Full Title of the Trial: A Study of INT-747 (6-ECDCA) in Combination with Ursodeoxycholic Acid (URSO®, UDCA) in Patients with Primary Biliary Cirrhosis

Additional study identifiers
Protocol Number: 747-202
EudraCT Number: 2007-001425-10
ISRCTN Number: 67465025
NCT Number: NCT00550862

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: 2009-08-26
Analysis stage: Final
Date of final analysis: 2014-10-30
Global end of trial reached?: Yes
Date of global end of trial: 2010-11-29

General information about trial
Note: INT-747 is now known as Obeticholic Acid (OCA).
Main objective of the trial: To assess the effects of INT-747 in subjects with proven or likely PBC, in combination with ursodeoxycholic acid (URSOUDCA), on alkaline phosphatase (AP) levels and safety
Actual start date of recruitment: 2007-10-30
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 subjects information protected.
Background Therapy: Ursodeoxycholic Acid

Actual Number of Subjects in Each Country Concerned

Austria	Canada	France	Germany	Netherlands	Spain	United_Kingdom	United_States
6	46	2	8	4	6	12	81

Actual Number of Subjects included in the EEA

EEA
38

Actual Number of Subjects included worldwide

Worldwide
165

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	139
From 65 years to 84 years	26
85 years and over	0

Subject disposition form
Recruitment Details: Recruitment for the 747-202 study began in OCT 2007 and concluded in MAY 2009. This was an international, multi-center, randomized, double-blind, placebo-controlled, multi-dose study with the majority of the sites being academic centers.
Screening Details: Subjects were required to meet the Inclusion and Exclusion requirements as per protocol. Subjects were screened and those who met the required criteria were randomized to the trial.

Dispostion Milestones

Milestone	Number of Subjects
Started	165
Completed	136
Not Completed	29

Reasons Not Completed

Reason	Number of Subjects
Adverse event, not serious	25
Adverse event, serious fatal	0
Adverse event, serious non-fatal	2
Consent withdrawn by subject	1
Physician decision	0
Pregnancy	0
Protocol Violation	0
Lost to Follow-Up	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	25 mg OCA	50 mg OCA	Placebo	Total
Started	38	48	41	38	165
Completed	32	42	25	37	136
Not Completed	6	6	16	1	29

Reasons Not Completed by Arm

Reason	10 mg OCA	25 mg OCA	50 mg OCA	Placebo	Total
Adverse event, not serious	6	5	13	1	25
Adverse event, serious fatal	0	0	0	0	0
Adverse event, serious non-fatal	0	0	2	0	2
Consent withdrawn by subject	0	0	1	0	1
Physician decision	0	0	0	0	0
Pregnancy	0	0	0	0	0
Protocol Violation	0	0	0	0	0
Lost to Follow-Up	0	1	0	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: 25 mg OCA
Arm Description: INT-747 (OCA) 25 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 Set 1

Subject analysis set	Intent-to-Treat (ITT) population
Subject analysis set description	Subjects who received at least one dose of treatment
Number of subjects	165

Subject Analysis Set 2

Subject analysis set	Modified Intent-to-Treat (mITT) population
Subject analysis set description	Subjects are assigned to the mITT if they were randomized and received at least one dose of study medication and had at least one post-baseline AP evaluation which was taken <= 7 days after their last dose of study medication.
Number of subjects	161

Baseline characteristics form

Age by Treatment Group, Categorical (ITT Population)

Age of Subjects	10 mg OCA	25 mg OCA	50 mg OCA	Placebo	Total
In Utero	0	0	0	0	0
Preterm newborn- gestational age < 37 wk	0	0	0	0	0
Newborns (0-27days)	0	0	0	0	0
Infants and toddlers (28days – 23months)	0	0	0	0	0
Children (2-11 years)	0	0	0	0	0
Adolescents (12-17 year)	0	0	0	0	0
Between 18 and 65 years	28	44	33	34	139
From 65 years to 84 years	10	4	8	4	26
85 years and over	0	0	0	0	0

Age by Treatment Group, Continuous (ITT Population)

	10 mg OCA	25 mg OCA	50 mg OCA	Placebo	Total
Mean (SD)	55.6 (9.3)	55.9 (8.0)	54.0 (9.7)	54.8 (8.5)	55.1 (8.8)

Gender (ITT Population)

Gender	10 mg OCA	25 mg OCA	50 mg OCA	Placebo	Total
F	38	45	38	36	157
M	0	3	3	2	8

BASELINE CHARACTERISTICS: SPECIFIC MEASURES (ITT/mITT SUBJECTS)

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

Statistic	10 mg OCA	25 mg OCA	50 mg OCA	Placebo	Total
N	38	47	39	37	161
Mean (SD)	294.4 (149.4)	289.4 (124.8)	286.1 (105.8)	276.4 (103.8)	286.8 (121.5)

