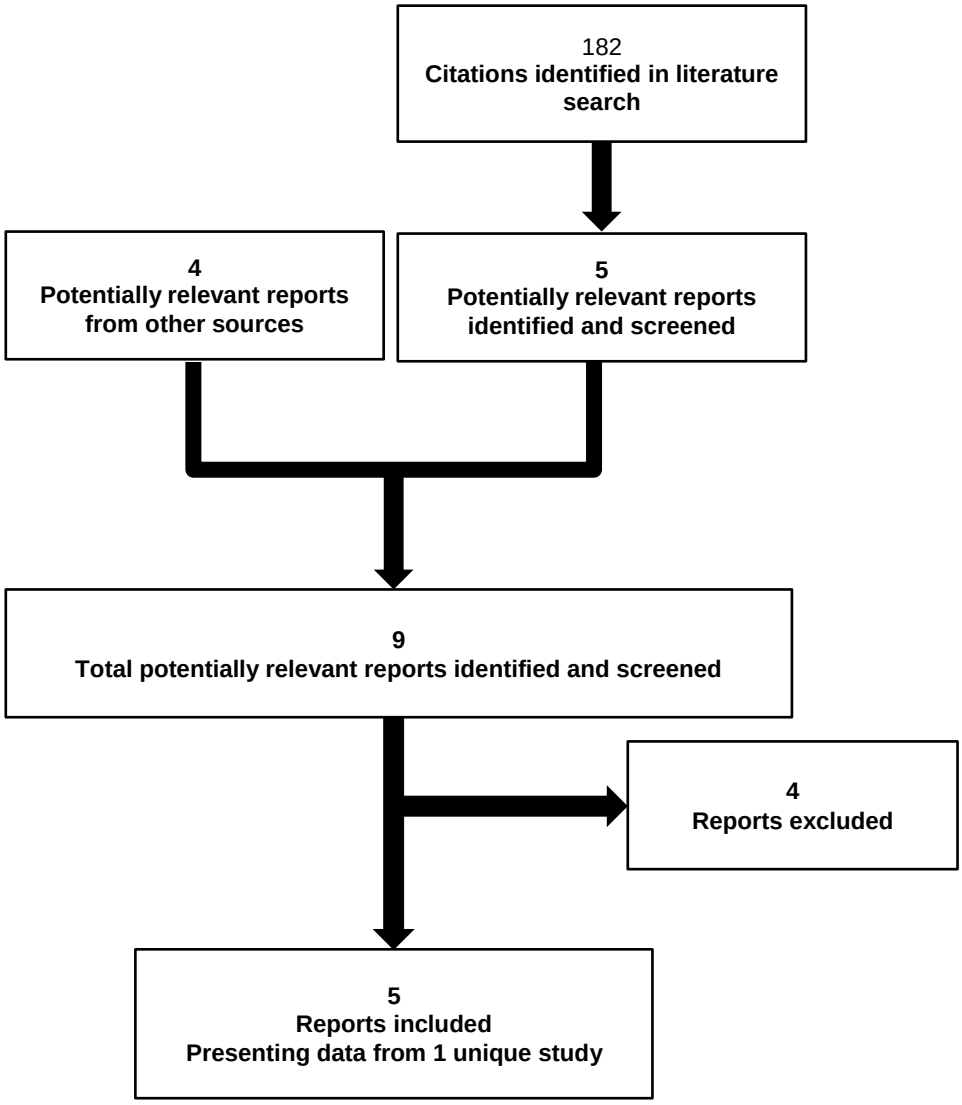


Table 4: Details of Included Study

		POISE
Designs and Populations	**Study Design**	DB RCT
	Locations	Canada, US, Europe, Australia
	Randomized (N)	216
	Study Period	March 2012 to December 2013
	Inclusion Criteria	Age ≥ 18 years, definite or probable PBC diagnosis (consistent with AASLD and EASL practice guidelines), as demonstrated by the presence of ≥ 2 of the following 3 diagnostic factors: • History of elevated ALP levels for at least 6 months • Positive AMA titre or, if AMA negative or low titre (< 1:80), PBC-specific antibodies (anti-GP210 or anti-SP100) or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex) • Liver biopsy consistent with PBC At least 1 of the following qualifying biochemistry values: • ALP ≥ 1.67 × ULN • Total bilirubin > ULN but < 2 × ULN Taking UDCA for at least 12 months (stable dose for ≥ 3 months) before day 0, or unable to tolerate UDCA (no UDCA for ≥ 3 months) before day 0
	Exclusion Criteria	1. History or presence of other concomitant liver diseases, including: • Hepatitis C virus infection; participants with active hepatitis B virus infection were excluded; however, participants who had seroconverted (Hbs Ag and Hbe Ag negative) could be included in this study after consultation with the medical monitor. • Primary sclerosing cholangitis • Alcoholic liver disease • Definite autoimmune liver disease or overlap hepatitis • Non-alcoholic steatohepatitis • Gilbert syndrome (due to interpretability of bilirubin levels) 2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including: • History of liver transplantation, current placement on a liver transplant list or current Model for End Stage Liver Disease score ≥ 15 • Portal hypertension with complications, including known gastric or large esophageal varices, poorly controlled or diuretic resistant ascites, history of variceal bleeds or related therapeutic or prophylactic interventions (e.g., beta blockers, insertion of variceal bands or transjugular intrahepatic portosystemic shunts), or hepatic encephalopathy • Cirrhosis with complications, including history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma, or bilirubin > 2 × ULN • Hepatorenal syndrome (type I or II) or screening serum creatinine > 2 mg/dL (178 µmol/L)
Drugs	**Intervention**	Obeticholic acid dose titration • 5 mg daily for first 6 months • up-titration to 10 mg daily based on ALP or total bilirubin Obeticholic acid 10 mg daily
	Comparator(s)	Placebo daily (matched)

		POISE
Duration	Screening	Up to 8 weeks
	Double-blind	12 months
	Follow-up	4 weeks (long-term extension study also available — see Appendix 6)
Outcomes	**Primary End Point**	ALP < 1.67 × ULN, total bilirubin ≤ ULN, and ALP decrease of ≥ 15% from baseline at month 12 for the OCA 10 mg group
	Other End Points	Key secondary end point: ALP < 1.67 × ULN, total bilirubin ≤ ULN, and ALP decrease of ≥ 15% from baseline at month 12 for the OCA titration group Percentage of participants with ALP < 1.67 × ULN, total bilirubin ≤ ULN, and ALP decrease of ≥ 15% from baseline at month 6 Absolute and percentage change from baseline in ALP at month 6 and at month 12 Percentage of participants with a decrease in ALP of ≥ 10%, ≥ 15%, ≥ 20%, and ≥ 40% from baseline Percentage of participants with ALP ≤ ULN PBC-40 Other measures of biochemical treatment response ELF score and its components Hepatic stiffness measurements (at selected study sites) Adverse events Pruritus Physical examination results, vital signs, weight, ECG results
Notes	**Publications**	Nevens et al. 2016[12]

AASLD = American Association for the Study of Liver Diseases; ALP = alkaline phosphatase; AMA = antimitochondrial antibody; DB = double-blind; EASL = European Association for the Study of the Liver; ECG = electrocardiogram; ELF = enhanced liver fibrosis; OCA = obeticholic acid; PBC = primary biliary cirrhosis; PBC-40 = primary biliary cholangitis 40-item questionnaire; RCT = randomized controlled trial; UDCA = ursodeoxycholic acid; ULN = upper limit of normal.

Note: Four additional reports were included (manufacturer's submission,[3] FDA clinical and statistical reviews,[15,16] clinical study report for POISE[13]).

Source: Clinical study report for POISE.[13]

Included Study

Description of Study

One manufacturer-sponsored, multi-centre, double-blind, randomized controlled trial met the inclusion criteria for this review. Study 747-301 (POISE) included adult patients with PBC who either had failed to achieve targets on UDCA or had not tolerated UDCA. These patients were randomized in a 1:1:1 manner by interactive Web response system (IWRS) to OCA 10 mg daily or placebo or a dose titration starting at 5 mg and increasing to 10 mg daily for patients with poor response. Of the two OCA interventions, the latter group reflects the Health Canada–approved recommended dose for OCA, as patients are not currently recommended to start on 10 mg daily of OCA therapy. Participants remained on therapy for 12 months. The study was designed to test the superiority of each of the OCA interventions with placebo, although the primary analysis tested the superiority of the OCA 10 mg intervention to placebo. The primary outcome was a composite outcome that reflected the proportion of participants reaching targets for both ALP and bilirubin after 12 months of therapy.

Participants were screened during a screening period of eight weeks or more before entering the study to allow for the collection of repeated serum chemistry samples (at least two weeks apart), if necessary, to confirm pre-treatment ALP and total bilirubin values. Other procedures performed during screening were evaluation of entry criteria, recording of medical and disease history and prior and concomitant medications, and evaluation of safety assessments. Participants could have undergone a pre-treatment liver biopsy or could have provided access to pre-treatment liver biopsy samples taken within one year before day 0; both actions were optional,

as histology is an optional diagnostic criterion in the guidelines of both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL).

Randomization

Allocation to treatment groups was based on a predefined randomization code generated by an external body (Sharp Clinical Services) and was conducted by use of an IWRS. The IWRS served as an investigational product inventory and management system. Participants were stratified according to pre-identified criteria: (1) a group at higher risk of developing clinical outcomes based on ALP, aspartate aminotransferase (AST), and total bilirubin levels (i.e., Paris I criteria); and (2) a group who could not tolerate UDCA therapy. At the time of enrolment, participants were stratified by the presence or absence of the following biochemical response criteria and tolerance to UDCA treatment and were randomized, in equal proportions, to each of the treatment groups:

- Pre-treatment ALP > 3 times upper limit of normal (ULN) and/or AST > 2 times ULN and/or bilirubin > ULN, intolerant to UDCA
- Pre-treatment ALP ≤ 3 times ULN and/or AST ≤ 2 times ULN and/or bilirubin ≤ ULN, intolerant to UDCA
- Pre-treatment ALP > 3 times ULN and/or AST > 2 times ULN and/or bilirubin > ULN, currently taking UDCA
- Pre-treatment ALP ≤ 3 times ULN and/or AST ≤ 2 times ULN and/or bilirubin < ULN, currently taking UDCA

Populations

Inclusion and Exclusion Criteria

Patient diagnosis of PBC was based on ALP, antibodies, and biopsy results. Participants also had to have met specific biochemical requirements for either ALP (1.67 times ULN or higher) or bilirubin (higher than ULN but < 2 times ULN). Additionally, participants either had to have been taking UDCA for at least 12 months before day 0 or had to be unable to tolerate UDCA. Participants with other liver disease (such as hepatitis C) were excluded, as were participants with evidence of advanced PBC, including clinically significant decompensation.

Baseline Characteristics

Participants were 56 years old on average and were predominantly female and white. Most (93%) had used UDCA at baseline, and the majority (63%) had a history of pruritus (Table 5). There were some differences in baseline characteristics between groups. There were numerically more women in the OCA titration and placebo groups compared with the OCA 10 mg group, and there were more white participants in the OCA groups compared with the placebo group. Participants in the placebo group were numerically more likely to have a history of fatigue compared with the two active treatment groups, and those in the OCA titration group were numerically less likely to have pruritus at baseline compared with the OCA 10 mg and placebo groups. There were some numerical differences in the severity of the most recent pruritus event between groups, with more mild cases and fewer moderate cases in the OCA 10 mg group compared with the other two groups.

Table 5: Summary of Baseline Characteristics

Characteristic	OCA Titration N = 70	OCA 10 mg N = 73	Placebo N = 73
Mean (SD) age, years	55.8 (10.5)	56.2 (11.0)	55.5 (10.0)
Age < 65 years, n (%)	60 (86)	56 (77)	60 (82)
Female, n (%)	65 (93)	63 (86)	68 (93)
White	67 (96)	70 (96)	66 (90)
BMI (kg/m^2)	25.8 (4.9)	26.3 (5.1)	26.2 (4.4)
Pre-treatment liver biopsy, n (%)	13 (19)	9 (12)	7 (10)
UDCA use at baseline, n (%)	65 (93)	67 (92)	68 (93)
History of pruritus, n (%)	45 (64)	45 (62)	47 (64)
Severity of most recent pruritus event, n (%)			

Characteristic	OCA Titration N = 70	OCA 10 mg N = 73	Placebo N = 73
Mild	29 (64)	34 (76)	31 (66)
Moderate	13 (29)	8 (18)	14 (30)
Severe	2 (4)	3 (7)	1 (2)
Unknown	1 (2)	0	1 (2)
Pruritus at baseline, n (%)	37 (53)	44 (60)	47 (64)
Mild	27 (39)	33 (45)	32 (44)
Moderate	10 (14)	10 (14)	13 (18)
Severe	0	1 (1)	2 (3)
History of fatigue, mean (SD) years	38 (54)	41 (56)	49 (67)
Overall severity of fatigue, n (%)			
Mild	17 (24)	29 (40)	28 (38)
Moderate	16 (23)	8 (11)	16 (22)
Severe	5 (7)	3 (4)	3 (4)
Age at PBC diagnosis, mean (SD) years	47.6 (11.7)	47.1 (10.6)	47.3 (9.3)
Age < 50 years at PBC diagnosis, n (%)	38 (54)	42 (58)	45 (62)
Duration of PBC, mean (SD) years	8.3 (5.8)	9.2 (6.9)	8.3 (5.4)
Duration of PBC > 7.5 years, n (%)	34 (49)	43 (59)	34 (47)

BMI = body mass index; OCA = obeticholic acid; PBC = primary biliary cholangitis; SD = standard deviation; UDCA = ursodeoxycholic acid.

Source: Clinical study report for POISE.[13]

Interventions

According to the manufacturer, the safety and tolerability of OCA had been previously evaluated in healthy participants (OCA single doses of 5 mg to 500 mg and repeated once daily doses of 5 mg up to 250 mg), which established that doses of OCA up to 100 mg were generally well tolerated. OCA has also been evaluated in six different participant populations, including those with PBC, with repeated doses up to 50 mg daily.[13]

POISE was designed to assess the efficacy, safety, and tolerability of lower doses (10 mg) of OCA in participants with PBC to provide pivotal data to support a marketing authorization for OCA in this indication. An additional treatment group (OCA titration) was also evaluated, in which participants started at 5 mg and the dose was then titrated up to 10 mg of OCA if (a) the participant had not had a successful biochemical response to therapy, as defined by the primary efficacy composite end point, and (b) the participant tolerated the therapy well.

Participants in the double-blind phase were instructed to begin taking the product on the day after the day 0 visit (i.e., on day 1) and to take the investigational product with water approximately 30 minutes before breakfast. Participants were instructed to swallow the tablet whole and not to chew, divide, or crush the tablet.

Participants randomized to the OCA titration group had their dose titrated from 5 mg to 10 mg at month 6, if appropriate. To maintain blinding, all participants (i.e., all treatment groups) were assessed by the investigator for titration eligibility at month 6 based on ALP or bilirubin response and tolerability of investigational product. However, only participants in the OCA titration group were eligible to receive an increase in their dose, which was controlled by the IWRS. The investigator could request up-titration via the IWRS for participants who met any of the criteria at the month 6 assessment; however, the investigator and participant remained blinded to whether titration occurred if the investigator deemed that the participant tolerated the investigational product. Blinding was also maintained by use of a matching placebo. The manufacturer noted that blinding was maintained throughout the dose-titration process; however no specific details were provided as to how the blind was maintained during dose titration.

Outcomes

The primary outcome in POISE was a composite outcome of the proportion of patients achieving an ALP less than 1.67 times ULN, total bilirubin less than ULN, and an ALP decrease of 15% or more from baseline at month 12 for the OCA 10 mg group. The key secondary outcome was the proportion of patients in the OCA titration group who achieved the same composite outcome. Other secondary outcomes included assessment of the composite outcome at month 6 and assessments of ALP at months 6 and 12 (change from baseline, proportion with a decrease of at least 10%, 15%, 20%, and 40% from baseline, and proportion less than ULN). Other markers assessed included gamma-glutamyl transpeptidase, alanine transaminase, AST, albumin, prothrombin time, and international normalized ratio, as measured by the absolute change from baseline and the per cent change from baseline. These assessments were also performed at month 6 and month 12.

Other secondary outcomes assessed liver fibrosis, including measures of hepatic stiffness using transient elastography (TE), measured by the FibroScan TE device, and the enhanced liver fibrosis (ELF) score. Hepatic stiffness was assessed at study sites that had the FibroScan TE equipment to collect hepatic stiffness measurements. These study sites had the staff trained in the use and data interpretation of the FibroScan device. TE is a mean liver stiffness measurement of fibrosis (measured in kilopascals) following 10 consecutive measurements with the potential of detecting and monitoring hepatic fibrosis and is considered to represent the elastic modulus of the liver.[17,18] It has been suggested that values of at least 12.5 kPa (threshold) are indicative of cirrhosis in patients with chronic liver disease, with a range between 12.5 kPa and 75.5 kPa. Because of variability in this measure, the clinical relevance remains unknown.[18] The scores and their correlation with fibrosis are as follows: less than 6 kPa, normal; 6 kPa to 8 kPa, grey range (F1 to F2); 8 kPa to 12.5 kPa, advanced fibrosis (F3); 12.5 kPa or more, cirrhosis (F4).[3] For a detailed review of the validity of this outcome, see 0. No minimal clinically important difference (MCID) was found for FibroScan TE scores.

ELF test scores are based on the biochemical markers serum hyaluronic acid, tissue inhibitor of metalloproteinase 1, and procollagen type III N-terminal propeptide.[19,20] Scores are calculated based on predefined formulas and on concentrations of the aforementioned biochemical markers. Scores under 7.7 indicate no or mild liver fibrosis, whereas scores between 7.7 and 9.8 or above 9.8 specify moderate or severe liver fibrosis, respectively.[21] For a detailed review of the validity of this outcome, see 0. No MCID was found for ELF scores.

Health-related quality of life was assessed by means of a validated 40-question questionnaire, the PBC-40. This questionnaire assesses participant symptoms across six domains: fatigue, emotional, social, cognitive function, general symptoms, and itch. A score for each domain was provided (but a total score was not calculated, as a total score is not calculated for PBC-40). Domain score ranges are as follows: general symptoms (6 to 35), itch (0 to 15), fatigue (11 to 55), cognitive function (6 to 30), social (8 to 50), and emotional (3 to 15). Higher scores indicate a poorer quality of life. Further details regarding this outcome are provided in 0. No MCID was found for the PBC-40.

Statistical Analysis

The primary efficacy analysis of the double-blind phase was completed using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor. Missing values were considered a nonresponse. The primary analysis compared the response rates in the OCA 10 mg group with those in the placebo group for the following: ALP less than 1.67 times ULN, total bilirubin less than ULN, and ALP decrease of 15% or more. Statistical significance was considered a *P* value of 0.05 or less.

