Full Title of the Trial: A Study of INT-747 (6-EDCA) Monotherapy in Patients With Primary Biliary Cirrhosis

Additional study identifiers
Protocol Number: 747-201
EudraCT Number: 2007-001424-12
ISRCTN Number: 68931598
NCT Number: NCT00570765

Sponsors
Sponsor: Intercept Pharmaceuticals, Inc.
Address: 4760 Eastgate Mall, San Diego, CA, 92121, USA
Scientific Point of Contact: David Shapiro, Chief Medical Officer. email: dshapiro@interceptpharma.com
Public Point of Contact: Cathi Sciacca, VP Clinical Operations. email: csciacca@interceptpharma.com
Is trial part of a Paediatric Investigation Plan?: No

Results analysis stage
Primary completion date reached?: Yes
Primary completion date: 2010-10-07
Analysis stage: Final
Date of final analysis: 2014-12-01
Global end of trial reached?: No

General information about trial
Note: INT-747 is now known as Obeticholic Acid (OCA).
Main objective of the trial: To assess the effects of OCA in subjects with primary biliary cirrhosis (PBC) on alkaline phosphatase (AP) levels and safety
Actual start date of recruitment: 2007-12-20
Long term follow up planned: Yes
Follow Up planning rationale: Provide opportunity for subjects to continue or start to receive open-label INT-747 therapy. This LTSE is designed to provide both clinical benefit to the participating subjects and appropriate safety and efficacy data from the longer term use of INT-747.
Long term follow up duration: Dependent upon the discretion of the investigator
Independent Data-Monitoring Committee (IDMC) involvement: Yes
Protection of trial subjects: Protection of clinical trial subjects was in accordance with ICH and GCP guidelines. Oversight by the Independent Data Safety Committee in addition to the Independent Ethics Committees ensured the protection of the rights, safety and well-being of the subjects participating in the clinical study.
In addition, subject confidentiality was maintained as follows: Data processing is performed indirectly personalized where within the CRF subjects will only be kept as ID-Number. Subject name, initials and subject's date of birth are not recorded. Only the site can match subject ID-Number with subject name.
All screened subjects are required to be entered into the electronic database. The database provides the next sequential ID-Number for each subject that is enrolled at the individual sites. It is the sites' responsibility to maintain all data and personal identification in relation to this ID-Number.
The site is also responsible for redacting subject's personal identifying information when sending documents to the sponsor, laboratory, etc in order to keep the subject's information protected.

Actual Number of Subjects in Each Country Concerned

Canada	France	Germany	Spain	United_Kingdom	United_States
9	4	8	2	19	17

Actual Number of Subjects included in the EEA

EEA
33

Actual Number of Subjects included worldwide

Worldwide
59

Age Group Breakdown for the Whole Trial

Age of Subjects	Number of Subjects
In Utero	0
Preterm newborn- gestational age < 37 wk	0
Newborns (0-27days)	0
Infants and toddlers (28days – 23months)	0
Children (2-11 years)	0
Adolescents (12-17 year)	0
Between 18 and 65 years	49
From 65 years to 84 years	10
85 years and over	0

Subject disposition form
Recruitment Details: Recruitment into hospitals and physicians' clinics started DEC 2007 and completed JUN 2010. Due to positive Phase 2 data in another study (747-202), power calculations were revised and recruitment ended early.
Screening Details: Screening interim allowed for pre-randomization eligibility assessment of 1 to 4 weeks. Other than 3-month (pre-Screening) washout for ursodeoxycholic acid (UDCA) and other medications, no washout or run-in period was defined between Screening and randomization.

Dispostion Milestones

Milestone	Number of Subjects
Started	59
Completed	48
Not Completed	11

Reasons Not Completed

Reason	Number of Subjects
Adverse event, not serious	9
Adverse event, serious fatal	0
Adverse event, serious non-fatal	0
Consent withdrawn by subject	1
Physician decision	0
Pregnancy	0
Protocol Violation	1

Period 1
Period 1 title: Double-Blind Phase
Blinding implementation details: Double blind
Roles blinded: Subject, Investigator, Monitor, Data analyst, Carer, Assessor
Allocation method: Randomised - controlled

Dispostion Milestones by Arm

Milestone	10 mg OCA	50 mg OCA	Placebo	Total
Started	20	16	23	59
Completed	16	9	23	48
Not Completed	4	7	0	11