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

Statistic	10 mg OCA	25 mg OCA	50 mg OCA	Placebo	Total
N	38	48	41	38	165
Mean (SD)	228 (212)	273 (267)	231 (182)	189 (139)	233 (209)

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

Statistic	10 mg OCA	25 mg OCA	50 mg OCA	Placebo	Total
N	38	48	41	38	165
Mean (SD)	51 (29)	51 (36)	53 (35)	47 (26)	51 (32)

END POINTS ANALYSES (ITT/mITT SUBJECTS)

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

Statistic	10 mg OCA	25 mg OCA	50 mg OCA	Placebo	Total
N	38	47	39	37	161
Mean (SD)	-23.7 (17.8)	-24.7 (17.9)	-21.0 (27.6)	-2.6 (12.5)	-18.5 (21.4)

ALP Wilcoxon (Mann-Whitney) Pairwise Comparisons (mITT)

Comparison	p_value
10 mg OCA vs. Placebo	<.0001
25 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 model was applied for testing of multiple treatment groups. Pairwise comparisons of the 50mg treatment group versus the placebo group were performed using the 2-sided Wilcoxon-Mann-Whitney test. In the event that a significant difference between this respective dose group and the placebo group was shown, the 25mg treatment group was compared versus the placebo group, as a confirmatory analysis. If a significant difference was demonstrated, the 10mg treatment group was compared to the placebo group.
All tests were performed at a significance level of 5%.
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 (ITT)
Measure type: Arithmetic Mean
Dispersion type: Standard Deviation
Note: One subject in the 50 mg group did not have a Day 85 / ET lab visit. All other subjects at baseline are present.

Statistic	10 mg OCA	25 mg OCA	50 mg OCA	Placebo	Total
N	38	48	40	38	164
Mean (SD)	-48 (30)	-63 (24)	-57 (31)	7 (28)	-42 (39)

GGT Wilcoxon (Mann-Whitney) Pairwise Comparisons (ITT)

Comparison	p_value
10 mg OCA vs. Placebo	<.0001
25 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 model was applied for testing of multiple treatment groups.
All tests were performed at a significance level of 5%.
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 (ITT)
Measure type: Arithmetic Mean
Dispersion type: Standard Deviation
Note: One subject in the 50 mg group did not have a Day 85 / ET lab visit. All other subjects at baseline are present.

Statistic	10 mg OCA	25 mg OCA	50 mg OCA	Placebo	Total
N	38	48	40	38	164
Mean (SD)	-28 (27)	-35 (22)	-21 (49)	-0 (35)	-22 (36)

ALT Wilcoxon (Mann-Whitney) Pairwise Comparisons (ITT)

Comparison	p_value
10 mg OCA vs. Placebo	<.0001
25 mg OCA vs Placebo	<.0001
50 mg OCA vs Placebo	0.0003

The null hypothesis was that OCA and Placebo are equivalent with respect to ALT percentage change from baseline at Day 85 / ET.
A hierarchical model was applied for testing of multiple treatment groups.
All tests were performed at a significance level of 5%.
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=38) n(%) / Events / Related Events	**25 mg OCA (N=48) n(%) / Events / Related Events**	**50 mg OCA (N=41) n(%) / Events / Related Events**	**Placebo (N=38) n(%) / Events / Related Events**
All Serious TEAEs	0 (0) / 0 / 0	1 (2) / 1 / 0	5 (12) / 6 / 4	1 (3) / 1 / 0
Hepatobiliary disorders	0 (0) / 0 / 0	0 (0) / 0 / 0	2 (5) / 2 / 2	0 (0) / 0 / 0
_____Biliary cirrhosis primary	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (2) / 1 / 1	0 (0) / 0 / 0
_____Jaundice	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (2) / 1 / 1	0 (0) / 0 / 0
Cardiac disorders	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (2) / 1 / 0	0 (0) / 0 / 0
_____Angina pectoris	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (2) / 1 / 0	0 (0) / 0 / 0
Gastrointestinal disorders	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (2) / 1 / 1	0 (0) / 0 / 0
_____Gastrointestinal haemorrhage	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (2) / 1 / 1	0 (0) / 0 / 0
General disorders and administration site conditions	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (2) / 1 / 1	0 (0) / 0 / 0
_____Chest pain	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (2) / 1 / 1	0 (0) / 0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0) / 0 / 0	1 (2) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
_____Salivary gland neoplasm	0 (0) / 0 / 0	1 (2) / 1 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
Respiratory, thoracic and mediastinal disorders	0 (0) / 0 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (3) / 1 / 0
_____Dyspnoea	0 (0) / 0 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (3) / 1 / 0
Skin and subcutaneous tissue disorders	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (2) / 1 / 0	0 (0) / 0 / 0
_____Angioedema	0 (0) / 0 / 0	0 (0) / 0 / 0	1 (2) / 1 / 0	0 (0) / 0 / 0