The primary efficacy composite end point was the percentage of participants at month 12 with ALP less than 1.67 times ULN, total bilirubin at ULN or lower, and decrease in ALP of 15% or more from baseline. The primary efficacy analysis of the composite end point compared the OCA 10 mg group with the placebo group. A hierarchical approach was used to control the overall significance level (type I error) for the key secondary efficacy analysis of the pairwise comparison of the OCA titration with placebo for the percentage of participants at month 12 with ALP less than 1.67 times ULN, total bilirubin at ULN or lower, and decrease in ALP of 15% or more from baseline. The key secondary efficacy end point was tested only if the primary end point was statistically significant. No other secondary end points appeared to have been included in the statistical hierarchy. A two-sided test at the 5% level of significance was used for all end points.

For continuous end points, such as the change from baseline in components of the composite such as ALP and bilirubin, as well as the PBC-40, *P* values for comparing OCA treatments with placebo were obtained using an analysis of covariance model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Assessments were often carried out at both month 6 and month 12. For example, other secondary outcomes included assessment of the composite at month 6, and assessments of ALP at months 6 and 12 (change from baseline, proportion with a decrease of at least 10%, 15%, 20% and 40% from baseline, and proportion less than ULN).

Power: The planned sample size was approximately 180 participants (60 participants in each of the three groups). An analysis of this study's end point was conducted on the phase II study (adding OCA to UDCA therapy) data set: 9% of the placebo participants and 40% of the participants receiving OCA 10 mg had a positive response. The sample size was then calculated using slightly more conservative numbers. Assuming responder rates in the placebo and the OCA 10 mg groups of 14% and 40%, respectively, and based on the use of a two-sided test of equality of binomial proportions at the 5% level of significance, a sample size of 60 participants per group would provide 90% power to detect a difference between the OCA 10 mg group and placebo.

Missing data: In the responder analyses, any participant who did not provide an assessment at the specified time point for the defining of response was considered a nonresponder. For sensitivity analyses using only "observed cases," participants with missing data were not imputed. For efficacy end points that utilized an analysis of covariance model, observed cases served as the primary analysis. Sensitivity analyses to assess the effect of missing data for continuous outcomes were conducted if missing data were imputed using last observation carried forward. For efficacy end points that utilized the mixed-effects models for repeated measures, no imputations were made for missing values.

Subgroups: The primary efficacy end point (the absolute and percentage change in ALP and bilirubin from baseline) and treatment-emergent adverse events were descriptively analyzed for several subgroup populations. The intention-to-treat (ITT) population was used for the efficacy end points and the safety population for adverse events. The cut-off for these analyses was either consistent with appropriate regulatory guidelines (e.g., age, gender, geographical region) or represented a clinically meaningful division. Subgroup variables were calculated at baseline, but only if there were sufficient participants (i.e., more than five participants per group).

Baseline subgroups of interest were as follows:

- Age categories (at time of informed consent): < 65 years, ≥ 65 years
- Age categories at PBC diagnosis: < 50 years, ≥ 50 years
- Sex: male, female
- Race: white, non-white
- Baseline body mass index: < 30 kg/m^2, ≥ 30 kg/m^2
- Baseline ALP level: ≤ 3 times ULN, > 3 times ULN
- Baseline ALP level: tertile (only for the absolute and per cent change in ALP)
- Baseline bilirubin level: > ULN, ≤ ULN
- Baseline use of UDCA: Yes, No
- Years since diagnosis of PBC (at time of informed consent): ≤ 7.5 years, > 7.5 years
- Geographic region: European centres, and Northern American and Australian centres combined

Additional subgroup analyses were performed on the primary efficacy end point (absolute and per cent change in ALP from baseline), and on the incidence of treatment-emergent pruritus using the following subgroups:

- Participants in the OCA titration group who completed the month 6 titration visit
    - Participants who remained at OCA 5 mg

- Participants who up-titrated from OCA 5 mg to OCA 10 mg

The subgroup of interest for this review was baseline use of UDCA (yes or no).

Analysis Populations

The ITT population included all randomized participants who received at least one dose of investigational product, with treatment assignment based on the randomized treatment. The ITT population was used for the summary of all baseline characteristics and all summaries and analyses of efficacy data.

The completer population included all randomized participants who received at least one dose of investigational product and participated to the end of the double-blind phase (month 12), with treatment assignment based on the randomized treatment.

The efficacy-evaluable population included all participants in the completer population who did not have any major protocol deviations that could affect the efficacy of the investigational product. Treatment assignment was based on the randomized treatment. The exclusion of participants from the efficacy-evaluable population was determined based on a review of blinded data before database lock and unblinding.

The safety population included all participants who received at least one dose of investigational product, with treatment assignment based on the treatment actually received. The safety population was used for the analysis of all safety data.

Patient Disposition

A higher proportion of participants in the OCA titration group than in the placebo group withdrew from POISE (10% versus 4% of participants) (Table 6). The most common reason for withdrawal in the OCA titration group was adverse events.

Table 6: Patient Disposition

	OCA Titration	OCA 10 mg	Placebo
Screened, N		316	
Randomized, N (%)	71 (100)	73 (100)	73 (100)
Randomized and treated, N (%)	70 (99)	73 (100)	73 (100)
Discontinued, N (%)	7 (10)	9 (12)	3 (4)
• Death	1 (1)	0 (0)	0 (0)
• Pruritus	1 (1)	7 (10)	0 (0)
• Other AEs	3 (4)	1 (1)	2 (3)
• Withdrew consent	2 (3)	1 (1)	1 (1)
ITT, N (%)	70 (99)	73 (100)	73 (100)
PP, N (%)	66 (93)	62 (85)	67 (92)
Safety, N (%)	70 (99)	73 (100)	73 (100)
Enrolled into LTSE phase, N (%)	63 (89)	64 (88)	66 (90)

AE = adverse event; ITT = intention-to-treat; LTSE = long-term safety extension; OCA = obeticholic acid; PP = per-protocol.

Source: Clinical study report for POISE.[13]

Exposure to Study Treatments

Exposure, measured as days on study drug, was similar between the OCA titration group (mean 342 [standard deviation (SD) 61] days) and the placebo group (346 [SD 59] days) (Table 8). The mean exposure for the OCA 10 mg group was 309 (SD 106) days.

There were 33 participants (47% of the randomized population) who up-titrated in the OCA titration group. There was > 99% compliance with the study drug in each of the groups in the study.

Critical Appraisal

Internal Validity

POISE was randomized and double-blinded, and steps such as the use of an IWRS and a matching placebo were taken to maintain blinding and allocation concealment. It was unclear from the description of the dose titration how blinding was maintained in that phase. There are also issues that may have compromised blinding that are beyond the investigators' control, most notably the higher proportion of participants who experienced pruritus with OCA compared with placebo. Pruritus is a known adverse effect of OCA therapy, and it is plausible that participants on OCA speculated (correctly) that they were assigned to the OCA group when they experienced pruritus. This is a potential limitation of the study; however, it would be more likely to affect subjective outcomes such as the PBC-40 than the primary and key secondary outcomes that relied on biochemical markers such as ALP and bilirubin, which were the focus of the primary analysis in POISE.

More participants in the OCA titration group withdrew from the study compared with those in the placebo group (10% versus 4% of participants). This difference in withdrawals may have biased results for harms, as the group with the higher proportion of early withdrawals had a shorter exposure to the study drug. The risk of bias might be lessened somewhat if a large proportion of the withdrawals were due to pruritus; however, this was not the case, as only one participant in the OCA titration group withdrew for this reason.

To account for missing data, the manufacturer used imputation that assumed that participants missing from the analysis were nonresponders and used a last-observation-carried-forward method to account for missing data for continuous outcomes. The assumption of nonresponse for missing data is a conservative approach, and may bias results if there is a difference in withdrawals between groups. There was a numerical difference in withdrawals in POISE, and the higher rate of withdrawals in the OCA group may have biased results against the study drug. However, a number of sensitivity analyses were reported using various populations, including the completer population (only participants who completed the study), and the results did not differ markedly among these different populations.

The manufacturer accounted for multiple testing by using a hierarchical statistical testing procedure. However, the hierarchy appears to have been applied only to the primary and first secondary outcomes, and not to any other secondary outcomes. Therefore, only the primary composite outcome was tested in a way that accounted for multiple comparisons.

The manufacturer does not appear to have identified an ITT population in this study. In all populations identified, participants had to have received at least one dose of study drug. In a true ITT analysis, participants are analyzed based on the group they are randomized to, regardless of whether they actually went on to receive the study drug.

Power calculations were performed and a rationale was provided for the assumptions made in performing the calculations; the assumptions appeared reasonable.

External Validity

The included study was relatively small and of short duration, and this likely limited the conclusions that could be drawn regarding important clinical outcomes in PBC such as morbidity and mortality. A 12-month double-blind phase is also unlikely to be long enough to reveal significant long-term safety issues that might arise with this novel drug. No new safety issues have arisen thus far from the long-term safety extension, with follow-up to 21 months.

According to the clinical expert, participants enrolled in POISE appeared to reflect the population that would be expected to use the drug. The clinical expert did note the exclusion of participants with more advanced liver disease and suggested that OCA may be prescribed to these patients as well. In the Health Canada–approved product monograph, the manufacturer notes that patients with severe hepatic impairment (Child–Pugh class B and C) should be monitored closely, as elimination of OCA would be impaired in these patients.

The primary composite outcome of POISE compared the OCA 10 mg dose with placebo, while the OCA titration group was compared with placebo as a secondary outcome. However, the OCA 10 mg dose is not a recommended starting dose based on the

Health Canada–approved product monograph; therefore, this OCA 10 mg dose is not of interest for this review, despite the fact that it is the primary outcome of the pivotal study.

The primary outcome was a composite of two established markers in liver disease, ALP and bilirubin. Both are considered acceptable markers for worsened clinical outcomes in PBC; however, there is no established MCID for either. Any elevation above the ULN for either ALP or bilirubin is considered clinically relevant (see 0 for further details on the validity of these outcomes). The clinical expert believed that the primary composite outcome was appropriate and validated for this disease condition.

Efficacy

Only those efficacy outcomes identified in the review protocol (Table 3) are reported below.

Primary Outcome

The primary outcome of POISE was a composite of participants who achieved ALP less than 1.67 times ULN, total bilirubin at ULN or lower, and a decrease in ALP of 15% or more from baseline at 12 months. The primary analysis compared the OCA 10 mg dose against placebo, although, because it is not the approved dose of OCA, this dose is not of key interest for this review. There was a larger proportion of participants in the OCA titration group who achieved the primary outcome when compared with the placebo group, with data being reported for the ITT population (46% versus 10% of participants), and this difference was statistically significant (odds ratio 9.1; 95% confidence interval [CI], 3.6 to 23.2; $P < 0.0001$) (Table 7). Responses were also reported in the titration group for participants who remained at the 5 mg dose versus those who up-titrated, and responses appeared to be higher in those participants who remained at the OCA 5 mg dose (53% response) compared with those who up-titrated to OCA 10 mg (39% response).

Mortality

There was one death in the study. A participant in the OCA titration group died as a result of heart failure (Table 7).

Liver Transplantation

There were no liver transplants reported during the study.

Cirrhosis

There were no cases of cirrhosis during the study.

Health-Related Quality of Life

Health-related quality of life was assessed using the PBC-40 scale, with the manufacturer reporting scores for subscales (the PBC-40 does not calculate an overall score). There were no statistically significant differences between the OCA titration and placebo groups for symptoms as assessed at month 12 using the PBC-40 subscales (general, itch, fatigue, cognitive function, social, and emotional) (Table 7).

Symptoms

Symptoms were not investigated as an efficacy outcome in the POISE study but were assessed as a safety outcome using the pruritus visual analogue scale and five-dimensions scale.

Morbidity

Morbidity was not specifically reported as an outcome.

Liver Enzymes

There was a larger per cent reduction in ALP from baseline to month 12 with OCA titration than with placebo, with a least squares mean difference (LSMD) versus placebo of −28.2% (standard error 3.4; *P* < 0.0001). There was a larger proportion of participants in the OCA titration group than in the placebo group with reductions from baseline in ALP of at least 10% (79% versus 40%, respectively), 15% (77% versus 29%), 20% (70% versus 23%), and 40% (30% versus 1%), and all these differences were statistically significant (*P* < 0.0001) (Table 7).

Bilirubin

There was a statistically significant mean per cent reduction in bilirubin from baseline to month 12 with OCA titration versus placebo, with an LSMD of −18.3% (standard error 6.3; *P* = 0.0039) (Table 7).

Hepatic Fibrosis

Hepatic fibrosis was assessed using the ELF score and FibroScan. There was no statistically significant difference in ELF scores at 12 months between the OCA titration group and the placebo group. FibroScans were carried out on only about half of the ITT population, and there were no statistically significant differences at 12 months between the OCA titration group and the placebo group for FibroScan scores (Table 7).

Table 7: Key Efficacy Outcomes

Composite Primary	OCA Titration[a]	OCA 10 mg	Placebo
Patients with ALP < 1.67 × ULN and total bilirubin ≤ ULN and ALP decrease ≥ 15% from baseline to month 12, n (%) — ITT	32/70 (46%)	34/73 (47%)	7/73 (10%)
Odds ratio (OCA/placebo) [95% CI]	9.1 [3.6 to 23.2] *P* < 0.0001[b]	9.4 [3.7 to 23.9] *P* < 0.0001[b]	N/A
Subgroup: UDCA use			
No	2/5 (40)	1/6 (17)	NR
	P = 0.0833[c]	*P* = 0.3173[c]	
Yes	30/65 (46)	33/67 (49)	NR
	P < 0.0001[c]	*P* < 0.0001[c]	
ALP Change From Baseline			
Mean (SE) baseline ALP, U/L	325.9 (13.9)	316.3 (12.2)	327.5 (13.5)
LS mean (SE) change at 12 months, U/L	−112.5 (14.4) N = 64	−129.9 (14.6) N = 62	−14.4 (14.7) N = 70
LS mean (SE) % change at 12 months	−33.0 (3.7)	−39.1 (3.8)	−4.8 (3.8)
LSMD % change (SE) vs. placebo	−28.2 (3.4)	−34.4 (3.4)	N/A
P value[d]	*P* < 0.0001	*P* < 0.0001	
Decrease ALP ≥ 10% at 12 months, n (%)	55 (79)	60 (82)	29 (40)
CMH *P* value[b]	*P* <0.0001	*P* < 0.0001	
Decrease ALP ≥ 15% at 12 months, n (%)	54 (77)	56 (77)	21 (29)
CMH *P* value[b]	*P* < 0.0001	*P* < 0.0001	
Decrease ALP ≥ 20% at 12 months, n (%)	49 (70)	53 (73)	17 (23)
CMH *P* value[b]	*P* < 0.0001	*P* < 0.0001	
Decrease ALP ≥ 40% at 12 months, n (%)	21 (30)	25 (34)	1 (1)
CMH *P* value[b]	*P* < 0.0001	*P* < 0.0001	
ALP ≤ ULN at 12 months, n (%)	1 (1)	5 (7)	0
CMH *P* value[b]	*P* = 0.3063	*P* = 0.0221	

Composite Primary	OCA Titration[a]	OCA 10 mg	Placebo
Total Bilirubin			
Mean (SE) baseline bilirubin, µmol/L	10.3 (0.7)	11.3 (0.8)	11.8 (0.9)
LS mean (SE) change at 12 months, µmol/L	−0.4 (0.7) N = 64	−1.0 (0.7) N = 62	1.9 (0.7) N = 70
P value[d]	*P* = 0.0004	*P* < 0.0001	
LS mean (SE) % change at 12 months	1.2 (6.7)	−0.2 (6.9)	19.5 (6.8)
LSMD % change (SE) vs. placebo	−18.3 (6.3)	−19.8 (6.3)	N/A
P value[d]	*P* = 0.0039	*P* = 0.0020	–
Mortality			
Deaths	1	0	0
Cause	Heart failure		
Symptoms — PBC-40 score[e]			
General Symptoms			
Baseline mean (SD)	13.8 (5.3)	12.9 (4.6)	13.6 (5.3)
Mean (SD) change from base to month 12	0.0 (3.7) N = 62	0.7 (3.5) N = 64	0.3 (2.9) N = 68
LSMD [95% CI] vs. placebo	−0.33 [−1.43 to 0.76] *P* = 0.5498[d]	0.22 [−0.87 to 1.31] *P* = 0.6920[d]	N/A
Itch			
Baseline mean (SD)	4.1 (3.6)	3.8 (3.3)	4.3 (3.7)
Mean (SD) change from base to month 12	0.9 (3.3)	1.1 (2.8)	0.2 (2.7)
LSMD [95% CI] vs. placebo	0.46 [−0.42 to 1.35] *P* = 0.3041[d]	0.62 [−0.25 to 1.50] *P* = 0.1617[d]	N/A
Fatigue			
Baseline mean (SD)	25.9 (10.8)	24.7 (9.4)	26.2 (11.2)
Mean (SD) change from base to month 12	−0.6 (5.9)	0.0 (7.3)	−2.1 (6.0)
LSMD [95% CI] vs. placebo	1.64 [−0.51 to 3.79] *P* = 0.1332[d]	1.92 [−0.21 to 4.06] *P* = 0.0766[d]	N/A
Cognitive Function			
Baseline mean (SD)	11.4 (5.4)	11.5 (5.3)	11.6 (6.0)
Mean (SD) change from base to month 12	0.1 (3.2)	0.5 (3.9)	0.3 (3.5)
LSMD [95% CI] vs. placebo	−0.16 [−1.35 to 1.03] *P* = 0.7928[d]	0.27 [−0.91 to 1.44] *P* = 0.6566[d]	N/A
Social			
Baseline mean (SD)	19.7 (8.6)	19.5 (7.7)	21.0 (8.8)
Mean (SD) change from base to month 12	0.1 (5.6)	0.5 (6.8)	−1.4 (6.2)
LSMD [95% CI] vs. placebo	1.22 [−0.86 to 3.30] *P* = 0.2494[d]	1.60 [−0.46 to 3.66] *P* = 0.1265[d]	N/A
Emotional			
Baseline mean (SD)	6.4 (2.9)	7.1 (2.7)	6.8 (3.3)
Mean (SD) change from base to month 12	−0.1 (2.1)	−0.2 (2.3)	−0.5 (2.1)
LSMD [95% CI] vs. placebo	0.34 [−0.36 to 1.04]	0.44 [−0.25 to 1.13]	N/A

Composite Primary	OCA Titration[a]	OCA 10 mg	Placebo
	P = 0.3366[d]	*P* = 0.2138[d]	
Morbidity	NR	NR	NR
Transplant	NR	NR	NR
Cirrhosis	NR	NR	NR
Markers of Fibrosis			
ELF Score,[f] Mean (SE) Baseline	9.76 (0.13)	9.81 (0.14)	10.03 (0.15)
LS mean (SE) change at 12 months	0.24 (0.12) N = 55	0.20 (0.12) N = 63	0.33 (0.13) N = 64
P value[d]	*P* = 0.4718	*P* = 0.2324	N/A
Hepatic Stiffness (FibroScan),[g] Mean (SE) Baseline	10.70 (1.46) N = 35	11.35 (1.45) N = 32	12.70 (1.71) N = 39
LS mean (SE) change at 12 months	1.28 (1.34) N = 32	0.46 (1.39) N = 26	1.82 (1.35) N = 34
P value[d]	*P* = 0.6818	*P* = 0.3267	N/A

ALP = alkaline phosphatase; ANCOVA = analysis of covariance; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; ELF = enhanced liver fibrosis; ITT = intention-to-treat; LS = least squares; MD = mean difference; N/A = not applicable; NR = not reported; OCA = obeticholic acid; PBC-40 = primary biliary cholangitis 40-item questionnaire; SD = standard deviation; SE = standard error; UDCA = ursodeoxycholic acid; ULN = upper limit of normal; vs. = versus.