Reasons Not Completed by Arm

Reason	10 mg OCA	50 mg OCA	Placebo	Total
Adverse event, not serious	3	6	0	9
Adverse event, serious fatal	0	0	0	0
Adverse event, serious non-fatal	0	0	0	0
Consent withdrawn by subject	1	0	0	1
Physician decision	0	0	0	0
Pregnancy	0	0	0	0
Protocol Violation	0	1	0	1

Subject disposition arm form

Arm Title: 10 mg OCA
Arm Description: INT-747 (OCA) 10 mg by mouth, daily
Arm Type: Experimental
Investigational medicinal product name: OBETICHOLIC ACID (OCA)
Investigational medicinal product code: INT-747
Route of Administration: PO
Pharmaceutical Form: Capsule
Dosage and Administration Details: QD

Arm Title: 50 mg OCA
Arm Description: INT-747 (OCA) 50 mg by mouth, daily
Arm Type: Experimental
Investigational medicinal product name: OBETICHOLIC ACID (OCA)
Investigational medicinal product code: INT-747
Route of Administration: PO
Pharmaceutical Form: Capsule
Dosage and Administration Details: QD

Arm Title: Placebo
Arm Description: Placebo by mouth, daily
Arm Type: Placebo Comparator
Route of Administration: PO
Pharmaceutical Form: Capsule
Dosage and Administration Details: QD

Subject analysis sets form

Subject Analysis Set

Subject analysis set	Intent-to-Treat (ITT) population
Subject analysis set description	Subjects who received at least one dose of treatment
Number of subjects	59

Baseline characteristics form

Age by Treatment Group, Categorical (ITT Population)

Age of Subjects	10 mg OCA	50 mg OCA	Placebo	Total
In Utero	0	0	0	0
Preterm newborn- gestational age < 37 wk	0	0	0	0
Newborns (0-27days)	0	0	0	0
Infants and toddlers (28days – 23months)	0	0	0	0
Children (2-11 years)	0	0	0	0
Adolescents (12-17 year)	0	0	0	0
Between 18 and 65 years	16	15	18	49
From 65 years to 84 years	4	1	5	10
85 years and over	0	0	0	0

Age by Treatment Group, Continuous (ITT Population)

	10 mg OCA	50 mg OCA	Placebo	Total
Mean (SD)	54.8 (10.9)	54.1 (7.3)	55.3 (10.0)	54.8 (9.5)

Gender (ITT Population)

Gender	10 mg OCA	50 mg OCA	Placebo	Total
F	14	16	20	50
M	6	0	3	9

BASELINE CHARACTERISTICS: SPECIFIC MEASURES (ITT SUBJECTS)

Baseline Serum Alkaline Phosphatase (U/L)
Baseline ALP (U/L) Descriptive Statistics
Measure type: Arithmetic Mean
Dispersion type: Standard Deviation

Statistic	10 mg OCA	50 mg OCA	Placebo	Total
N	20	16	23	59
Mean (SD)	461.6 (298.7)	431.1 (177.2)	408.4 (223.0)	432.6 (238.2)

Baseline ALP Wilcoxon (Mann-Whitney) Pairwise Comparisons

Comparison	p_value
10 mg OCA vs. Placebo	0.8360
50 mg OCA vs Placebo	0.3609

Baseline Gamma-Glutamyl Transferase (GGT) (U/L)
Baseline GGT (U/L) Descriptive Statistics
Measure type: Arithmetic Mean
Dispersion type: Standard Deviation

Statistic	10 mg OCA	50 mg OCA	Placebo	Total
N	20	16	23	59
Mean (SD)	653 (370)	455 (418)	466 (321)	527 (371)

Baseline GGT Wilcoxon (Mann-Whitney) Pairwise Comparisons

Comparison	p_value
10 mg OCA vs. Placebo	0.0697
50 mg OCA vs Placebo	0.6376

Baseline Alanine Transaminase (ALT) (U/L)
Baseline ALT (U/L) Descriptive Statistics
Measure type: Arithmetic Mean
Dispersion type: Standard Deviation

Statistic	10 mg OCA	50 mg OCA	Placebo	Total
N	20	16	23	59
Mean (SD)	86 (44)	71 (38)	83 (60)	81 (49)

Baseline ALT Wilcoxon (Mann-Whitney) Pairwise Comparisons

Comparison	p_value
10 mg OCA vs. Placebo	0.4576
50 mg OCA vs Placebo	0.6788

END POINTS ANALYSES (ITT SUBJECTS)

Primary Endpoint
Percent (%) Change in Serum Alkaline Phosphatase from baseline to end of treatment
ALP Descriptive Statistics
Measure type: Arithmetic Mean
Dispersion type: Standard Deviation
Note: All subjects at baseline are represented here.