[a] Dose titration to 10 mg daily occurred at 6 months for inadequate responders; remaining patients stayed at the 5 mg dose.

[b] *P* values obtained using CMH test stratified by randomization strata factor.

[c] Subgroup *P* values based on LS mean (SE) difference between OCA treatment and placebo and were obtained using CMH general association test stratified by randomization strata factor.

[d] *P* values for comparing OCA treatments with placebo were obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

[e] PBC-40 domain score ranges are as follows: general symptoms (6 to 35), itch (0 to 15), fatigue (11 to 55), cognitive function (6 to 30), social (8 to 50), and emotional (3 to 15). Higher scores indicate a poorer quality of life.

[f] ELF scores for fibrosis range as follows: 7.7 for a high sensitivity exclusion of fibrosis, 9.8 for a high specificity identification of fibrosis (sensitivity 69%, specificity 98% for moderate fibrosis), and 11.3 to discriminate cirrhosis (sensitivity 83%, specificity 97%).

[g] Hepatic stiffness: < 6 kPa, normal; ≥ 6 kPa to < 8 kPa, grey range (F1 to F2) — these 2 fibrosis stages are not well discriminated via FibroScan TE device; ≥ 8 kPa to < 12.5 kPa, advanced fibrosis (F3); ≥ 12.5 kPa, cirrhosis (F4).

Source: Clinical study report for POISE.[13]

Harms

Only those harms identified in the review protocol (Table 3) are reported below.

Adverse Events

The proportions of participants with adverse events after 12 months of therapy were similar in the OCA titration group and the placebo group (93% versus 90% of participants, respectively) (Table 8). The most common adverse event, which occurred in a numerically larger proportion of OCA titration than placebo participants, was pruritus (56% versus 38%, respectively), and the next most common adverse event was fatigue (16% versus 14%).

Serious Adverse Events

The proportion of participants with a serious adverse event was higher with OCA titration than with placebo (16% versus 4% of participants, respectively) (Table 8). None of the serious adverse events were considered to be related to OCA, and there was no pattern of specific serious adverse events that occurred more frequently than others.

Withdrawals Due to Adverse Events

There were more withdrawals due to adverse events in the OCA titration group than in the placebo group (7% versus 3% of participants) (Table 8).

Notable Harms

The notable harms for this review were pruritus and fatigue, and they were the most common harms in POISE, as reported above. Pruritus was also assessed as a safety outcome using the pruritus visual analogue scale and five-dimensions scale. There were no statistically significant differences reported between the OCA titration and placebo groups for change from baseline to month 12 on either scale (Table 8).

Table 8: Harms

	OCA Titration	OCA 10 mg	Placebo
Adverse Events			
Participants with > 0 AEs, N (%)	65 (93)	69 (95)	66 (90)
Most common AEs			
Pruritus	39 (56)	50 (68)	28 (38)
Fatigue	11 (16)	17 (23)	10 (14)
Nasopharyngitis	17 (24)	13 (18)	13 (18)
Serious Adverse Events			
Participants with > 0 SAEs, N (%)	11 (16)	8 (11)	3 (4)
Most common SAEs			
Osteoarthritis	0	2 (3)	0
Varicose veins	2 (3)	0	0
Withdrawals due to AEs			
WDAEs, N (%)	5 (7)	8 (11)	2 (3)
Notable Harms			
Pruritus	39 (56)	50 (68)	28 (38)
Pruritus VAS,[a] mean (SD) baseline	21.2 (25.9)	20.2 (24.5)	25.3 (27.5)
Mean (SD) change, baseline to month 12	4.6 (21.9)	2.1 (20.0)	−0.02 (22.2)
LS (SE) mean change, baseline to month 12	5.95 (3.80)	2.69 (3.84)	2.73 (3.82)
LSMD (95% CI) vs. placebo	3.22 (−3.80 to 10.25) *P* = 0.3664[b]	0.04 (−7.05 to 6.97) *P* = 0.9911[b]	N/A
Pruritus 5D,[c] mean (SD) total baseline	10.2 (3.6)	9.6 (4.3)	10.9 (5.0)
Mean (SD) change, baseline to month 12	1.4 (4.4)	1.2 (4.2)	−0.2 (3.3)
LS (SE) mean change, baseline to month 12	1.70 (0.75)	1.38 (0.75)	0.54 (0.76)
LSMD (95% CI) vs. placebo	1.16 (−0.20 to 2.53) *P* = 0.0929[b]	0.85 (−0.52 to 2.21) *P* = 0.2236[b]	N/A
Fatigue	11 (16)	17 (23)	10 (14)
HDL below LLN	8	11	5
Exposure, mean (SD) days on drug	341.7 (60.8)	308.9 (105.5)	346.0 (58.6)

5D = five-dimensions scale; AE = adverse event; ANCOVA = analysis of covariance; CI = confidence interval; HDL = high-density lipoprotein; LLN = lower limit of normal; LS = least squares; MD = mean difference; OCA = obeticholic acid; SAE = serious adverse event; SD = standard deviation; VAS = visual analogue score; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Pruritus VAS scores range from 0 to 100 (no pruritus to severe pruritus).

[b] *P* values for comparing active treatments with placebo obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

[c] Pruritus 5D score ranges from 5 to 25 (no pruritus to severe pruritus).

Source: Clinical study report for POISE.[13]

Discussion

Summary of Available Evidence

One manufacturer-sponsored, multi-centre, double-blind, randomized controlled trial met the inclusion criteria for this review. The POISE study randomized 216 participants with PBC in a 1:1:1 manner to OCA 10 mg, OCA titration (5 mg to 10 mg, depending on response), or placebo. Patients were treated for 12 months. The primary outcome of the study was the proportion of patients in the OCA 10 mg group compared with the placebo group who achieved an ALP less than 1.67 times the ULN, total bilirubin at ULN or lower, and a decrease in ALP of 15% or more from baseline at 12 months. Secondary outcomes included the proportion of patients in the OCA titration group compared with the placebo group who achieved the primary outcome. Limitations of POISE include the fact that it evaluated health-related quality of life only as an exploratory outcome and that the study was not powered to assess key clinical outcomes such as mortality and various PBC-related morbidities. Although treatment with OCA titration did improve various liver-related markers such as ALP and bilirubin, pruritus, which is one of the key symptoms and quality-of-life issues of PBC, appeared to be more common in the OCA treatment groups than in the placebo group.

Interpretation of Results

Efficacy

The indication for OCA and the reimbursement request suggest that OCA either will be combined with UDCA or will be used as monotherapy in patients who cannot tolerate UDCA. More than 90% of patients in POISE were already on UDCA, and therefore there is a lack of data on the use of OCA as monotherapy. One of the phase II studies that did not meet the inclusion criteria for the CDR systematic review compared OCA monotherapy with placebo and found superiority for the primary outcome versus placebo. However, this study used OCA 10 mg, which is not the recommended starting dose in Canada (see 0 for further details). The clinical expert consulted for this review believes that only a small minority of patients with PBC will use OCA as monotherapy; however, this is still a gap in evidence. According to the product monograph, Health Canada granted approval for the use of OCA as monotherapy based on a pooled analysis of data from the OCA 10 mg group in POISE and the 10 mg group from the phase II study. Note that this is not the Health Canada–approved starting dose for OCA.[7] Additionally, little is known about the relative efficacy of OCA compared with UDCA. There were no network meta-analyses identified that would be relevant for this review, and POISE was a placebo-controlled study. Therefore, the relative efficacy and harms of these two drugs are unknown. Pruritus is also an adverse effect associated with UDCA, so it is not clear whether patients who are unable to tolerate UDCA will see an improvement with OCA. This is especially important given how important pruritis is as a quality-of-life issue to patients with PBC.

The POISE study was not of sufficient duration or size to assess clinical outcomes such as mortality or the various morbidities (e.g., cirrhosis, need for transplant) associated with PBC. Therefore, the primary analysis in POISE was composed of surrogate markers such as ALP and bilirubin, and the various secondary outcomes all focused on these as well. PBC is a relatively uncommon disease; therefore, the lack of large-scale trials is not unusual. Both ALP and bilirubin are considered acceptable markers for worsened clinical outcomes in PBC (see review in 0); however, no specific MCID was found for either biomarker. Any elevation in ALP or bilirubin above the ULN is associated with worse clinical outcomes. Both the FDA and the European Medicines Agency gave OCA fast-track approval based on these surrogate end points. The FDA noted that, in the majority of participants, response to OCA for the primary composite end point was based on ALP, as 90% of participants had normal bilirubin at baseline. After reviewing data from other groups studying PBC, as well as its own independent review, the FDA concluded that ALP is predictive of clinical outcomes. The response seen for primary and secondary end points in POISE resulted in the recommendation for accelerated approval of OCA for PBC.[15] The European Medicines Agency granted OCA conditional approval based on ALP and bilirubin data, pending results from two additional studies — one designed to assess the effects of OCA on clinical outcomes and the other to assess OCA in patients with moderate to severe liver disease.[22] Health Canada granted an NOC/c to OCA, also on the condition of the completion of these two studies, with results expected in April 2023.[7] The clinical expert consulted on this review also believed the composite outcome to be appropriate and validated for this disease condition.

Health-related quality-of-life results reported using the PBC-40 suggested that there were no statistically significant differences between OCA-treated and placebo groups for any subscales, including itch. The fact that pruritus is a major symptom of PBC but also a common adverse effect of OCA therapy makes it challenging to determine the impact of OCA on patients' overall quality of life. Although 56% of participants in the OCA group experienced pruritus, 38% of placebo-treated participants also experienced pruritus. Patients identified pruritus as one of their major quality-of-life issues with respect to PBC; given this importance, the overall impact of OCA therapy is unclear.

A limitation of this review is that the findings are all based on a single study, POISE. There were two additional double-blind randomized controlled trials, both phase II studies, which did not meet the inclusion criteria for this review, as neither used the recommended dose of OCA (see 0 for detailed review). These studies were only three months in duration; however, they did report findings that were similar to those in POISE, with statistically significant improvements compared with placebo for the same primary composite outcome and indications of an increased risk of pruritus in patients treated with OCA.

An additional gap in evidence for OCA in PBC includes the lack of data in patients with advanced liver disease. This may be of particular relevance because OCA is eliminated by the liver and because of the hepatic-related harms seen at higher doses, described in the next section. In the Health Canada–approved product monograph, it is noted that plasma levels of OCA increase in patients with moderate to severe hepatic impairment (Child–Pugh classes B and C). Study 747-401 is an ongoing trial that will include patients with advanced liver disease, and this was a condition for the Health Canada authorization of OCA.

Harms

There were more OCA-treated patients with a serious adverse event compared with placebo-treated patients (16% versus 4% of participants). However, there was no clear increase in risk of any specific serious adverse events; therefore, the interpretation of this finding for overall serious adverse events is challenging.

The Health Canada–approved product monograph notes that, in the two six-month phase II studies, there was a dose-related increase in the risk of hepatic-related adverse events — including jaundice, worsening ascites, and flares of PBC — associated with OCA at doses between 10 mg and 50 mg daily. In a pooled analysis of three placebo-controlled, double-blind randomized controlled trials, the exposure-adjusted incidence rates for all serious and otherwise clinically significant liver-related adverse reactions, and isolated elevations in liver biochemical tests, were 5.2 per 100 patient exposure years in the OCA 10 mg group, 19.8 in the OCA 25 mg group, and 54.5 in the OCA 50 mg group compared with 2.4 in the placebo group. The Health Canada–approved product monograph advises close monitoring of patients for elevations in liver-related biochemical tests and liver-related adverse reactions. In POISE, there was no dose-related increase in hepatic-related adverse events, even at the OCA 10 mg dose.

Potential Place in Therapy[2]

Before the approval of OCA, there was only one approved therapy for PBC, UDCA, which has been shown to increase overall and transplant-free survival.[8,9] Approximately 40% to 50% of patients experience an inadequate response to UDCA, as defined by biochemical measures (i.e., ALP, bilirubin),[4,5] and an additional 10% of individuals with PBC cannot tolerate UDCA. In patients who have a suboptimal response, there is a poorer prognosis, and there are currently no other therapies available. These are two important unmet medical needs in the therapy of PBC.

Obeticholic acid is a farnesoid X receptor agonist affecting biliary homeostasis; it has been shown to decrease inflammation and to have antifibrotic activity.[10,11] In the phase III POISE study,[12] the addition of OCA to UDCA resulted in a biochemical response in 46% of patients (versus 10% of patients in the placebo group) who had a prior suboptimal response or intolerance to UDCA. The POISE study primary end point (i.e., composite of the proportion of participants achieving an ALP less than 1.67 times ULN, total bilirubin at ULN or lower, and decrease in ALP of 15% or more from baseline at month 12) is a validated outcome and has previously been shown to be predictive of the natural history of PBC. In clinical practice, OCA would be added to UDCA in patients who did not respond adequately to UDCA (defined as ALP more than 1.67 times ULN after one year) or would be used as stand-alone therapy in patients who could not tolerate UDCA. The criterion for initiating OCA is the ALP level and is independent of fibrosis.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Not surprisingly, given that the phase III study was of short duration, there was no improvement in fibrosis regression or mortality seen.

Overall, OCA is well tolerated, although there is a signal of increased pruritus, which is dose-dependent. Thus, OCA is to be titrated up from 5 mg to 10 mg daily at six months, depending on the patient's biochemical response to the drug. In the majority of patients, pruritus was manageable and did improve to some degree.[12] Prescribers should ensure that patients are adequately informed of the risks of pruritus at the 10 mg dose and that a management strategy for pruritus is available.

According to the clinical expert consulted for this review, OCA is a welcome and important addition to the therapy of PBC, as there has been a significant unmet medical need. PBC can result in decompensated liver disease and increased mortality if not treated adequately.

Conclusions

One manufacturer-sponsored, double-blind randomized controlled trial met the inclusion criteria for this CDR review. The POISE study randomized 216 patients with PBC in a 1:1:1 manner to OCA titration (initiated at 5 mg daily, inadequate responders increased to 10 mg daily after six months), OCA 10 mg daily, or placebo. The primary analysis compared the OCA 10 mg dose with placebo; however, according to the Health Canada–approved product monograph, this dose is not approved as an initial starting dose in Canada. Therefore, the focus of this review was on comparisons between OCA titration and placebo. The OCA titration group was superior to placebo for the primary composite outcome consisting of combined reductions in ALP and bilirubin after 12 months of therapy (secondary efficacy analysis), and was also superior to placebo for ALP and bilirubin reductions separately. There were no statistically significant differences in any health-related quality-of-life subscales on the PBC-40, including itch and fatigue, versus placebo. Pruritus was the most common adverse event in the OCA titration group but it is also a common symptom of PBC, which complicates the interpretation of the benefit of OCA for symptoms of PBC. Serious adverse events were numerically more common in the OCA titration than the placebo group; however, there was no specific pattern of serious adverse events attributable to OCA.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input

Two patient groups provided input for this submission.

The Canadian Primary Biliary Cholangitis Society, founded in 2003, is a non-profit charitable organization comprising volunteers, primary biliary cholangitis (PBC) patients, and their families and caregivers. The Society's mission is to provide compassionate support, develop and deliver information including education programs, raise awareness, and raise funds for PBC research, treatment, and a cure. The Society has received unrestricted grants and sponsorships from Intercept Pharmaceuticals in 2016 and 2017 and declares no conflicts of interest in the preparation of this submission.

The Canadian Liver Foundation, founded in 1969, is a national organization committed to reducing the incidence and impact of liver disease for Canadians living with or at risk of liver disease through investment in scientific research on the causes of, preventive measures for, and potential treatments for liver disease, including viral hepatitis. The Foundation reaches more than 250,000 Canadians through public and professional education, patient support programs, fundraising, and outreach efforts. The Foundation has received unrestricted educational grants or has worked on joint initiatives with AbbVie Corporation, Alexion Pharma Canada, Astellas Pharma Canada Inc., BD Biosciences, BTG Biocompatibles, Bristol-Myers Squibb Canada, Gilead Sciences Canada, Intercept Pharmaceuticals Inc., Lupin Pharma Canada, Merck Canada, Pendopharm, Qiagen, and Sirtex Medical and declares no conflicts of interest in the preparation of this submission.

2. Condition-Related Information

The Canadian Liver Foundation and the Canadian Primary Biliary Cholangitis Society gathered information for this submission via online surveys. Additionally, the Canadian Primary Biliary Cholangitis Society gathered information from in-person conversations during PBC self-management workshops.

PBC is an incurable autoimmune disease in which the immune system attacks the liver, which results in slow, progressive damage to the bile ducts. Once bile ducts are sufficiently damaged, bile and other substances cannot be eliminated and accumulate in the liver. The accumulation of toxic substances results in inflammation, cirrhosis, and ultimately liver failure. PBC primarily affects women between 40 and 60 years of age, and approximately 9,000 to 11,000 people in Canada are diagnosed with this condition. The manifestation of PBC symptoms includes fatigue, constant itching (pruritus), joint pain, insomnia, mood swings, social isolation, depression, diarrhea, dry eyes, nausea, cognitive dysfunction, night sweats, and osteoarthritis. In addition, according to patient groups, more than half of patients suffering from PBC also suffer from at least one additional autoimmune disease such as thyroiditis, rheumatoid arthritis, Raynaud syndrome, or inflammatory bowel disease.