Statistic	10 mg OCA	50 mg OCA	Placebo	Total
N	20	16	23	59
Mean (SD)	-44.5 (24.4)	-37.6 (21.0)	0.4 (15.3)	-25.1 (28.8)

ALP Wilcoxon (Mann-Whitney) Pairwise Comparisons

Comparison	p_value
10 mg OCA vs. Placebo	<.0001
50 mg OCA vs Placebo	<.0001

The null hypothesis was that OCA and Placebo are equivalent with respect to ALP percentage change from baseline at end of treatment.
A hierarchical testing strategy (Lubsen and Kirwan, 2005) was proposed to account for multiple comparisons.
The statistical significance was to be evaluated in order as follows: if statistical significance at alpha = 0.05 was observed for the OCA 10 mg group versus placebo, then the statistical significance at alpha = 0.05 for the OCA 50 mg versus placebo was to be performed. If no statistical significance was observed at alpha = 0.05 at the first step, then the subsequent comparisons were not considered statistically significant, regardless of the p-value.
Method: Wilcoxon (Mann-Whitney) (2-sided)
Analysis Type: Superiority
Comparison group: All reporting groups
Analysis Specification: Pre-specified

Secondary Endpoint
Percent (%) Change in Gamma-Glutamyl Transferase (GGT) from baseline to Day 85 / ET
GGT Descriptive Statistics
Measure type: Arithmetic Mean
Dispersion type: Standard Deviation
Note: Each treatment group has one fewer subject than at baseline. Test results for these subjects were not collected at the Day 85 or ET visits.

Statistic	10 mg OCA	50 mg OCA	Placebo	Total
N	19	15	22	56
Mean (SD)	-73 (18)	-65 (25)	-3 (22)	-43 (39)

GGT Wilcoxon (Mann-Whitney) Pairwise Comparisons

Comparison	p_value
10 mg OCA vs. Placebo	<.0001
50 mg OCA vs Placebo	<.0001

The null hypothesis was that OCA and Placebo are equivalent with respect to GGT percentage change from baseline at Day 85 / ET.
A hierarchical testing strategy (Lubsen and Kirwan, 2005) was proposed to account for multiple comparisons.
Method: Wilcoxon (Mann-Whitney) (2-sided)
Analysis Type: Superiority
Comparison group: All reporting groups
Analysis Specification: Pre-specified

Secondary Endpoint
Percent (%) Change in Alanine Transaminase(ALT) from baseline to Day 85 / ET
ALT Descriptive Statistics
Measure type: Arithmetic Mean
Dispersion type: Standard Deviation
Note: Each treatment group has one fewer subject than at baseline. Test results for these subjects were not collected at the Day 85 or ET visits.

Statistic	10 mg OCA	50 mg OCA	Placebo	Total
N	19	15	22	56
Mean (SD)	-37 (35)	-35 (25)	-4 (40)	-23 (38)

ALT Wilcoxon (Mann-Whitney) Pairwise Comparisons

Comparison	p_value
10 mg OCA vs. Placebo	0.0042
50 mg OCA vs Placebo	0.0068

The null hypothesis was that OCA and Placebo are equivalent with respect to ALT percentage change from baseline at Day 85 / ET.
A hierarchical testing strategy (Lubsen and Kirwan, 2005) was proposed to account for multiple comparisons.
Method: Wilcoxon (Mann-Whitney) (2-sided)
Analysis Type: Superiority
Comparison group: All reporting groups
Analysis Specification: Pre-specified

ADVERSE EVENTS, MedDRA Version 12.1
Method: Systematic
Frequency threshold for reporting non-serious adverse events: 5%
Time Frame for Adverse Event Reporting: Day of first treatment until end of study

There were 0 Fatalities.