Patients indicated that PBC deteriorates quality of life, mainly as a result of fatigue and itch. Fatigue was described as debilitating and independent of the amount of sleep, making most tasks impossible. Patients expressed difficulty with employment, driving, caring for children, cooking, cleaning, and participating in physical or social activities. Those suffering from PBC also indicated that fatigue impairs their ability to maintain personal relationships, frequently resulting in social isolation and depression. In addition, some patients associated fatigue with cognitive dysfunction resulting in work absenteeism and workplace stigma. Itch was described as another PBC symptom leading to the deterioration of quality of life. One patient described itch as "a thousand ants crawling on the inside of your skin," far beyond the itch associated with topical rash or insect bite. Patients suffering from PBC indicated that itch is typically worse during the night and may interrupt or prevent sleep, further contributing to fatigue. Patients described lack of itch relief with the use of medication or intense scratching, which can result in dangerous skin infections. Patient groups indicated that the unrelenting itch can be associated with feelings of suicide or attempted suicide. One patient described life with PBC: "Falling asleep while at my desk or fighting to stay awake was all encompassing. Reducing my work days to four days per week made no difference nor did sleeping for eight to 10 hours per night. It definitely hampered my social life as well as my family's social life. Outings became difficult to plan ahead due to fatigue. Itching was also a factor in daily life. Evenings were more difficult with itching as well at bedtime. Sharing a bed with my spouse became next to impossible as my constant scratching kept him awake. Skin sensitivity was a major factor in shopping and wearing of clothes. My skin was so sensitive to buttons, seams, tags, fabrics. Once I

was prescribed cholestyramine it helped. The other factor is arthritis, painful joints, bones, and muscles, and dealing with osteoarthritis as well."

According to patient groups, advanced PBC may result in complications such as liver failure, liver transplant, variceal bleeding, portal hypertension, hepatocellular carcinoma, and jaundice. Those suffering from PBC expressed fear, stress, and anxiety with respect to disease progression: "There is always a cloud of fear lingering above my head. Will I be able to go to work tomorrow? Will I need a transplant? Will I live to see my grandchildren?"

3. Current Therapy–Related Information

Only one therapy is currently available for treatment of PBC — ursodeoxycholic acid (UDCA) — which can be used to slow the progression of the disease. Although UDCA is effective in the management of PBC for some, 40% to 50% of patients do not respond adequately to treatment, and approximately 5% are intolerant to treatment with UDCA. Despite treatment, some patients will progress to advanced liver disease and suffer jaundice, variceal bleeding, and portal hypertension and may develop liver cancer.

Side effects associated with UDCA treatment vary widely from patient to patient. Some experience no side effects while others can experience weight gain, dizziness, flu-like symptoms, indigestion, acid reflux, constipation, stomach pain, and hair loss in addition to PBC-like symptoms such as fatigue, nausea, diarrhea, and itching.

Patients expressed their dissatisfaction with UDCA treatment, emphasizing the financial burden resulting directly from the treatment cost and indirectly from the plethora of concomitant treatments necessary to manage PBC symptoms. One patient stated, "I have chronic diarrhea now. Also terribly bloated, I look about 8 months pregnant. Since I am on CPP disability and my husband works for the federal government, we do have 80% coverage. I am a cardiac patient and have meds for that. I suffer from depression/anxiety and have meds for that. I have reflux and on meds for that. I am on sleeping meds and pain meds. My husband is a cardiac patient, meds for that, has type 2 diabetes so meds for that. It adds up to more than half of my disability cheque. I have not been on Urso or Zaxine for three weeks as I can't afford them."

In addition to the financial burden, patients also expressed their discontent with the time commitments required for follow-ups. One patient said, "The financial burden of this disease is terrible. I can no longer work and have so many appointments and tests to manage."

According to patient groups, those who suffer from PBC rely heavily on caregivers (typically spouses and family members) for support. Caregivers are required to take on more household and financial responsibilities. In more advanced disease, caregivers must also help coordinate medical appointments, tests, and medications as well as try to provide emotional support. One patient stated, "I can no longer work and have so many appointments and tests to manage. People get tired of it after a while and no longer offer any assistance. … I have to have regular endoscopies to monitor these. Regular ultrasounds and CT scans are another two tests that are repeated frequently." As patients become physically and socially isolated due to PBC symptoms, additional fear, frustration, and stress are placed on relationships. One patient reported, "…I've really found out who will stand by me on my bad days and be a support when I need someone…"

4. Expectations About the Drug Being Reviewed

Patients with no experience with obeticholic acid (OCA) are generally excited and hopeful for another option to treat PBC. These patients expect OCA to slow and control disease progression, leading to better quality of life and normal life expectancy. In addition, patients expect OCA to address symptoms such as fatigue, leading to more independence and productivity, and requiring less support from caregivers. On the contrary, some patients are concerned about increased side effects, accessibility, and cost. One patient stated, "I would like to try this drug to see if it is easier for me to tolerate than Urso and if it would improve my quality of life. I would like to know what the side effects are as I have heard that it increases itching."

Patients with experience with OCA expect the therapy to slow PBC progression and improve liver condition. In addition, these patients expect decreased risk of liver failure, fewer liver transplants, and fewer deaths. Patient groups indicated that OCA is expected to improve PBC in UDCA responders and nonresponders alike, based on a clinical trial. One patient with OCA experience

indicated itching as a side effect: “The only side effect that I experienced was itching at the beginning; after a few weeks, the itching resolved.”

One of the patient groups was not able to include patients with OCA experience and instead consulted a clinician who provided information that echoed the voice of patients with OCA experience.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 27, 2017
Alerts:	Weekly search updates until June 21, 2017
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid database code; **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1**946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(obeticholic* or ocaliva* or int747 or int-747).ti,ab,ot,kf,hw,nm,rn.
2	(459789-99-2 or 0462Z4S4OZ).rn,nm.
3	1 or 2
4	3 use ppez
5	(obeticholic* or ocaliva* or int747 or int-747).ti,ab,kw.
6	obeticholic acid/

MULTI-DATABASE STRATEGY	
#	**Searches**
7	5 or 6
8	7 use oemezd
9	4 or 8
10	remove duplicates from 9
11	conference abstract.pt.
12	10 not 11

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	January 23 – 24, 2017
Keywords:	Ocaliva (obeticholic acid)
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
THOMAS Nat Rev Gastroenterol Hepatol 2016;13(10):558-9	Not an RCT (Review)
GERKEN et al. Internist (Berl). 2017 Feb;58(2):202-204	German language
Nature Reviews Gastroenterology and Hepatology 2015;12(62)	Not an RCT (Review)
HIRSCHFIELD et al. Gastroenterology 2015;148(4):751-61	Not an approved dose

RCT = randomized controlled trial.

Appendix 4: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- serum alkaline phosphatase (ALP)
- serum bilirubin
- enhanced liver fibrosis (ELF) test
- transient elastography (TE)
- primary biliary cholangitis 40-item questionnaire (PBC-40)

Findings

A summary of findings for serum ALP, serum bilirubin, PBC-40, ELF test, and TE can be found in Table 9.

Table 9: Summary of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
Serum ALP	Serum ALP is a measure of alkaline phosphatase in the blood.	Yes	Unknown	Lammers et al. [23]
Serum bilirubin	Serum bilirubin is a measure of bilirubin in the blood.	Yes	Unknown	Lammers et al. [23]
PBC-40	Patient-reported disease-specific HRQoL questionnaire based on six domains evaluated on a 5-point Likert scale.	Yes	Unknown	Jacoby et al. [24]
ELF test	Test scores are calculated based on predefined formula and biochemical marker concentrations of serum hyaluronic acid, tissue inhibitor of metalloproteinase 1, and procollagen type III N-terminal propeptide.	Yes	Unknown	Mayo et al.[19]
TE	Liver stiffness measurement is considered to represent the elastic modulus based on 10 consecutive measurements as measured in kilopascals.	Yes	Unknown	Corpechot et al. [25]

ALP = alkaline phosphatase; ELF = enhanced liver fibrosis; HRQoL = health-related quality of life; MCID = minimal clinically important difference; PBC-40 = primary biliary cholangitis 40-item questionnaire; TE = transient elastography.

Alkaline Phosphatase and Bilirubin

Serum ALP and serum bilirubin are biochemical surrogate markers that historically have been suggested to predict clinical outcomes in patients with primary biliary cholangitis (PBC).[4,26-29]

Generally, elevated ALP may indicate cholestasis at any stage of PBC and is a major component in the diagnosis of PBC according to US and European guidelines.[30,31] Many studies have attempted to evaluate the association of ALP with clinical outcomes as well as the surrogate markers' ability to predict PBC progression. A meta-analysis conducted by Lammers et al. combined the data from international, multi-centre, long-term follow-up cohorts to specifically assess the prognostic potential of ALP and bilirubin in PBC.[23] A total of 4,885 patients with PBC and treated with or without ursodeoxycholic acid (UDCA) were included in the study and were followed up for a median of 7.3 years. Overall, ALP and bilirubin levels at baseline and each following year, up to five years, were correlated with clinical outcomes (death and liver transplantation). Lower levels of ALP and bilirubin typically corresponded to better clinical outcomes, whereas higher levels corresponded to poorer clinical outcomes. Predictive abilities based on ALP thresholds ranging from 1.0 times upper limit of normal (ULN) to 3.0 times ULN (in increments of 0.1) were analyzed to determine the most predictive end point. ALP 2.0 times ULN was identified as the most predictive (C-statistic 0.71; hazard ratio [HR] 2.49; 95% confidence interval [CI], 2.14 to 2.89; $P < 0.001$); however, it was not significantly better than any other analyzed thresholds. ALP 1.67 times ULN was also analyzed (C-statistic 0.70; HR 2.18; 95% CI, 1.88 to 2.53; $P < 0.001$). Results for the per cent change in ALP also demonstrated that greater per cent decreases in ALP were associated with better clinical outcomes (10% reduction in ALP; HR 0.98; 95% CI, 0.96 to 0.99; $P < 0.01$). However, only > 40% decrease in ALP thresholds were found to be significant in predicting clinical outcomes. Overall, the absolute ALP level was reported as a better predictor than the percentage change in ALP. Furthermore, the predictive abilities of bilirubin were also assessed at multiple thresholds and found to be even more strongly correlated with poor clinical outcomes. Bilirubin times 1.0 ULN was identified as the most predictive (C-statistic 0.79; HR 5.06; 95% CI, 4.34 to 5.89; $P < 0.001$). The study also suggested that the combination of ALP and bilirubin threshold criteria increased the prognostic abilities to detect clinical outcomes. In addition, the study analyzed the predictive abilities of the biochemical surrogate markers in multiple subgroups (e.g., with or without UDCA, age, and gender) and suggested similar predictive abilities in all subgroups. Lammers et al. concluded that ALP and bilirubin are associated with death and liver transplantation in patients with PBC and can be considered as appropriate biochemical surrogate markers in clinical trials.

Lammers et al. also performed another international, multi-centre meta-analysis that combined the data from long-term follow-up cohorts to assess prognostic factors in PBC. A total of 4,119 patients with PBC and treated with UDCA were included in the study. Overall, Lammers et al. suggested that levels of ALP and bilirubin greater than ULN are associated with clinical outcomes (death or liver transplant: HR 1.40; 95% CI, 1.18 to 1.62; $P = 0.0002$; and HR 2.56; 95% CI, 2.22 to 2.95; $P < 0.0001$; respectively).[32]

Corpechot et al. conducted two studies (n = 165 and n = 292) following patients with PBC and treated with UDCA for one to five years.[4,27] One study suggested that total bilirubin levels greater than 1 mg/dL and ALP greater than three times ULN were associated with HR 2.14 (95% CI, 1.16 to 4.21; $P < 0.05$) and HR 3.49 (95% CI, 1.52 to 14.94; $P < 0.01$) for the following end points: liver-related death, liver transplantation, complications of cirrhosis, or histological evidence of cirrhosis development.[27] A second study also reported that total bilirubin levels greater than 1 mg/dL and ALP greater than three times ULN were associated with relative risk (RR) 1.7 (95% CI, 1.1 to 2.6; $P < 0.0131$) and RR 1.6 (95% CI, 1.2 to 2.0; $P < 0.0039$) for death or liver transplant.[4] Both studies suggest that the risk of death or liver transplant was increased with higher levels of bilirubin and ALP.

Bonnand et al. combined the data from three long-term trials evaluating the effect of UDCA in patients with PBC to assess the effect of bilirubin on orthotopic liver transplantation or death.[29] A total of 548 participants were included and followed for up to four years. Overall, survival free of orthotopic liver transplantation was significantly longer in patients treated with UDCA achieving normalized bilirubin levels (RR 3.7; 95% CI, 2.0 to 6.9; $P < 0.0001$). This was not significantly different when compared with patients not treated with UDCA but with normalized bilirubin levels ($P = 0.69$). To conclude, Bonnand et al. suggested that normalization of bilirubin is associated with improved clinical outcome and can be considered as an adequate prognostic factor in PBC.

Zhao et al. aimed to study prognostic factors associated with liver failure in patients with PBC treated with UDCA. A total of 398 patients were included. The results suggested that higher serum concentrations of bilirubin (43.7 µmol/L versus 23.2 µmol/L) were associated with the development of liver failure ($P = 0.013$).[26]

Overall, higher levels of serum ALP and bilirubin were associated with poorer clinical outcomes such as liver transplant and death.

Enhanced Liver Fibrosis Test

ELF test scores are based on the biochemical markers serum hyaluronic acid, tissue inhibitor of metalloproteinase 1, and procollagen type III N-terminal propeptide.[19,20] Scores are calculated based on predefined formulas and concentrations of these biochemical markers. Scores under 7.7 indicate no or mild liver fibrosis, whereas scores between 7.7 and 9.8 or above 9.8 specify moderate or severe liver fibrosis, respectively.[21]

In a study conducted by Mayo et al., serum fibrosis markers were evaluated in a large cohort of patients (161 patients with a 7.3-year median follow-up period) with PBC (between 1993 and 2003) in a multi-centre US clinical trial to examine their ability to predict clinical outcomes.[20] Only patients with established PBC (compensated only) were included, as measured by either a positive antimitochondrial antibody and either an abnormal ALP or stage I disease on liver biopsy. Patients underwent testing (including a physical and serum blood tests) at baseline and every three months thereafter, in addition to percutaneous liver needle core biopsy ("gold standard" liver function test), endoscopy (for varices), and ultrasounds (for ascites) performed at baseline and every two years thereafter. Serum blood tests were also collected on the same day as liver biopsies for further investigation. Four independent pathologists reviewed all biopsies, and a mean PBC stage was assigned based on the predefined criteria in Table 10. All prognostic tests (such as ELF and serum bilirubin) were examined to determine their predictive ability for clinical progression (defined as the development of one of the following events: new varices, variceal bleed, ascites, encephalopathy, liver-related death, or liver transplantation). Overall, all prognostic tests were significantly higher at baseline in patients who experienced clinical progression. Overall, 8%, 24%, and 46% of patients with low, intermediate, and high baseline ELF scores, respectively, progressed clinically during follow-up. ELF scores demonstrated correlation with biopsy findings using the Spearman rank order correlation test ($r = 0.60$; $P < 0.0001$). An ELF score increase of 1 point was estimated to be associated with a threefold increase in clinical progression. ELF diagnostic test performance was also assessed using area under the receiver operating characteristics (AUROC) curves representing sensitivity versus specificity to assess the ability of the ELF score to predict all stages of fibrosis. The Ishak method and ELF score demonstrated the greatest predictive values (no statistically significant difference in the AUROC of ELF and histological staging). The diagnostic accuracies based on this method were 0.76 (95% CI, 0.63 to 0.89) to predict cirrhosis and 0.72 (95% CI, 0.67 to 0.82) to predict fibrosis. The prognostic performance of ELF score was also greater than other non-invasive tests (such as bilirubin). Mayo et al. suggested that, overall, the ELF score was an accurate non-invasive marker that may be superior to PBC stage (liver biopsy) for predicting clinical progression, although no test is without error.

Another study (Friedrich-Rust et al.) aimed to compare the results of the non-invasive test (ELF) in patients with chronic liver disease (28 with PBC) between 2005 and 2008 who received a liver biopsy. Comparisons were made using histology as the reference method.[19] One independent and experienced pathologist reviewed all biopsies in a blinded manner and assigned a histological stage of fibrosis based on Ludwig's classification (defined in Table 11). ELF scores demonstrated correlation with biopsy findings using the Spearman rank order correlation test ($r = 0.61$; $P < 0.0001$). ELF diagnostic test performance was also assessed using AUROC curves representing sensitivity versus specificity to assess the ability of the ELF score to predict all stages of fibrosis. The diagnostic accuracies based on this method for the diagnosis of fibrosis (stage II, stage III, and stage IV) were 0.78 (95% CI, 0.67 to 0.89), 0.79 (95% CI, 0.67 to 0.91), and 0.92 (95% CI, 0.83 to 1.00), respectively. Further details with respect to the diagnostic performance of ELF in the prediction of significant fibrosis (stage II), severe fibrosis (stage III), and cirrhosis for PBC patients are summarized in (Table 13) [19] Friedrich-Rust et al. suggested that, overall, the ELF score can be performed with comparable diagnostic accuracy for the non-invasive staging of liver fibrosis.[19]

Table 10: Fibrosis Scoring Systems

	Ishak Score
0	No fibrosis
1	Fibrous expansion of some portal areas, with or without short septae
2	Fibrous expansion of most portal areas, with or without short septae
3	Fibrous expansion of most portal areas with occasional portal to portal (P-P) and/or portal to central (P-C) bridging
4	Fibrous expansion of portal areas with marked bridging (P-P as well as P-C)
5	Marked bridging (P-P as well as P-C) with occasional nodules (incomplete cirrhosis)
6	Cirrhosis (probable or definite)
	Primary Biliary Cholangitis Histological Stage
1	No fibrosis (some portal inflammation at baseline biopsy)
2	Non-bridging fibrosis (any grade of fibrosis under stage III with portal tracts expanded beyond the limiting plate)
3	Bridging fibrosis (at least two P-P bridges)
4	Cirrhosis (one or more regenerative nodules surrounded by fibrosis)

P-C = portal to central; P-P = portal to portal.

Source: Mayo et al.[20]

Table 11: Ludwig's Classification (PBC Histological Stage)

1	Inflammation and/or abnormal connective tissue is confined to portal triads
2	Number of normal bile ducts is reduced; the inflammation and/or fibrosis is confined to portal and periportal areas
3	Fibrous septa link adjacent portal triads (bridging fibrosis)
4	Cirrhosis with regenerative nodules

Source: Friedrich-Rust et al.[19]

Table 12: Diagnostic Performance of ELF in the Prediction of Fibrosis in PBC Patients

Fibrosis	ELF Score Cut-Off	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR
Stage II	9.69	0.65	0.75	0.87	0.46	2.60	0.47
Stage III	9.71	0.62	0.53	0.53	0.62	1.32	0.72
Stage IV	9.89	1.00	0.52	0.07	1.00	2.01	0.00

ELF = enhanced liver fibrosis; LR = likelihood ratio; NPV = negative predictive value; PBC = primary biliary cholangitis; PPV = positive predictive value.

Source: Friedrich-Rust et al.[19]

Transient Elastography

TE is a mean liver stiffness measurement of fibrosis (measured in kilopascals) following 10 consecutive measurements with the potential of detecting and monitoring hepatic stiffness, and is considered to represent the elastic modulus of the liver.[17,18] It has been suggested that values of at least 12.5 kPa (threshold) are indicative of cirrhosis in patients with chronic liver disease, with a range between 12.5 kPa and 75.5 kPa. Due to the variability in this measure, its clinical relevance remains unknown.[18]

Friedrich-Rust et al. aimed to compare the results of the non-invasive test (TE) in patients with chronic liver disease (only in patients with available TE data) between 2005 and 2008 who received a liver biopsy. Comparisons were made using histology as the reference method.[19] One independent and experienced pathologist reviewed all biopsies in a blinded manner and assigned a histological stage of fibrosis based on Ludwig's classification (defined in Table 11). TE scores demonstrated correlation with biopsy findings using the Spearman rank order correlation test ($r = 0.58$; $P < 0.001$). TE diagnostic test performance was also assessed using AUROC curves representing sensitivity versus specificity to assess the ability of the TE score to predict all stages of fibrosis. The diagnostic accuracies based on this method for the diagnosis of fibrosis (stage II, stage III, and stage IV) were 0.80 ($P = 0.42$),

0.66 (*P* = 0.60), and 0.94 (*P* = 0.60), respectively. Further details with respect to the diagnostic performance of TE in the prediction of significant fibrosis (stage II), severe fibrosis (stage III), and cirrhosis for PBC patients are summarized in Table 13. Friedrich-Rust et al. suggested that larger randomized trials assessing long-term survival devoid of liver disease complications (such as death, liver transplantation, decompensation, variceal bleeding, and hepatocellular carcinoma) are required to compare TE non-invasive methods with liver biopsy.

A similar study conducted by Corpechot et al. also aimed to compare the results of the non-invasive test (TE) with liver biopsy in patients with chronic hepatitis C (73 with PBC) in a multi-centre study.[25] Histological and fibrosis stages were assessed through liver biopsy by two pathologists. TE scores demonstrated correlation with biopsy findings using the Spearman rank order correlation test (r = 0.86; *P* < 0.001). TE diagnostic test performance was also assessed using AUROC curves representing sensitivity versus specificity to assess the ability of the TE score to predict all stages of fibrosis. AUROCs were 0.92 (95% CI, 0.87 to 0.98), 0.95 (95% CI, 0.91 to 0.99), and 0.96 (95% CI, 0.93 to 1.00) for fibrosis stage II or greater, stage III or greater, and stage IV, respectively. Corpechot et al. suggested that, overall, TE is a simple and reliable non-invasive method and should be a promising tool to assess biliary fibrosis.

A study by Gomez-Dominguez et al. also aimed to compare the results for hepatic fibrosis of the non-invasive test (TE) with liver biopsy in patients with PBC (80 patients).[17] Histological and fibrosis stages were assessed through liver biopsy by one independent pathologist in a blinded manner according to Scheuer's criteria. TE scores demonstrated correlation with biopsy findings using the Kendall coefficient (0.56, *P* < 0.005). TE diagnostic test performance was also assessed using AUROC curves representing sensitivity versus specificity to assess the ability of the TE score to predict all stages of fibrosis. AUROCs were 0.86 and 0.96 for fibrosis stage III or greater and stage IV, respectively. Further details with respect to the diagnostic performance of TE in the prediction of significant fibrosis for PBC patients are summarized in Table 14. In conclusion, Gomez-Dominguez et al. suggested that TE is an easy, safe, and rapid non-invasive procedure that can be used to provide a useful index and monitor of hepatic fibrosis in patients with PBC.

Table 13: Diagnostic Performance of TE in the Prediction of Fibrosis in PBC Patients; Friedrich-Rust et al. Study

Fibrosis	TE Cut-Off (kPa)	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR
Stage II	7.30	0.39	1.00	1.00	0.31	Invalid	0.61
Stage III	9.80	0.25	0.91	0.75	0.53	2.75	0.83
Stage IV	17.30	1.00	0.95	0.50	1.00	22.00	0.00

TE = transient elastography; LR = likelihood ratio; NPV = negative predictive value; PBC = primary biliary cholangitis; PPV = positive predictive value.

Source: Friedrich-Rust et al.[19]

Table 14: Diagnostic Performance of TE in the Prediction of Fibrosis in PBC Patients; Gomez-Dominguez et al. Study

Fibrosis	TE Cut-Off (kPa)	Sensitivity	Specificity	PPV	NPV
Stage III	14.7	0.56	1.00	1.00	0.83
Stage IV	15.6	0.88	0.98	0.88	0.98

TE = transient elastography; NPV = negative predictive value; PBC = primary biliary cholangitis; PPV = positive predictive value.

Source: Gomez-Dominguez et al.[17]

Primary Biliary Cholangitis–40-Item Questionnaire

PBC-40 is a disease-specific health assessment questionnaire that has been used in clinical trials to study the impact of PBC on health-related quality of life. The PBC-40 consists of six domains and 40 items: symptoms (7 items), itch (3 items), fatigue (11 items), cognition (6 items), social (10 items), and emotional (3 items). Individual items are scored on Likert scales ranging from 1 ("not at all" or "never") to 5 ("very much" or "always"). Item scores in a given domain are summed to provide a total domain score. Domain score ranges are as follows: general symptoms (6 to 35), itch (0 to 15), fatigue (11 to 55), cognitive function (6 to 30), social

(8 to 50), and emotional (3 to 15). The directions of some items are reversed when calculating the total domain scores so that, overall, high scores indicate greater impact and low scores indicate lower impact of PBC on quality of life.[24] No minimal clinically important difference (MCID) was found for the PBC-40.

Jacoby et al. developed, validated, and evaluated the PBC-40 in patients (985 participants) with definite or probable PBC in the UK.[24] The study included three phases. The first phase consisted of in-depth interviews with patients (30 participants) to derive initial measures based on how PBC has affected their lives. These measures were subsequently reduced and refined after administration in a large patient cohort (> 500 patients). The second phase validated the refined PBC-40 questionnaire in a cohort of 400 patients to evaluate the psychometric properties (validity, reliability, precision, and acceptability) in PBC patients.

Test–retest reliability was assessed in a subgroup of the included cohort two weeks after completing the original survey using intraclass correlation coefficients with a minimum threshold of 0.9 and 0.5 for individual and group comparisons, respectively. Furthermore, intraclass correlation ranged from 0.83 to 0.96; therefore, all domains satisfied the criteria for group comparisons. Furthermore, three domains (fatigue, cognitive, and itch) also met the criteria for individual comparisons (coefficient > 0.9). Internal consistency of the domains was evaluated using Cronbach's alpha coefficient with a minimum threshold of 0.70 to be deemed internally consistent. Overall, coefficients ranged from 0.72 to 0.95 for all domains, thereby satisfying the criteria for adequate internal consistency. Precision was recognized by considering floor and ceiling effects, which demonstrated minor ceiling effects (maximum of 5% in the emotion domain) and significant floor effects (maximum 36.7% in the itch domain).

In instances where fewer than half of the data were missing for a given domain, data were imputed based on the mean values of the remaining answered questions. If more than half of the data were missing for a given domain, responses were deemed as "missing." The acceptability was determined by a test cohort of patients assessing appropriateness of items and responses and length of survey. Only four of 240 cases reported missing data in more than 50% of items for a given domain, indicating adequate acceptability among respondents.

The third phase compared the PBC-40 with previously used health-related quality-of-life measures (such as the Short Form [36] Health Survey). Validity was assessed in three ways: face validity (measuring intended criteria), content validity (adequate number of items to evaluate health-related quality of life in PBC), and construct validity (correlation for prediction with other measures). Pearson correlations between the PBC-40 and the Short Form (36) Health Survey ranged between 0.50 and 0.80, indicating moderate to high correlations, with the exception of the itch domain (coefficient = 0.2). Overall, Jacoby et al. concluded that the PBC-40 satisfies the requirements to be considered a standard tool for outcome assessment in clinical trial and that it is an important addition to patient-reported outcome measures, given that it is the only disease-specific health-related quality of life measure for PBC.

Conclusion

Overall, elevated levels of ALP and bilirubin were associated with worse clinical outcomes (e.g., liver transplant or death) and were considered to be acceptable biochemical surrogate markers and prognostic factors for PBC. Both ELF score and TE have similar diagnostic accuracy to liver biopsy for the non-invasive staging of liver fibrosis. The PBC-40 is a valid and reliable disease-specific health-related quality-of-life measure for PBC. No MCIDs were found for any of the outcome measures.

Appendix 5: Summary of the Long-Term Safety Extension of the POISE Trial

Objective

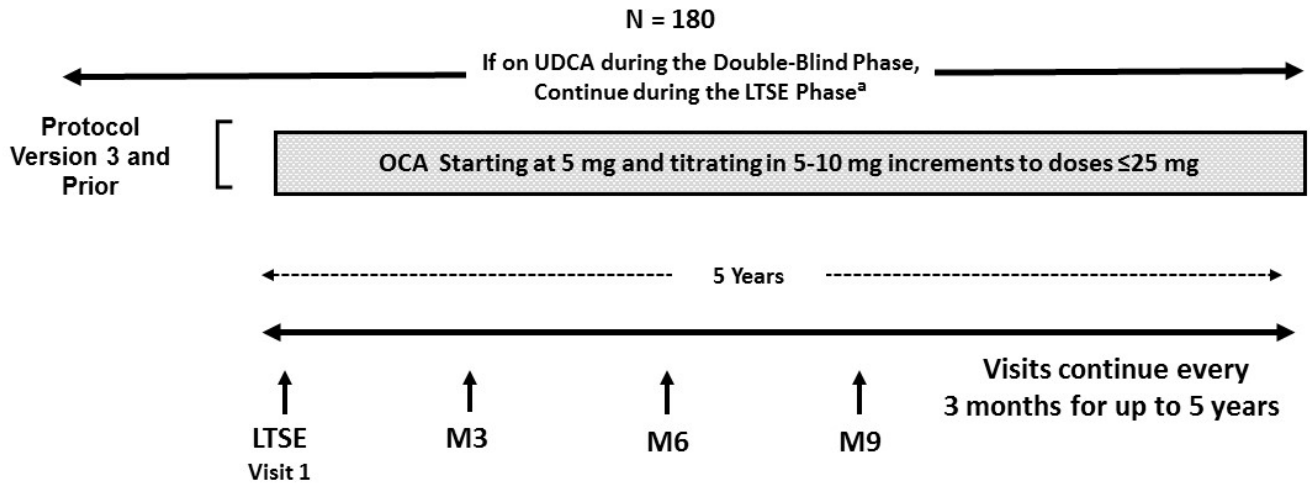
To summarize the results of a long-term safety extension (LTSE) of the POISE trial, which evaluated the effects of obeticholic acid (OCA) in adult patients with primary biliary cholangitis (PBC).

Findings

Study Design

Study design and characteristics of the international, multi-centre, open-label, non-randomized, multi-dose LTSE are summarized in Table 15 and Figure 2. Any patient who participated in the double-blind period of POISE and continued to meet the eligibility requirements was eligible to continue in the LTSE. All patients started treatment with the initial dose of OCA (5 mg once daily) regardless of the dose received during the double-blind period. Dose titrations (reductions or increases) in three-month intervals were permitted during the LTSE based on treatment response per the primary composite end point (patients achieving a serum alkaline phosphatase [ALP] less than 1.67 times the upper limit of normal [ULN], total bilirubin at ULN or lower, and decrease in ALP of ≥ 15% or more from baseline) and tolerability. Doses above 25 mg once daily were permitted during the POISE LTSE at the investigator's discretion. This review focuses on doses in the Health Canada–approved product monograph (i.e., OCA ≤ 10 mg). Results for the POISE LTSE are based on an interim analysis, as the five-year study is still ongoing.

Figure 2: POISE Long-Term Safety Extension Study Design



LTSE = long-term safety extension; M = month; OCA = obeticholic acid; UDCA = ursodeoxycholic acid.

Source: Clinical study report.[33]

Table 15: Summary of the Design and Characteristics of the POISE Long-Term Safety Extension

		POISE LTSE
DESIGNS AND POPULATIONS	**Study Design**	International, multi-centre, OL, multi-dose, LTSE
	Number of Participants (N)	193
	Eligibility	Age ≥ 18 years Definite or probable PBC diagnosis as demonstrated by the presence of ≥ 2 of the following 3 diagnostic factors: • History of elevated ALP levels for at least 6 months • Positive AMA titre or, if AMA negative or in low titre (< 1:80), PBC-specific antibodies (anti-GP210 or anti-SP100) or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex) • Liver biopsy consistent with PBC At least 1 of the following qualifying biochemistry values: • ALP ≥ 1.67 × ULN • Total bilirubin > ULN but < 2 × ULN Taking UDCA for at least 12 months (stable dose for ≥ 3 months) before day 0, or unable to tolerate UDCA (no UDCA for ≥ 3 months) before day 0 Any patient who participated in the double-blind period of POISE and continued to meet the eligibility requirements was eligible to continue in the LTSE.
	Primary Objective	To evaluate the long-term efficacy and safety of OCA
DRUGS	**Intervention**	OCA 5 mg, 10 mg, 25 mg tablets orally once daily Patients who were also treated with UDCA during the double-blind phase remained on UDCA during the LTSE phase. However, discontinuations of UDCA were permitted depending on therapeutic response during the LTSE. Patients treated with OCA monotherapy in the double-blind period received OCA as a monotherapy during the LTSE.
	Comparators	N/A
DURATION	**Screening Period**	N/A
	Treatment Period	5 years or to study discontinuation
	Follow-Up Period	N/A
	Visits	Initial visit of LTSE for patients who did not complete POISE (final visit in POISE for those who completed the DB period) Every three months thereafter
OUTCOMES	**Primary End Point**	Patients achieving an ALP < 1.67 × ULN, total bilirubin ≤ ULN, and ALP decrease of ≥ 15% from baseline
	Other End Points	Absolute and percentage change from baseline in ALP Absolute and percentage change from baseline in bilirubin Absolute and percentage change from baseline in ELF score Absolute change from baseline in hepatic stiffness measurements Absolute change from baseline in PBC-40 questionnaire Absolute change from baseline in pruritus 5D questionnaire and VAS Harms

5D = five-dimensions scale; ALP = alkaline phosphatase; AMA = antimitochondrial antibody; DB = double-blind; ELF = enhanced liver fibrosis; LTSE = long-term safety extension; N/A = not applicable; OCA = obeticholic acid; OL = open-label; PBC = primary biliary cholangitis; PBC-40 = primary biliary cholangitis 40-item questionnaire; UDCA = ursodeoxycholic acid; ULN = upper limit of normal; VAS = visual analogue scale.

Source: Clinical study report.[33]

Methods

In the POISE LTSE, all analyses (efficacy and safety) were based on the safety population, defined as all participants who received any amount of OCA during the LTSE. Patients were designated to dosage groups based on a weighted average of the daily dose taken throughout the study to account for the flexibility of dose adjustments, titration, and frequency. For patients who received placebo in the double-blind phase, OCA baseline was the last assessment before the first OCA dose in LTSE. For patients who received OCA in the double-blind phase, OCA baseline was the mean of all available evaluations before double-blind treatment. The primary outcome in the POISE LTSE was the composite of patients achieving an ALP < 1.67 times ULN, total bilirubin ≤ ULN, and ALP decrease of ≥ 15% from baseline. All other efficacy outcomes were considered as secondary outcomes. Safety was measured by treatment-emergent adverse events, serious adverse events, and withdrawal due to adverse events. If a patient was withdrawn before study completion (regardless of the cause), all analyses were performed at the time of withdrawal. Demographics and patient characteristics represent the data as collected before dosing in the double-blind phase.

Disposition

The disposition of participants is summarized in Table 16.

A total of 172 participants enrolled in POISE LTSE and were treated with a weighted average daily dose (accounts for the flexibility of dose adjustments, titration) ≤ 10 mg of OCA, of which 44 participants received 5 mg or less of OCA and 128 participants received more than 5 mg to 10 mg of OCA, respectively. The majority (59%) of patients in the 5 mg or less of OCA group were treated with placebo during the double-blind period of POISE versus 23% in the more than 5 mg to 10 mg of OCA group. In addition, a minority (5%) of patients in the 5 mg or less of OCA group were treated with 10 mg of OCA during the double-blind period of POISE versus 43% in the more than 5 to 10 mg of OCA group. Overall, there were relatively few discontinuations during the LTSE.

Table 16: Disposition of Participants in POISE Long-Term Safety Extension

	OCA ≤ 5 mg	OCA > 5 to 10 mg	OCA ≤ 10 mg
Enrolled, n	44	128	172
Double-Blind Phase Treatment, n (%)			
Placebo	26 (59)	30 (23)	56 (33)
Titration OCA	16 (36)	43 (34)	59 (34)
10 mg OCA	2 (5)	55 (43)	57 (33)
Reasons for Discontinuation, n (%)			
Withdrew consent	0	2 (2)	2 (1)
Death	0	1 (< 1)	1 (< 1)
Withdrew due to pruritus	0	1(< 1)	1 (< 1)
Discontinued due to other clinical or laboratory TEAE	2 (5)	2 (2)	4 (2)
Lost to follow-up	2 (5)	0	2 (1)
Safety Population, n (%)	44 (100)	128 (100)	172 (100)

OCA = obeticholic acid; TEAE = treatment-emergent adverse event.

Note: Weighted average daily dose accounts for the flexibility of dose adjustments, titration, and frequency as specified by the protocol.

Source: Clinical study report.[33]

Results

The main demographic and baseline characteristics of participants are summarized in Table 17.

Patients had a mean age of approximately 56 years (standard deviation [SD] 10.2), with 82% being younger than 65 years of age, and a mean PBC duration of 8.6 years (SD 6.0). The majority of patients were female (92%) and white (94%), had a body mass index of more than 25 kg/m^2, had a history of mild PBC-related pruritus (98%), and were experiencing pruritus and fatigue at baseline (55% and 57%, respectively). Furthermore, most patients had a duration of PBC of more than 7.5 years (52%) and were treated with ursodeoxycholic acid (UDCA) (92%). The mean total duration of exposure to OCA during the POISE LTSE was 576.5 (SD 202.3) days and the mean number of days without OCA during the POISE LTSE because of lack of adherence, prescribed temporary discontinuation, or alternative dosage regimen was 58.1 (SD 74.3) days. Detailed exposure data are presented in Table 18.