Serious Treatment-Emergent AEs (ITT Population)

	10 mg OCA (N=20) n(%) / Events / Related Events	**50 mg OCA (N=16) n(%) / Events / Related Events**	**Placebo (N=23) n(%) / Events / Related Events**
All Serious TEAEs	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (4) / 1 / 0
Skin and subcutaneous tissue disorders	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (4) / 1 / 0
_____Rash	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (4) / 1 / 0

Non-Serious Common (>=5%) Treatment-Emergent AEs (ITT Population)

	10 mg OCA (N=20) n(%) / Events / Related Events	50 mg OCA (N=16) n(%) / Events / Related Events	Placebo (N=23) n(%) / Events / Related Events
All Common Non-Serious TEAEs	18 (90) / 70 / 40	15 (94) / 70 / 43	19 (83) / 59 / 26
Skin and subcutaneous tissue disorders	15 (75) / 33 / 31	15 (94) / 24 / 23	9 (39) / 14 / 12
_____Pruritus	14 (70) / 24 / 24	15 (94) / 22 / 21	7 (30) / 11 / 10
_____Dry skin	0 (0) / 0 / 0	1 (6) / 1 / 1	1 (4) / 2 / 2
_____Rash	0 (0) / 0 / 0	1 (6) / 1 / 1	1 (4) / 1 / 0
_____Rash macular	1 (5) / 2 / 2	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Rash papular	1 (5) / 2 / 2	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Acne	1 (5) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Alopecia	1 (5) / 1 / 1	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Palmar-plantar erythrodysaesthesia syndrome	1 (5) / 1 / 1	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Skin lesion	1 (5) / 1 / 1	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Vitiligo	1 (5) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
Gastrointestinal disorders	4 (20) / 5 / 1	8 (50) / 22 / 14	7 (30) / 12 / 7
_____Nausea	0 (0) / 0 / 0	4 (25) / 4 / 3	4 (17) / 5 / 3
_____Abdominal pain	1 (5) / 1 / 0	2 (13) / 2 / 2	1 (4) / 1 / 0
_____Diarrhoea	0 (0) / 0 / 0	2 (13) / 2 / 1	1 (4) / 1 / 1
_____Vomiting	1 (5) / 1 / 0	1 (6) / 1 / 1	1 (4) / 1 / 1
_____Abdominal distension	0 (0) / 0 / 0	2 (13) / 2 / 1	0 (0) / 0 / 0
_____Abdominal pain upper	0 (0) / 0 / 0	0 (0) / 0 / 0	2 (9) / 2 / 1
_____Constipation	0 (0) / 0 / 0	2 (13) / 2 / 1	0 (0) / 0 / 0
_____Dry mouth	1 (5) / 1 / 1	0 (0) / 0 / 0	1 (4) / 1 / 1
_____Faeces pale	0 (0) / 0 / 0	2 (13) / 2 / 2	0 (0) / 0 / 0
_____Haemorrhoids	0 (0) / 0 / 0	2 (13) / 2 / 1	0 (0) / 0 / 0
_____Toothache	0 (0) / 0 / 0	1 (6) / 1 / 0	1 (4) / 1 / 0
_____Faecal incontinence	0 (0) / 0 / 0	1 (6) / 1 / 1	0 (0) / 0 / 0
_____Flatulence	1 (5) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Gastrooesophageal reflux disease	0 (0) / 0 / 0	1 (6) / 1 / 1	0 (0) / 0 / 0
_____Glossodynia	1 (5) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Parotid gland enlargement	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
_____Salivary gland enlargement	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
Nervous system disorders	5 (25) / 6 / 0	3 (19) / 5 / 0	7 (30) / 11 / 3