Table 17: Baseline Characteristics in POISE Long-Term Safety Extension

	OCA ≤ 5 mg N = 44	OCA > 5 to 10 mg N = 128	OCA ≤ 10 mg N = 172
Mean (SD) Age, Years	58.0 (9.9)	54.8 (10.1)	55.6 (10.2)
Age < 65 years, n (%)	36 (82)	105 (82)	141 (82)
Female, n (%)	40 (91)	118 (92)	158 (92)
Caucasian, n (%)	40 (91)	122 (95)	162 (94)
Mean (SD) BMI, kg/m^2	25.4 (3.9)	26.3 (5.1)	26.1 (4.9)
UDCA Use at Baseline, n (%)	38 (86)	121 (95)	159 (92)
History of PBC-Related Pruritus, n (%)	25 (57)	81 (63)	106 (62)
Severity of most recent pruritus event			
Mild	15 (60)	56 (69)	71 (67)
Moderate	10 (40)	18 (22)	28 (26)
Severe	0	5 (6)	5 (5)
Unknown	0	2 (2)	2 (2)
Pruritus at Baseline, n (%)	21 (48)	74 (58)	95 (55)
Overall severity			
Mild	11 (25)	58 (45)	69 (40)
Moderate	10 (23)	14 (11)	24 (14)
Severe	0	2 (2)	2 (1)
None	23 (52)	54 (42)	77 (45)
History of Fatigue, n (%)	27 (61)	71 (55)	98 (57)
Overall severity			
Mild	16 (36)	42 (33)	58 (34)
Moderate	10 (23)	19 (15)	29 (17)
Severe	1 (2)	9 (7)	10 (6)
Mean (SD) Duration of PBC, Years	7.9 (5.4)	8.9 (6.2)	8.6 (6.0)
Duration of PBC > 7.5 years, n (%)	20 (45)	70 (55)	90 (52)

BMI = body mass index; OCA = obeticholic acid; PBC = primary biliary cholangitis; SD = standard deviation; UDCA = ursodeoxycholic acid.

Notes: Weighted average daily dose accounts for the flexibility of dose adjustments, titration, and frequency as specified by the protocol. Data are based on double-blind period baseline characteristics.

Source: Clinical study report.[33]

Table 18: Obeticholic Acid Exposure During POISE Long-Term Safety Extension

	All OCA Doses N = 193
Mean total duration of exposure, days (SD)	576.5 (202.3)
Mean number of days on OCA, days (SD)	555.5 (208.4)
≥ 1 day to < 1 week	0
≥ 1 week to < 2 weeks	2 (1)
≥ 2 weeks to < 1 month	1 (< 1)
≥ 1 month to < 3 months	1 (< 1)
≥ 3 months to < 6 months	3 (2)
≥ 6 months to < 1 year	42 (22)
≥ 1 year to < 1.5 years	26 (13)
≥ 1.5 years to < 2 years	78 (40)
≥ 2 years	40 (21)
Mean number of subjects on an alternative dosage schedule, n (%)[a]	31 (16)
Mean number of days off OCA, days (SD)[b]	58.1 (74.3)

OCA = obeticholic acid; SD = standard deviation.

Note: Based on full POISE population (i.e., all OCA doses).

[a] Alternative dosage schedule is defined as administration every other day, every third day, or every seventh day.

[b] Days off includes days off OCA due to alternative dosage schedule, prescribed drug holidays, or drug interruptions due to lack of adherence.

Source: Clinical study report.[33]

Efficacy

A summary of all efficacy outcomes is presented in Table 19.

Overall, 53% and 66% of patients treated with OCA ≤ 10 mg achieved the primary composite efficacy end point (patients with ALP less than 1.67 times ULN, total bilirubin at ULN or lower, and a decrease in ALP of 15% or more from baseline) at LTSE month 12 and month 21, respectively. ALP decreased (33.6% reduction from baseline) at LTSE month 12 and stabilized through month 21 (32.5% reduction from baseline). The results for bilirubin were inconsistent (1.6% reduction from baseline) at LTSE month 12 and increased through month 21 (1.6% greater than baseline). Hepatic stiffness, as measured by transient elastography (FibroScan), increased by 0.17 from baseline at LTSE month 12. Overall, five of the domain scores of the PBC-40 questionnaire (general symptoms, itch, fatigue, cognitive function, and social) increased from baseline (range 0.1 to 0.8) at both LTSE month 12 and month 21, and one domain (emotional) decreased from baseline (reduction of 0.2 and 0.3 at LTSE month 12 and month 21, respectively). Pruritus five-dimensions questionnaire scores also increased by 1.6 and 0.9 from baseline at LTSE month 12 and LTSE month 21, as did the pruritus visual analogue scale (increase of 4.5 and 2.3 at LTSE month 12 and month 21, respectively).

One death occurred (OCA > 5 to 10 mg dose) during the LTSE due to endocarditis, sepsis, and acute renal failure deemed unrelated to the investigational product, according to the investigator. No further details were provided.

Table 19: Efficacy Outcomes, POISE Long-Term Safety Extension

	OCA ≤ 5 mg N = 44	OCA > 5 to 10 mg N = 128	OCA ≤ 10 mg N = 172
Patients completing LTSE month 12, n	26	107	133
Patients completing LTSE month 21, n	16	81	97
Patients With ALP < 1.67 × ULN, Total Bilirubin ≤ ULN, and ALP Decrease ≥ 15% From OCA Baseline, n (%)[a]			
LTSE month 12	18 (69)	52 (49)	70 (53)
LTSE month 21	14 (88)	50 (62)	64 (66)
ALP (U/L) Change From OCA Baseline[a]			
Mean (SE) ALP at OCA baseline	281.1 (16.6)	328.0 (10.8)	316.0 (9.2)
LTSE month 12			
Mean (SE) absolute change	−84.2 (14.6)	−117.4 (7.7)	−110.9 (6.9)
Mean (SE) per cent change	−31.1 (4.2)	−34.2 (1.6)	− 33.6 (1.5)
LTSE month 21			
Mean (SE) absolute change	−103.3 (18.8)	−103.7 (12.1)	−103.7 (10.5)
Mean (SE) per cent change	−35.5 (4.4)	−31.9 (2.7)	−32.5 (2.4)
Total Bilirubin (µmol/L) Change From OCA Baseline[a]			
Mean (SE) total bilirubin at OCA baseline	11.5 (1.0)	11.3 (0.6)	11.4 (0.5)
LTSE month 12			
Mean (SE) absolute change	−1.1 (0.5)	−1.0 (0.40)	−1.0 (0.3)
Mean (SE) per cent change	−6.6 (4.5)	−0.4 (3.6)	−1.6 (3.0)
LTSE month 21			
Mean (SE) absolute change	−1.1 (0.8)	−0.2 (0.6)	−0.3 (0.5)
Mean (SE) per cent change	−0.4 (7.7)	2.0 (4.3)	1.6 (3.8)
Hepatic Stiffness (FibroScan) Change From OCA Baseline[a]			
Mean (SE) TE at OCA baseline	11.31 (2.01)	11.24 (0.98)	11.26 (0.90)
LTSE month 12	n = 12	n = 50	n = 62
Mean (SE) absolute change	0.03 (0.83)	0.20 (0.94)	0.17 (0.77)
Symptoms — PBC-40 score[a]			
General symptoms			
Mean (SE) at OCA baseline	13.4 (0.7)	13. 0 (0.4)	13.1 (0.4)
Mean (SE) absolute change at LTSE month 12	0.9 (0.6)	0.5 (0.4)	0.6 (0.3)
Mean (SE) absolute change at LTSE month 21	−0.1 (0.7)	0.6 (0.5)	0.5 (0.4)
Itch			
Mean (SE) at OCA baseline	3.4 (0.5)	4.0 (0.3)	3.8 (0.3)
Mean (SE) absolute change at LTSE month 12	1.3 (0.7)	1.1 (0.3)	1.1 (0.3)
Mean (SE) absolute change at LTSE month 21	1.4 (0.5)	0.7 (0.3)	0.8 (0.3)
Fatigue			
Mean (SE) at OCA baseline	23.2 (1.6)	24.9 (0.9)	24.5 (0.8)
Mean (SE) absolute change at LTSE month 12	−0.6 (1.2)	0.3 (0.6)	0.1 (0.6)
Mean (SE) absolute change at LTSE month 21	3.5 (1.2)	0.9 (0.7)	0.2 (0.7)
Cognitive function			
Mean (SE) at OCA baseline	11.7 (0.9)	11.5 (0.5)	11.6 (0.4)
Mean (SE) absolute change at LTSE month 12	−0.5 (0.6)	0.4 (0.4)	0.2 (0.3)
Mean (SE) absolute change at LTSE month 21	−0.1 (0.4)	0.7 (0.5)	0.6 (0.4)
Social			
Mean (SE) at OCA baseline	19.5 (1.3)	19.1 (0.7)	19.2 (0.6)

	OCA ≤ 5 mg N = 44	OCA > 5 to 10 mg N = 128	OCA ≤ 10 mg N = 172
Mean (SE) absolute change at LTSE month 12	−0.7 (1.1)	0.9 (0.6)	0.6 (0.5)
Mean (SE) absolute change at LTSE month 21	2.1 (1.5)	1.3 (0.7)	0.7 (0.7)
Emotional			
Mean (SE) at OCA baseline	6.4 (0.5)	6.6 (0.3)	6.6 (0.2)
Mean (SE) absolute change at LTSE month 12	−0.3 (0.4)	−0.2 (0.2)	−0.2 (0.2)
Mean (SE) absolute change at LTSE month 21	−0.9 (0.5)	−0.2 (0.3)	−0.3 (0.3)
Pruritus 5D score[a]			
Total score			
Mean (SE) at OCA baseline	9.3 (0.6)	10.3 (0.4)	10.0 (0.3)
Mean (SE) absolute change at LTSE month 12	1.2 (0.9)	1.7 (0.4)	1.6 (0.4)
Mean (SE) absolute change at LTSE month 21	1.3 (1.0)	0.8 (0.5)	0.9 (0.4)
Pruritus VAS score[a]			
Mean (SE) at OCA baseline	15.9 (3.5)	21.7 (2.2)	20.1 (1.9)
Mean (SE) absolute change at LTSE month 12	8.5 (4.8)	3.4 (2.0)	4.5 (1.9)
Mean (SE) absolute change at LTSE month 21	8.7 (4.8)	0.9 (2.7)	2.3 (2.4)
Mortality			
Death, n (%)	0	1 (< 1)	1 (< 1)

5D = five-dimensions scale; ALP = alkaline phosphatase; DB = double-blind; LTSE = long-term safety extension; OCA = obeticholic acid; PBC-40 = primary biliary cholangitis 40-item questionnaire; SE = standard error; TE = transient elastography; ULN = upper limit of normal; VAS = visual analogue scale.

Note: Weighted average daily dose accounts for the flexibility of dose adjustments, titration, and frequency as specified by the protocol.

[a] For patients that received placebo in the double-blind phase, OCA baseline is the last assessment before the first OCA dose in LTSE. For patients that received OCA in the double-blind phase, OCA baseline is the mean of all available evaluations before double-blind treatment.

Source: Clinical study report.[33]

Safety

A summary of the adverse events during the LTSE is presented in Table 25.

Most participants (87%) experienced adverse events during the POISE LTSE. Pruritus was reported as the most frequently experienced adverse event (41%) followed by fatigue (10%). Generally, occurrences of serious adverse events were uncommon (9%), with no one serious adverse event frequency greater than one per cent. Adverse events resulting in study discontinuation were uncommon (5%). Pruritus was reported as the most frequently experienced adverse event leading to study withdrawal (3%).

Table 20: Safety Outcomes in POISE Long-Term Safety Extension

	OCA ≤ 5 mg N = 44	OCA > 5 to 10 mg N = 128	OCA ≤ 10 mg N = 172
Adverse Events, n (%)[a]			
Participants with > 0 AEs	40 (91)	110 (86)	150 (87)
Pruritus	21 (48)	50 (39)	71 (41)
Fatigue	5 (11)	12 (9)	17 (10)
Serious Adverse Events, n (%)[b]			
Participants with > 0 SAEs	6 (14)	9 (7)	15 (9)
Discontinuations, n (%)[c]			
WDAE	3 (7)	6 (5)	9 (5)
Subjects who withdrew due to pruritus	2 (5)	3 (2)	5 (3)

AE = adverse event; OCA = obeticholic acid; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Notes: Weighted average daily dose accounts for the flexibility of dose adjustments, titration, and frequency as specified by the protocol. Data are during LTSE period.

[a] Adverse events ≥ 10%.

[b] Serious adverse events > 1%.

[c] Withdrawals due to adverse events > 1%.

Source: Clinical study report.[33]

Limitations

There are several limitations to the long-term, open-label, non-randomized safety extension of the POISE trial. First, given that this was an uncontrolled study, it remains unclear whether the changes observed in the safety and efficacy profile were due to the natural course of the disease or were attributable to long-term treatment with OCA. Open-label trial designs in which both the investigators and the participants are unblinded to treatment allocation may have an impact on subjective outcomes, such as some patient-reported adverse events, symptom assessments. and health-related quality-of-life measures. In addition, during the LTSE, patients were able to add, discontinue, or dose-adjust concomitant UDCA; this makes it difficult to ascertain the absolute safety and efficacy of OCA alone. Moreover, patients were eligible to receive higher doses of OCA (upwards of 25 mg daily) during the LTSE versus what was allowed during the randomized placebo-controlled phase (≤ 10 mg daily), making it difficult to draw concrete comparisons between the effects and harms observed in the two phases. The Health Canada–approved product monograph recommends doses of OCA of 5 mg and 10 mg; therefore, the use of doses above 10 mg may limit the generalizability to the population in Canada.

The majority of patients who were enrolled in the LTSE were treated with OCA during the double-blind period of the POISE trial; therefore, the number of adverse events may have been underestimated and the efficacy overestimated, given that patients may have been more tolerant or more inclined to benefit from treatment. Furthermore, most patients enrolled in the POISE LTSE were concomitantly treated with UDCA; therefore, the long-term effect of OCA as monotherapy is uncertain. The results presented are based on an interim analysis of an ongoing study; therefore, not all patients were exposed to OCA for the full five-year intended study duration. The reduced sample size can lead to uncertainty in the long-term effects of treatment with OCA, as these results may change as more patients complete the extension phase.

Summary

Results from an international, multi-centre, multi-dose, open-label, non-randomized LTSE of the POISE trial suggested that patients continue to experience benefit with OCA therapy based on the primary composite end point (patients with ALP less than 1.67 times ULN, total bilirubin at ULN or lower, and a decrease in ALP of 15% or more from baseline) and changes in ALP levels at 12 and 21 months of treatment. Results based on bilirubin are inconsistent at month 12 and month 21. In addition, based on the PBC-40 questionnaire, OCA therapy appears to be associated with a numerical increase in scores in all domains, with the exception of the emotional domain at 12 months and 21 months. OCA treatment effects identified through a pruritus five-dimensions questionnaire and a visual analogue scale also appear to increase from baseline values at both 12 months and 21 months. Almost all participants' experienced adverse events with OCA treatment, the most frequent being pruritus. No deaths related to the investigational product were reported in any of the studies. Considering the open-label nature of the LTSE, the limited data for patients receiving OCA as monotherapy, and the relatively small number of patients completing month 12 and month 21 of the extension phase, there remains some uncertainty about the long-term safety and efficacy of OCA therapy.

Appendix 6: Summary of Phase II Studies

Objective

To summarize the results from two short-term phase II studies and their long-term safety extensions (LTSEs) that evaluated the effects of obeticholic acid (OCA) in adult patients with primary biliary cholangitis (PBC).

Findings

Study Design

Study design and characteristics of the two short-term, phase II, international, multi-centre, randomized, double-blind (DB), placebo-controlled, multi-dose, parallel-group studies and their open-label non-randomized extensions are summarized in Table 21. Patients were randomized in the phase II portion of study 747-202 (747-202 DB) in a 1:1:1:1 ratio to OCA 10 mg, 25 mg, and 50 mg or to matching placebo using a computerized randomization schedule (block size of four at each centre). No details regarding the randomization for the phase II portion of study 747-201 (747-201 DB) were provided. Both study investigator and patients were blinded to treatment allocation during the DB periods. Patients entering the LTSEs were unblinded before their initial visit as part of the LTSEs, but only after the final visit during the DB periods. Patients were required to discontinue treatment with OCA for two weeks after the DB periods before enrolment in the LTSE. Patients were then offered to restart the initial dose of OCA (10 mg once daily) or to continue the dose assigned during the DB phase. Dose titrations (reductions or increases) in eight-week intervals were permitted during the LTSE based on alkaline phosphatase response and tolerability, including alternative or every third day dosage of a 10 mg tablet to help manage pruritus. Doses above 50 mg once daily, at a maximum of 10 mg increments, were permitted during the LTSEs only if the drug was well tolerated and patients had been treated with 50 mg for at least three months during the LTSE. This review focuses on doses in the Health Canada–approved product monograph (i.e., OCA 5 mg or 10 mg). Results for 747-201 LTSE are based on an interim analysis, as the study is still ongoing.

Table 21: Summary Design and Characteristics of Short-Term Phase II Studies and Their Safety Extensions

		DB		LTSE	
		747-201	747-202	747-201	747-202
DESIGNS AND POPULATIONS	**Study Design**	International, multi-centre, randomized, DB, placebo-controlled, multi-dose, parallel-group, phase II		International, multi-centre, OL, multi-dose, parallel-group, LTSE	
	Number of Participants (N)	60	165	28	78
	Eligibility	Adults aged 18 to 70 (up to 75 in the UK) Proven or likely PBC, as demonstrated by the patient presenting with at least 2 of the following 3 diagnostic factors: • History of increased ALP levels for ≥ 6 months • Positive AMA titre (> 1:40 titre on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay) or PBC-specific antinuclear antibodies (antinuclear dot and nuclear rim positive) • Liver biopsy consistent with PBC Screening ALP level between 1.5 × ULN and 10 × ULN 747-202 also required a stable dose of UDCA for ≥ 6 months before screening Use of UDCA was prohibited in 747-201		Any patients who participated in 747-201 or 747-202 and continued to meet the eligibility requirements were able to continue in their respective LTSE Patients were required to discontinue OCA therapy for two weeks before enrolment in the LTSE	
	Primary Objective	To evaluate the effects of OCA		To evaluate the long-term safety of OCA	
DRUGS	**Intervention**	OCA 10 mg or 50 mg tablets orally once daily	OCA 10 mg, 25 mg, or 50 mg tablets orally once daily in combination with UDCA	OCA 10 mg, 25 mg, or 50 mg tablets orally once daily Additions, titrations, or discontinuations of UDCA were permitted	
	Comparators	Placebo		N/A	
DURATION	**Screening Period**	Four weeks		N/A	
	Treatment Period	12 weeks double-blind		Up to six years or discontinuation	21 months or discontinuation
	Follow-Up Period	Two weeks		N/A	
	Visits	Days 15, 29, 57, and 85 747-202 also included a visit at day 8 for select centres		Initial visit of LTSE for patients who did not complete 747-201 or 747-202 (final visit in 747-201 or 747-202 for those who completed the DB period) Week 2 visit only for those treated with placebo during DB period Month 3 visit Every three months thereafter	

		DB		LTSE	
		747-201	747-202	747-201	747-202
Outcomes	**Primary End Point**	Per cent change in serum ALP from baseline		Pruritus and TEAE	
	Other End Points	Achieving an ALP < 1.67 × ULN, total bilirubin ≤ ULN, and ALP decrease of ≥ 15% from baseline Absolute and percentage change from baseline in ALP Absolute and percentage change from baseline in bilirubin Absolute and percentage change from baseline in ELF score Absolute change from baseline in SF-36 questionnaire Absolute change from baseline in PBC-40 questionnaire Absolute change from baseline in pruritus 5D questionnaire and VAS Harms			

5D = five-dimensions scale; ALP = alkaline phosphatase; AMA = antimitochondrial antibody; DB = double-blind; ELF = enhanced liver fibrosis; LTSE = long-term safety extension; N/A = not applicable; OCA = obeticholic acid; OL = open-label; PBC = primary biliary cholangitis; PBC-40 = primary biliary cholangitis 40-item questionnaire; SF-36 = Short Form (36) Health Survey; TEAE = treatment-emergent adverse event; UDCA = ursodeoxycholic acid; ULN = upper limit of normal; VAS = visual analogue scale.

Source: Clinical study reports.[34-37]

Methods

In 747-201 DB, the intention-to-treat (ITT) principle was used to evaluate the primary efficacy end point (change in alkaline phosphatase [ALP]) and all secondary efficacy end points (change in bilirubin, quality of life, enhanced liver fibrosis [ELF] score, and the composite of patients with ALP less than 1.67 times upper limit of normal [ULN] and total bilirubin at ULN or lower, and decrease in ALP of 15% or more from baseline), with the exception of the pruritus five-dimensions scale end points, which were evaluated using the safety population. While in 747-202 DB, the modified ITT population (patients who had at least one post-baseline ALP evaluation taken 7 days or less after their last dose of investigational product) was used to evaluate the primary efficacy end points (change in ALP). All secondary and other efficacy end points were evaluated based on the ITT principle in 747-202 DB. Both 747-201 DB and 747-202 DB used the safety population for the analyses of all safety end points. Adverse events with unclear causes were assumed to be related to the treatment product in both studies. Missing data in 747-201 DB and 747-202 DB were imputed using a last-observation-carried-forward method for the primary end points only; all other missing data were not imputed (including safety data).

A two-sided Wilcoxon–Mann–Whitney test at the 5% level of significance was used to analyze end points in both 747-201 DB and 747-202 DB. Hierarchical testing strategies were implemented to account for multiple statistical testing in the primary end points only, in the following order: $P = 0.05$ for the OCA 10 mg group, followed by $P = 0.05$ for the OCA 50 mg in 747-201 DB and $P = 0.05$ for the OCA 10 mg group, followed by $P = 0.05$ for the OCA 25 mg, followed by $P = 0.05$ for the OCA 50 mg in 747-202 DB. No corrections for multiple statistical testing were applied for any other analyses in both studies.

In 747-201 DB, a sample size of 120 participants (40 in each treatment group) was expected to provide 80% power to detect a clinically meaningful difference in the primary end point between OCA and placebo (effect size of 0.6466, or 70% power to detect an effect size of 0.5770) assuming a type I error of 5% (Wilcoxon–Mann–Whitney rank sum test, two-sided significance level). However, only 60 participants (20 in each treatment group) were enrolled due to difficulties with patient recruitment, providing 49% power to detect an effect size of 0.6466 for the difference in the primary efficacy end point.

In 747-202 DB period, a sample size of 140 participants (35 in each treatment group) was expected to provide 80% power to detect a difference in the primary end point between OCA and placebo (effect size of 0.70, or at least a 10% mean reduction in ALP), assuming a type I error of 5% (Wilcoxon–Mann–Whitney rank sum test, two-sided significance level).

In both of the LTSEs, all analyses were based on the safety population, which was defined as all participants who received any amount of OCA during the LTSEs. Generally, any missing data were not imputed, with the exception of domain scores in the PBC-40 questionnaire. If fewer than 50% of questions per domain were not answered, missing data were imputed by the mean of available question scores for the respective domain. No corrections were applied to adjust for multiplicity, and all efficacy end points

were considered secondary and exploratory outcomes. The primary outcomes in both LTSEs were safety, as measured by treatment-emergent adverse events, specifically pruritus. Other safety end points included serious adverse events and withdrawals due to adverse events. Two-sided Wilcoxon–Mann–Whitney tests at the 5% level of significance were also used to analyze end points in both LTSEs.

Disposition

The disposition of participants across the phase II studies and their respective LTSEs are summarized in Table 22.

Twenty-three participants were enrolled in the placebo group and 20 in the OCA group in 747-201 DB period, four (20%) of whom discontinued OCA 10 mg treatment. A total of 12 patients who participated in 747-201 DB period were treated with ≤ 10 mg of OCA during the LTSE. Six (50%) discontinued treatment because of other reasons or other clinical or laboratory treatment-emergent adverse events.

Thirty-eight participants were enrolled in each of the placebo and OCA treatment groups in 747-202 DB period, nine (24%) of whom discontinued OCA 10 mg treatment. A total of 36 patients who participated in 747-201 DB period were treated with ≤ 10 mg of OCA during the LTSE. Fourteen (39%) discontinued treatment owing to pruritus, other reasons, and other clinical or laboratory treatment-emergent adverse events.

Table 22: Disposition of Participants in Short-Term Phase II Studies and Their Safety Extensions

	DB				LTSE	
	747-201		747-202		747-201	747-202
	PLA	OCA 10 mg	PLA	OCA 10 mg	OCA ≤ 10 mg[a]	OCA ≤ 10 mg[a]
Enrolled, n	23	20	38	38	14	36
Completed, n (%)	23 (100)	16 (80)	37 (97)	32 (84)	8 (57)	22 (61)
Reasons for Discontinuation						
Withdrew consent	0	1 (5)	0	0	0	0
Major protocol violation	0	0 (0)	0	0	0	1
Withdrew due to pruritus	0	3 (15)	0	3 (8)	2 (14)	9 (25)
Elevated conjugated bilirubin	0	0	0	1 (3)	0	0
Discontinued due to other clinical or laboratory TEAE	0	0	1 (3)	5 (13)	3 (21)	3 (8)
Discontinued due to other reasons	0	0	0	0	1 (7)	1 (3)
Safety Population	23 (100)	20 (100)	38 (100)	38 (100)	28 (100)[b]	78 (100)[b]
ITT Population	23 (100)	20 (100)	38 (100)	38 (100)	N/A	N/A
mITT Population	N/A	N/A	37 (97)	38 (100)	N/A	N/A

DB = double-blind; ITT = intention-to-treat; LTSE = long-term safety extension; mITT = modified intention-to-treat; N/A = not applicable; OCA = obeticholic acid; PLA = placebo; TEAE = treatment-emergent adverse event.

[a] Based on last available dose.

[b] Based on full safety population (all OCA doses).

Source: Clinical study reports.[34-37]

Results

The main demographic and baseline characteristics of participants are summarized in Table 23.

Overall, both studies and their LTSEs included a relatively small number of patients in each treatment group. For example, the OCA treatment group in 747-201 LTSE included the fewest patients (n = 14) and the OCA treatment group in 747-202 DB included the most patients (n = 38). There was some variability in demographics and baseline characteristics of participants between studies —

most notably, concomitant treatment with ursodeoxycholic acid (UDCA) was prohibited in study 747-201 DB and required in study 747-202 DB (UDCA use at baseline 0% and 100%, respectively).

Generally, baseline characteristics were relatively balanced between treatment groups (placebo versus OCA) in both 747-201 DB and 747-202 DB, with the exception of the proportion of patients with PBC duration 7.5 years or more in 747-202 DB (37% versus 53%), and the distribution of women and body mass index in 747-201 DB (87% versus 70% and 29.9 kg/m^2 versus 27.2 kg/m^2, respectively).

Table 23: Demographics of Participants in Short-Term Phase II Studies and Their Safety Extensions

	DB				LTSE	
	747-201		747-202		747-201	747-202
	PLA N = 23	OCA 10 mg N = 20	PLA N = 38	OCA 10 mg N = 38	OCA ≤ 10 mg[a] N = 14	OCA ≤ 10 mg[b] N = 36
Mean (SD) age, years	55.3 (10.0)	54.8 (10.9)	54.8 (8.5)	55.6 (9.3)	54.6 (8.9)	55.8 (8.1)
Women, n (%)	20 (87)	14 (70)	36 (95)	38 (100)	11 (79)	34 (94)
White, n (%)	21 (91)	19 (95)	34 (89)	37 (97)	14 (100)	33 (92)
Mean (SD) BMI, kg/m^2	29.9 (7.7)	27.2 (4.7)	27.4 (5.2)	27.8 (4.7)	29.3 (7.0)	27.3 (5.5)
Pre-treatment liver biopsy, n (%)	20 (87)	16 (80)	33 (87)	35 (92)	NR	NR
UDCA use at baseline, n (%)	0	0	38 (100)	38 (100)	NR	NR
Mean (SD) Duration of PBC, Years	4.6 (6.4)	4.9 (6.7)	NR	NR	NR	NR
Duration of PBC > 7.5 years, n (%)	5 (22)	5 (25)	14 (37)[c]	20 (53)[c]	NR	NR

DB = double-blind; BMI = body mass index; LTSE = long-term safety extension; NR = not reported; OCA = obeticholic acid; PBC = primary biliary cholangitis; PLA = placebo; SD = standard deviation; UDCA = ursodeoxycholic acid.

[a] Weighted average daily dose accounts for the flexibility of dose adjustments, titration, and frequency as specified by the protocol.

[b] Based on last available dose.

[c] Duration of PBC was based on a cut-off of ≥ 7.5 years in study 747-202.

Source: Clinical study reports.[34-37]

Efficacy

A summary of all efficacy outcomes is presented in Table 24.

Both 747-201 DB and 747-202 DB reported statistically significant differences in favour of treatment with OCA compared with placebo for the composite end point (percentage of patients with ALP less than 1.67 times ULN and total bilirubin at ULN or lower, and decrease in ALP of 15% or more from baseline). In total, seven (44%) patients compared with one (5%) patient achieved the composite end point in the OCA treatment groups compared with placebo, respectively, in 747-201 DB, whereas 12 (40%) patients compared with three (9%) patients achieved the composite end point in the OCA treatment groups compared with placebo, respectively, in 747-202 DB.

For the primary end point (reduction in ALP) of the phase II double-blind trials, statistically significantly greater reductions in ALP were observed in the OCA treatment groups compared with the placebo groups (−44.5% versus 0.4% and −23.7% versus −2.7% [P < 0.0001] in 747-201 DB and 747-202 DB, respectively). Both LTSEs suggest ALP reduction with continued OCA treatment compared with baseline values.

With respect to bilirubin, a statistically significant difference in mean per cent change from baseline was observed in the OCA treatment group compared with the placebo group in 747-201 DB (0.7% versus 30.3%; P = 0.0184), whereas a non-statistically significant difference was observed in 747-202 DB (0% versus 3.7%; P = 0.5119). Overall, patients treated with OCA experienced a

numerically smaller increase in bilirubin compared with placebo in both 747-201 DB and 747-202 DB (0.7% versus 30.3% and 0% versus 3.7%, respectively). Both LTSEs suggest bilirubin increases compared with baseline values with continued OCA treatment.

Both 747-201 DB and 747-202 DB reported non-statistically significant differences with OCA treatment compared with placebo in ELF score. Study 747-202 LTSE suggests a reduction in ELF score compared with baseline values with continued OCA treatment.

With respect to the PBC-40 questionnaire, non-statistically significant differences between OCA treatment and placebo were observed for all domains with the exception of itch and fatigue. There were statistically significantly greater increases in scores for the itch domain in the OCA treatment group compared with the placebo group in both 747-201 DB and 747-202 DB (2.8 versus 0.2 [*P* = 0.0564] and 1.1 versus −0.8 [*P* = 0.0023], respectively). The fatigue domain suggests a greater reduction in score in the OCA treatment group compared with the placebo group in study 747-201 DB; by contrast, study 747-202 DB reported a statistically significantly greater reduction in the placebo group compared with the OCA treatment group (−3.5 versus −0.4 [*P* = 0.0451] and −0.5 versus −2.6 [*P* = 0.0441], respectively).

Both 747-201 DB and 747-202 DB reported non-statistically significant differences with OCA treatment compared with placebo in both the physical component summary and mental component summary of the Short Form (36) Health Survey. Generally, greater increases in the physical component summary and mental component summary were observed in the placebo groups compared with the OCA treatment groups in both phase II trials, with the exception of the physical component summary in 747-201 DB. Both LTSEs suggest a reduction in the physical component summary and mental component summary scores with continued OCA treatment compared with baseline values.

For the pruritus five-dimensions questionnaire, non-statistically significant differences were observed in the OCA treatment group compared with the placebo group in 747-201 DB (2.8 versus −0.5; *P* = 0.1962); however, statistically significant differences in favour of placebo were reported in 747-202 DB (1.3 versus −1.5; *P* = 0.0081). Both LTSEs suggest an increase in the pruritus five-dimensions scores with continued OCA treatment compared with baseline values.

For the pruritus visual analogue scale, non-statistically significant differences were observed in the OCA treatment group compared with the placebo group in 747-202 DB (6.5 versus −5.8; *P* = 0.0581); however, statistically significant differences in favour of placebo were reported in 747-201 DB (19.7 versus −2.1; *P* = 0.0164). Both LTSEs suggest an increase in the pruritus visual analogue scale with continued OCA treatment compared with baseline values.

There were no deaths in any of the short-term phase II studies or their LTSEs.

Table 24: Efficacy Outcomes in Short-Term Phase II Studies and Their Safety Extensions

	DB				LTSE	
	747-201		747-202		747-201	747-202
	PLA N = 23	OCA 10 mg N = 20	PLA N = 38	OCA 10 mg N = 38	OCA ≤ 10 mg[a] N = 14	OCA ≤ 10 mg[b] N = 36
Patients meeting baseline criteria[c]	21 (91)	16 (80)	32 (84)	30 (79)	13 (93)	27 (75)
Patients with ALP < 1.67 × ULN and total bilirubin ≤ ULN and ALP decrease ≥ 15% from baseline, n (%)[d]	1 (5)	7 (44)	3 (9)	12 (40)	2 (25)	4 (15)
P value	0.0032		0.0071		NR	NR
ALP Change From Baseline						
Mean (SE) baseline ALP, U/L	408.4 (46.5)	461.6 (66.8)	276.4 (103.8)[e]	294.4 (149.4)[e]	401.6 (88.0)	299.7 (16.8)
Mean (SE) change from baseline, U/L	11.7 (13.1)	−233.5 (47.5)	−4.9 (34.9)[e]	−76.9 (83.7)[e]	−136.2 (78.4)	−55.5 (19.8)
Mean (SE) % change from	0.4 (3.2)	−44.5 (5.5)	−2.7	−23.7 (17.8)[e]	−19.2 (11.3)	−11.5 (5.0)

	DB				LTSE	
	747-201		747-202		747-201	747-202
	PLA N = 23	OCA 10 mg N = 20	PLA N = 38	OCA 10 mg N = 38	OCA ≤ 10 mg[a] N = 14	OCA ≤ 10 mg[b] N = 36
baseline			(12.4)[e]			
P value[f]	< 0.0001		< 0.0001		NR	NR
Conjugated (Direct) Bilirubin (µmol/L) Change From Baseline						
Mean (SE) baseline total bilirubin, µmol/L	3.9 (0.6)	5.5 (0.9)	3.6 (2.8)[e]	4.2 (3.1)[e]	5.8 (1.1)	4.9 (0.6)
Mean (SE) change from baseline, µmol/L	0.8 (0.3)	−0.7 (1.0)	0.1 (1.1)[e]	−0.2 (2.5)[e]	0.1 (1.1)	−0.4 (0.6)
Mean (SE) % change from baseline	30.3 (14.9)	0.7 (15.9)	3.7 (48.2)[e]	0.0 (49.6)[e]	30.2 (21.6)	5.7 (7.4)
P value[f]	0.0184		0.5119		NR	NR
Markers of Fibrosis						
ELF score, mean (SD) baseline	9.25 (1.26)	9.03 (0.94)	9.61 (1.22)	9.97 (1.27)	NR	9.67 (1.27)[g]
Mean (SD) change from baseline	0.01 (0.59)	0.19 (0.46)	−0.21 0.63)	−0.1 (0.59)	NR	−0.22 (0.83)
P value	0.2334		0.4793		NR	NR
Symptoms — PBC-40 score						
General symptoms						
Baseline mean (SD)	14.0 (5.0)	12.5 (4.2)	13.5 (4.5)	13.3 (3.7)	13.3 (3.0)	14.3 (4.3)
Mean (SD) change from baseline	0.9 (3.0)	−0.8 (2.6)	−0.4 (2.2)	0.3 (2.9)	2.0 (2.8)	1.0 (2.0)
P value	0.0654		0.2561		NR	NR
Itch						
Baseline mean (SD)	4.1 (3.4)	3.6 (2.9)	5.5 (3.0)	4.9 (3.0)	3.8 (3.5)	5.8 (3.6)
Mean (SD) change from baseline	0.2 (2.7)	2.8 (3.7)	−0.8 (2.3)	1.1 (2.6)	1.7 (3.3)	−0.2 (3.9)
P value	0.0564		0.0023		NR	NR
Fatigue						
Baseline mean (SD)	25.2 (12.0)	27.5 (10.1)	28.6 (9.2)	26.1 (9.2)	23.6 (9.1)	27.6 (8.5)
Mean (SD) change from baseline	−0.4 (5.8)	−3.5 (3.6)	−2.6 (4.2)	−0.5 (4.6)	3.4 (4.6)	0.2 (6.3)
P value	0.0451		0.0441		NR	NR
Cognitive function						
Baseline mean (SD)	10.7 (5.6)	12.0 (5.3)	12.1 (5.4)	11.4 (4.4)	12.2 (5.5)	11.5 (4.6)
Mean (SD) change from baseline	−0.2 (1.3)	−0.2 (1.8)	−0.3 (3.0)	−0.2 (2.5)	0.4 (1.5)	0.0 (3.7)
P value	0.8515		0.3976		NR	NR
Emotional and social						
Baseline mean (SD)	26.7 (11.9)	30.8 (11.3)	28.4 (11.1)	26.7 (10.0)	30.4 (13.0)	28.4 (10.0)
Mean (SD) change from baseline	1.2 (6.2)	−1.4 (5.7)	−1.3 (4.9)	0.5 (4.6)	0.4 (4.8)	2.0 (7.0)
P value	0.3761		0.0673		NR	NR
SF-36						
PCS						
Baseline mean (SD)	43.8 (11.8)	46.5 (8.6)	45.4	45.8 (11.1)	−0.2 (1.1)[h]	41.6 (11.5)