	10 mg OCA (N=20) n(%) / Events / Related Events	50 mg OCA (N=16) n(%) / Events / Related Events	Placebo (N=23) n(%) / Events / Related Events
_____Headache	4 (20) / 5 / 0	2 (13) / 3 / 0	5 (22) / 6 / 1
_____Dizziness	0 (0) / 0 / 0	0 (0) / 0 / 0	4 (17) / 5 / 2
_____Facial neuralgia	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
_____Irregular sleep phase	1 (5) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Migraine	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
Infections and infestations	6 (30) / 9 / 0	4 (25) / 6 / 1	2 (9) / 2 / 0
_____Nasopharyngitis	3 (15) / 3 / 0	1 (6) / 1 / 0	2 (9) / 2 / 0
_____Urinary tract infection	3 (15) / 3 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
_____Upper respiratory tract infection	2 (10) / 3 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Cystitis	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
_____Eye infection	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
_____Lower respiratory tract infection	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
_____Sinusitis	0 (0) / 0 / 0	1 (6) / 1 / 1	0 (0) / 0 / 0
General disorders and administration site conditions	1 (5) / 1 / 0	4 (25) / 4 / 2	6 (26) / 8 / 2
_____Fatigue	0 (0) / 0 / 0	1 (6) / 1 / 0	3 (13) / 3 / 1
_____Influenza like illness	0 (0) / 0 / 0	1 (6) / 1 / 1	2 (9) / 2 / 1
_____Chills	1 (5) / 1 / 0	0 (0) / 0 / 0	1 (4) / 1 / 0
_____Pyrexia	0 (0) / 0 / 0	0 (0) / 0 / 0	2 (9) / 2 / 0
_____Asthenia	0 (0) / 0 / 0	1 (6) / 1 / 1	0 (0) / 0 / 0
_____Feeling cold	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
Musculoskeletal and connective tissue disorders	1 (5) / 1 / 1	1 (6) / 1 / 0	5 (22) / 7 / 0
_____Back pain	0 (0) / 0 / 0	0 (0) / 0 / 0	4 (17) / 4 / 0
_____Arthralgia	0 (0) / 0 / 0	0 (0) / 0 / 0	2 (9) / 2 / 0
_____Muscle spasms	1 (5) / 1 / 1	0 (0) / 0 / 0	1 (4) / 1 / 0
_____Pain in extremity	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
Respiratory, thoracic and mediastinal disorders	3 (15) / 3 / 0	1 (6) / 1 / 0	3 (13) / 3 / 1
_____Cough	1 (5) / 1 / 0	1 (6) / 1 / 0	1 (4) / 1 / 0
_____Oropharyngeal pain	1 (5) / 1 / 0	0 (0) / 0 / 0	1 (4) / 1 / 1
_____Sinus congestion	1 (5) / 1 / 0	0 (0) / 0 / 0	1 (4) / 1 / 0
Psychiatric disorders	1 (5) / 2 / 2	2 (13) / 2 / 1	1 (4) / 1 / 0
_____Insomnia	1 (5) / 2 / 2	2 (13) / 2 / 1	1 (4) / 1 / 0

	10 mg OCA (N=20) n(%) / Events / Related Events	**50 mg OCA (N=16) n(%) / Events / Related Events**	**Placebo (N=23) n(%) / Events / Related Events**
Eye disorders	1 (5) / 1 / 0	1 (6) / 1 / 1	1 (4) / 1 / 1
_____Dry eye	0 (0) / 0 / 0	1 (6) / 1 / 1	1 (4) / 1 / 1
_____Iritis	1 (5) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
Reproductive system and breast disorders	2 (10) / 3 / 2	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Breast tenderness	1 (5) / 1 / 1	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Gynaecomastia	1 (5) / 1 / 1	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Menorrhagia	1 (5) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
Investigations	0 (0) / 0 / 0	2 (13) / 2 / 1	0 (0) / 0 / 0
_____Weight decreased	0 (0) / 0 / 0	1 (6) / 1 / 1	0 (0) / 0 / 0
_____White blood cells urine	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
Blood and lymphatic system disorders	1 (5) / 2 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Lymphadenopathy	1 (5) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Lymphoid tissue hyperplasia	1 (5) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
Hepatobiliary disorders	1 (5) / 1 / 1	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Hepatic pain	1 (5) / 1 / 1	0 (0) / 0 / 0	0 (0) / 0 / 0
Immune system disorders	1 (5) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Sarcoidosis	1 (5) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
Injury, poisoning and procedural complications	1 (5) / 1 / 1	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Contusion	1 (5) / 1 / 1	0 (0) / 0 / 0	0 (0) / 0 / 0
Metabolism and nutrition disorders	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
_____Diabetes mellitus	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
_____Lung neoplasm	0 (0) / 0 / 0	1 (6) / 1 / 0	0 (0) / 0 / 0
Vascular disorders	1 (5) / 1 / 1	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Hot flush	1 (5) / 1 / 1	0 (0) / 0 / 0	0 (0) / 0 / 0

More Information: Global Substantial Protocol Amendments

Amendment Number / Date	Description
Version 1/ 08 Aug 2007	Original Protocol
Version 2/ 12 Nov 2007	Collection of additional blood samples for PK analysis
Version 5/ 13 Nov 2008	• Additional results in non-clinical toxicity studies
	• Change in contraception requirements based on no Adverse Events in reproductive/development toxicity
	• Fibroscan Transient Elastography device to be used at select sites
	• Revision to mandatory discontinuation criteria
Addendum 4 to Protocol Version 5 / 12 Feb 2010	Correction to Schedule of Procedures
Version 5.1 and Addendum 6/ 26 Apr 2012	Protocol modified to include that investigational product can be provided as either capsules or tablets