	DB				LTSE	
	747-201		747-202		747-201	747-202
	PLA N = 23	OCA 10 mg N = 20	PLA N = 38	OCA 10 mg N = 38	OCA ≤ 10 mg[a] N = 14	OCA ≤ 10 mg[b] N = 36
			(11.9)			
Mean (SD) change from baseline	−0.5 (6.2)	2.5 (6.1)	1.1 (5.7)	0.0 (5.5)	−0.3 (0.4) [h]	−3.7 (9.3)
P value	0.3769		0.6079		NR	NR
MCS						
Baseline mean (SD)	50.1 (11.2)	48.2 (10.3)	47.7 (12.9)	51.1 (8.5)	−0.6 (0.9) [h]	49.8 (9.6)
Mean (SD) change from baseline	−0.7 (7.7)	−2.0 (11.1)	1.7 (9.3)	−2.2 (7.0)	−0.1 (0.5) [h]	−3.6 (10.5)
P value	0.7962		0.0968		NR	NR
Pruritus 5D score						
Total score						
Baseline mean (SD)	11.1 (4.2)	10.8 (4.2)	12.1 (4.3)	10.5 (4.0)	10.8 (5.0)	12.6 (3.7)
Mean (SD) change from baseline	−0.5 (2.4)	2.8 (5.9)	−1.5 (3.8)	1.3 (3.8)	3.8 (3.9)	1.9 (4.3)
P value	0.1962		0.0081		NR	NR
Pruritus VAS score						
Baseline mean (SD)	28.4 (29.4)	21.3 (21.6)	32.1 (25.0)	25.2 (22.2)	17.5 (26.6)	28.5 (23.5)
Mean (SD) change from baseline	−2.1 (21.1)	19.7 (31.3)	−5.8 (20.5)	6.5 (22.2)	11.5 (24.0)	8.1 (26.3)
P value	0.0164		0.0581		NR	NR
Mortality						
Death	0	0	0	0	0	0

5D = five-dimensions scale; ALP = alkaline phosphatase; DB = double-blind; ELF = enhanced liver fibrosis; LTSE = long-term safety extension; MCS = mental component summary; NR = not reported; OCA = obeticholic acid; PBC-40 = primary biliary cholangitis 40-item questionnaire; PCS = physical component summary; PLA = placebo; SD = standard deviation; SE = standard error; SF-36 Short Form (36) Health Survey; ULN = upper limit of normal; VAS = visual analogue scale.

[a] Weighted average daily dose accounts for the flexibility of dose adjustments, titration, and frequency as specified by the protocol.

[b] Based on last available dose.

[c] The baseline criteria was defined as follows: ALP ≥ 1.67 x ULN or total bilirubin > ULN.

[d] Post hoc analysis.

[e] Mean (SD).

[f] Wilcoxon–Mann–Whitney *P* values compared with placebo.

[g] Based on full safety population (all OCA doses).

[h] Aggregate physical or mental component scale.

Source: Clinical study reports.[34-37]

Safety

A summary of the adverse events during the short-term phase II studies and their LTSEs are presented in Table 25.

Most participants (range 84% to 97%) experienced adverse events in 747-201 DB and 747-202 DB and their LTSEs. The adverse events rates varied across all studies; however, pruritus was reported as the most frequently experienced adverse event in every study (range 30% to 87%). In 747-201 DB, pruritus appears to occur more frequently in the OCA treatment group than in the placebo group (70% versus 30%, respectively). Overall, a numerically greater discrepancy in pruritus between OCA treatment and placebo was reported in 747-201 DB (OCA monotherapy) compared with 747-202 DB (OCA combination therapy with UDCA).

Generally, occurrences of serious adverse events were uncommon (range 3% to 6%); however, the frequency of serious adverse events was greater in 747-201 LTSE (21%). Adverse events resulting in study discontinuation were uncommon among patients treated with placebo (0% and 3% in 747-201 DB and 747-202 DB, respectively); by contrast, withdrawals due to adverse events were more frequently experienced in patients treated with OCA (range 15% to 21%). The most common reason for discontinuation in patients treated with OCA across all studies was pruritus (range 8% to 15%). Generally, numerically fewer discontinuations due to pruritus were observed in patients treated with OCA in 747-202 DB (OCA combination therapy with UDCA) than in 747-201 DB (OCA monotherapy [8% versus 15%, respectively]).

Table 25: Safety Outcomes in Short-Term Phase II Studies and Their Safety Extensions

	DB				LTSE	
	747-201		747-202		747-201	747-202
	PLA N = 23	OCA 10 mg N = 20	PLA N = 38	OCA 10 mg N = 38	OCA ≤ 10 mg[a] N = 14	OCA ≤ 10 mg[b] N = 78
Adverse Events[c]						
Participants with > 0 AEs, n (%)	21 (91)	18 (90)	32 (84)	34 (89)	NR	76 (97)
Pruritus	7 (30)	14 (70)	19 (50)	18 (47)	11 (79)	68 (87)
Headache	5 (22)	4 (20)	4 (11)	3 (8)	5 (36)	8 (10)
Nasopharyngitis	2 (9)	3 (15)	NR	NR	3 (21)	NR
Urinary tract infection	0	3 (15)	NR	NR	1 (7)	NR
Upper respiratory tract infection	0	2 (10)	NR	NR	1 (7)	10 (13)
Nausea	4 (17)	0	1 (3)	4 (11)	6 (43)	NR
Back pain	4 (17)	0	NR	NR	4 (29)	NR
Dizziness	4 (17)	0	NR	NR	2 (14)	NR
Fatigue	3 (13)	0	5 (13)	7 (18)	5 (36)	10 (13)
Insomnia	1 (4)	1 (5)	NR	NR	2 (14)	10 (13)
Rash	NR	NR	NR	NR	1 (7)	8 (10)
Serious Adverse Events						
Participants with > 0 SAEs, n (%)	1 (4)	0	1 (3)	0	3 (21)	5 (6)
Discontinuations						
WDAE, n (%)	0	3 (15)	1 (3)	6 (16)	3 (21)	14 (18)
Subjects who withdrew due to pruritus, n (%)	0	3 (15)	0	3 (8)	2 (14)	10 (13)
Subjects meeting mandatory discontinuation criteria, n (%)	NR	NR	1 (3)	1 (3)	NR	NR

AE = adverse event; DB = double-blind; LTSE = long-term safety extension; NR = not reported; OCA = obeticholic acid; PLA = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Weighted average daily dose accounts for the flexibility of dose adjustments, titration, and frequency as specified by the protocol.

[b] Based on full safety population (all OCA doses).

[c] Adverse events ≥ 10%.

Source: Clinical study reports.[34-37]

Limitations

The Health Canada–approved product monograph states that patients receiving OCA for the treatment of PBC should start on an initial dose of 5 mg. Doses should subsequently be titrated to 10 mg based on normalization of ALP levels.[38] The initial doses used in 747-201 DB and 747-202 DB as well as their LTSEs were 10 mg; therefore, patients were not treated according to the

recommendations in the product monograph. Consequently, the treatment effect associated with OCA therapy according to the recommended dosage is unclear (i.e., there is a potential for overestimating the efficacy and adverse events related to OCA treatment). Treatment with 10 mg of OCA without titration may lead to more adverse events than would be expected with treatment starting at a 5 mg dose; starting at a lower dose would help patients develop a tolerance to the drug.

Study duration for the short-term phase II trials was limited to three months. The clinical expert consulted for this CADTH Common Drug Review indicated that improvements in liver enzyme levels are typically manifested between six and 12 months of treatment, and it is therefore unclear whether the results of 747-201 DB and 747-202 DB at three months provide sufficient time for most patients to improve or to fully benefit from treatment.

No details with respect to the randomization in 747-201 DB were provided. The distribution of baseline characteristics between treatment groups in 747-201 DB and 747-202 DB appears to be relatively balanced; however, the small sample size of the trials creates greater risk for imbalances between treatment groups. Differences in treatment groups can lead to uneven distribution of unknown confounders and to uncertainty associated with treatment effect. In addition, hierarchical testing strategies were implemented to account for multiple statistical testing in the primary end points only (change in ALP); no corrections for multiple statistical testing were applied for all other analyses in either 747-201 DB or 747-202 DB. As a result, uncertainty with respect to any inferences based on these end points was introduced, given that they are susceptible to inflated type I error.

There are several limitations to the long-term, open-label, non-randomized safety studies. First, given that they were uncontrolled studies, it remains unclear whether the changes observed in the safety profile were due to a natural course of the disease or were attributable to long-term treatment with OCA. Open-label trial designs in which both the investigators and the participants are unblinded to treatment allocation may have an impact on subjective outcomes, such as some patient-reported adverse events, health-related quality-of-life measures, and symptom scales. In addition, all efficacy end points were considered exploratory, and no corrections were applied to adjust for multiplicity. Therefore, the efficacy results are susceptible to inflated type I error, which can lead to uncertainty when statistically significant differences are found.

Summary

Results from two short-term, phase II, international, multi-centre, randomized, double-blind, placebo-controlled, multi-dose, parallel-group studies and their open-label, non-randomized LTSEs suggested benefit of OCA therapy in the composite end point (patients with ALP less than 1.67 times ULN and total bilirubin at ULN or lower, and decrease in ALP of 15% or more from baseline) and the primary outcome of 747-201 DB and 747-202 DB (changes in ALP). In addition, based on the PBC-40 questionnaire, OCA therapy appears to be associated with increased scores in the itch domain, suggesting exacerbation of itch. Almost all participants' experienced adverse events with OCA treatment, the most frequent being pruritus. No deaths were reported in any of the studies. Considering the limitations of the short-term phase II studies and their LTSEs, the results should be interpreted with caution.

References

1. Myers RP, Shaheen AA, Fong A, Burak KW, Wan A, Swain MG, et al. Epidemiology and natural history of primary biliary cirrhosis in a Canadian health region: a population-based study. Hepatology. 2009 Dec;50(6):1884-92.
2. Prince M, Chetwynd A, Newman W, Metcalf JV, James OF. Survival and symptom progression in a geographically based cohort of patients with primary biliary cirrhosis: follow-up for up to 28 years. Gastroenterology. 2002 Oct;123(4):1044-51.
3. CDR submission: Ocaliva (obeticholic acid), 5 and 10 mg tablets. Company: Intercept Pharmaceuticals Canada [**CONFIDENTIAL** manufacturer's submission]. Vancouver (BC): Intercept Pharmaceuticals Canada; 2017 Jan 16.
4. Corpechot C, Abenavoli L, Rabahi N, Chretien Y, Andreani T, Johanet C, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2008 Sep;48(3):871-7.
5. Kumagi T, Guindi M, Fischer SE, Arenovich T, Abdalian R, Coltescu C, et al. Baseline ductopenia and treatment response predict long-term histological progression in primary biliary cirrhosis. Am J Gastroenterol. 2010 Oct;105(10):2186-94.
6. Draft letter of undertaking: Ocaliva (obeticholic acid, 5 and 10 mg tablets) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2017 May 15.
7. Ocaliva (obeticholic acid): 5 and 10 mg tablets [product monograph]. Vancouver (BC): Intercept Pharmaceuticals Canada; 2017 May 24.
8. Heathcote EJ, Cauch-Dudek K, Walker V, Bailey RJ, Blendis LM, Ghent CN, et al. The Canadian multicenter double-blind randomized controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology. 1994 May;19(5):1149-56.
9. Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology. 1997 Sep;113(3):884-90.
10. Pellicciari R, Fiorucci S, Camaioni E, Clerici C, Costantino G, Maloney PR, et al. 6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 2002 Aug 15;45(17):3569-72.
11. Fiorucci S, Distrutti E, Ricci P, Giuliano V, Donini A, Baldelli F. Targeting FXR in cholestasis: hype or hope. Expert Opin Ther Targets. 2014 Dec;18(12):1449-59.
12. Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med. 2016 Aug 18;375(7):631-43.
13. Clinical Study Report: 747-301. A Phase 3, double blind, placebo controlled trial and long term safety extension of obeticholic acid in patients with primary biliary cirrhosis [**CONFIDENTIAL** internal manufacturer's report]. San Diego (CA): Intercept Pharmaceuticals, Inc.; 2015 Apr 17.
14. e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2009 -. URSO (ursodeoxycholic acid); 2014 Aug 18 [cited 2017 Mar 27]. Available from: https://www.e-therapeutics.ca Subscription required.
15. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: Ocaliva (obeticholic acid). Company: Intercept Pharms Inc. Application no.: 207999. Approval date: 27/05/2016 [Internet]. Rockville (MD): FDA; 2016 May 27 [cited 2017 Jan 17]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207999Orig1s000TOC.cfm
16. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: Ocaliva (obeticholic acid). Company: Intercept Pharms Inc. Application no.: 207999. Approval date: 27/05/2016 [Internet]. Rockville (MD): FDA; 2016 May 27 [cited 2017 Jan 17]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207999Orig1s000TOC.cfm
17. Gomez-Dominguez E, Mendoza J, Garcia-Buey L, Trapero M, Gisbert JP, Jones EA, et al. Transient elastography to assess hepatic fibrosis in primary biliary cirrhosis. Aliment Pharmacol Ther. 2008 Mar 1;27(5):441-7.
18. Foucher J, Chanteloup E, Vergniol J, Castera L, Le BB, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut [Internet]. 2006 Mar [cited 2017 Mar 14];55(3):403-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1856085
19. Friedrich-Rust M, Rosenberg W, Parkes J, Herrmann E, Zeuzem S, Sarrazin C. Comparison of ELF, FibroTest and FibroScan for the non-invasive assessment of liver fibrosis. BMC Gastroenterol [Internet]. 2010 Sep 9 [cited 2017 Mar 6];10:103. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2944336
20. Mayo MJ, Parkes J, ms-Huet B, Combes B, Mills AS, Markin RS, et al. Prediction of clinical outcomes in primary biliary cirrhosis by serum enhanced liver fibrosis assay. Hepatology [Internet]. 2008 Nov [cited 2017 Mar 6];48(5):1549-57. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2597274
21. ADVIA Centaur Enhanced Liver Fibrosis (ELF) test: specification sheet. Erlangen (DE): Siemens Healthcare GmbH; 2016.
22. European Medicines Agency. European Public Assessment Report (EPAR): Ocaliva. In: Ocaliva Product Information [Internet]. London (GB): EMA; 2016 Dec 19 [cited 2017 Mar 27]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004093/WC500218418.pdf
23. Lammers WJ, van Buuren HR, Hirschfield GM, Janssen HL, Invernizzi P, Mason AL, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology. 2014 Dec;147(6):1338-49.
24. Jacoby A, Rannard A, Buck D, Bhala N, Newton JL, James OF, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut [Internet]. 2005 Nov [cited 2017 Mar 6];54(11):1622-9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1774759
25. Corpechot C, El NA, Poujol-Robert A, Ziol M, Wendum D, Chazouilleres O, et al. Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. Hepatology. 2006 May;43(5):1118-24.
26. Zhao P, Liu WW, Li JF, Wang CY, Wang H, Xu J, et al. Predictors of liver failure in primary biliary cirrhosis. Ups J Med Sci [Internet]. 2015 Mar [cited 2017 Mar 6];120(1):47-51. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4389007

27. Corpechot C, Chazouilleres O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. J Hepatol. 2011 Dec;55(6):1361-7.

28. Krzeski P, Zych W, Kraszewska E, Milewski B, Butruk E, Habior A. Is serum bilirubin concentration the only valid prognostic marker in primary biliary cirrhosis? Hepatology. 1999 Oct;30(4):865-9.

29. Bonnand AM, Heathcote EJ, Lindor KD, Poupon RE. Clinical significance of serum bilirubin levels under ursodeoxycholic acid therapy in patients with primary biliary cirrhosis. Hepatology. 1999 Jan;29(1):39-43.

30. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ, et al. Primary biliary cirrhosis. Hepatology. 2009 Jul;50(1):291-308.

31. European Association for the Study of the Liver. EASL clinical practice guidelines: management of cholestatic liver diseases. J Hepatol. 2009 Aug;51(2):237-67.

32. Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen HL, et al. Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. Gastroenterology. 2015 Dec;149(7):1804-12.

33. Clinical Study Report: 747-301. A Phase 3, double blind, placebo controlled trial and long term safety extension of obeticholic acid in patients with primary biliary cirrhosis - Long term safety extension phase [**CONFIDENTIAL** internal manufacturer's report]. San Diego (CA): Intercept Pharmaceuticals, Inc.; 2015 Apr 21.

34. Clinical Study Report: 747-201. A study of INT-747 (6-ECDCA) monotherapy in patients with primary biliary cirrhosis [**CONFIDENTIAL** internal manufacturer's report]. San Diego (CA): Intercept Pharmaceuticals, Inc.; 2015 Feb 20.

35. Clinical Study Report: 747-201. A study of INT-747 (6-ECDCA) monotherapy in patients with primary biliary cirrhosis - Long term safety extension phase [**CONFIDENTIAL** internal manufacturer's report]. San Diego (CA): Intercept Pharmaceuticals, Inc.; 2015 May 2.

36. Clinical Study Report: 747-202. A study of INT-747 (6-ECDCA) in combination with ursodeoxycholic acid (URSO, UCDA) in subjects with primary biliary cirrhosis [**CONFIDENTIAL** internal manufacturer's report]. San Diego (CA): Intercept Pharmaceuticals, Inc.; 2015 Apr 3.

37. Clinical Study Report: 747-202. A study of INT-747 (6-ECDCA) in combination with ursodeoxycholic acid (URSO, UCDA) in subjects with primary biliary cirrhosis - Long term safety extension [**CONFIDENTIAL** internal manufacturer's report]. San Diego (CA): Intercept Pharmaceuticals, Inc.; 2015 Mar 31.

38. Ocaliva (obeticholic acid): 5 and 10 mg tablets [product monograph]. Vancouver (BC): Intercept Pharmaceuticals Canada; 2016 Sep 16.