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

	10 mg OCA (N=38) n(%) / Events / Related Events	**25 mg OCA (N=48) n(%) / Events / Related Events**	**50 mg OCA (N=41) n(%) / Events / Related Events**	**Placebo (N=38) n(%) / Events / Related Events**
All Common Non-Serious TEAEs	30 (79) / 66 / 42	45 (94) / 94 / 72	38 (93) / 113 / 93	31 (82) / 61 / 37
Skin and subcutaneous tissue disorders	18 (47) / 23 / 23	41 (85) / 52 / 50	33 (80) / 60 / 58	19 (50) / 21 / 19
_____Pruritus	18 (47) / 23 / 23	41 (85) / 52 / 50	33 (80) / 60 / 58	19 (50) / 21 / 19
Gastrointestinal disorders	13 (34) / 15 / 9	13 (27) / 18 / 11	13 (32) / 20 / 15	8 (21) / 10 / 7
_____Constipation	3 (8) / 3 / 2	4 (8) / 4 / 2	3 (7) / 4 / 2	3 (8) / 3 / 1
_____Diarrhoea	3 (8) / 3 / 2	4 (8) / 4 / 2	3 (7) / 4 / 4	3 (8) / 3 / 3
_____Nausea	4 (11) / 4 / 3	3 (6) / 3 / 3	4 (10) / 4 / 3	1 (3) / 1 / 1
_____Abdominal distension	2 (5) / 2 / 1	0 (0) / 0 / 0	4 (10) / 4 / 4	1 (3) / 1 / 0
_____Abdominal pain	1 (3) / 1 / 1	2 (4) / 2 / 2	2 (5) / 2 / 0	2 (5) / 2 / 2
_____Dyspepsia	2 (5) / 2 / 0	2 (4) / 2 / 0	2 (5) / 2 / 2	0 (0) / 0 / 0
_____Vomiting	0 (0) / 0 / 0	3 (6) / 3 / 2	0 (0) / 0 / 0	0 (0) / 0 / 0
General disorders and administration site conditions	8 (21) / 11 / 5	3 (6) / 3 / 3	5 (12) / 7 / 6	5 (13) / 6 / 4
_____Fatigue	7 (18) / 8 / 5	3 (6) / 3 / 3	5 (12) / 7 / 6	5 (13) / 6 / 4
_____Pyrexia	3 (8) / 3 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
Infections and infestations	7 (18) / 7 / 1	2 (4) / 2 / 0	3 (7) / 3 / 0	8 (21) / 9 / 0
_____Sinusitis	1 (3) / 1 / 0	0 (0) / 0 / 0	2 (5) / 2 / 0	2 (5) / 3 / 0
_____Nasopharyngitis	2 (5) / 2 / 0	1 (2) / 1 / 0	0 (0) / 0 / 0	1 (3) / 1 / 0
_____Tooth abscess	2 (5) / 2 / 1	0 (0) / 0 / 0	1 (2) / 1 / 0	0 (0) / 0 / 0
_____Upper respiratory tract infection	0 (0) / 0 / 0	1 (2) / 1 / 0	0 (0) / 0 / 0	2 (5) / 2 / 0
_____Urinary tract infection	0 (0) / 0 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0	3 (8) / 3 / 0
_____Bronchitis	2 (5) / 2 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0
Nervous system disorders	3 (8) / 3 / 1	5 (10) / 7 / 4	7 (17) / 8 / 6	4 (11) / 6 / 5
_____Headache	3 (8) / 3 / 1	5 (10) / 7 / 4	7 (17) / 8 / 6	4 (11) / 6 / 5
Musculoskeletal and connective tissue disorders	3 (8) / 3 / 1	3 (6) / 5 / 0	4 (10) / 4 / 1	3 (8) / 3 / 2
_____Arthralgia	2 (5) / 2 / 0	2 (4) / 3 / 0	0 (0) / 0 / 0	1 (3) / 1 / 1
_____Pain in extremity	0 (0) / 0 / 0	1 (2) / 2 / 0	4 (10) / 4 / 1	0 (0) / 0 / 0
_____Myalgia	1 (3) / 1 / 1	0 (0) / 0 / 0	0 (0) / 0 / 0	2 (5) / 2 / 1

Continuing contents of page 13, which would not fit on a single physical page

	10 mg OCA (N=38) n(%) / Events / Related Events	**25 mg OCA (N=48) n(%) / Events / Related Events**	**50 mg OCA (N=41) n(%) / Events / Related Events**	**Placebo (N=38) n(%) / Events / Related Events**
Respiratory, thoracic and mediastinal disorders	2 (5) / 2 / 0	4 (8) / 4 / 2	4 (10) / 5 / 2	1 (3) / 1 / 0
_____Oropharyngeal pain	2 (5) / 2 / 0	4 (8) / 4 / 2	0 (0) / 0 / 0	1 (3) / 1 / 0
_____Epistaxis	0 (0) / 0 / 0	0 (0) / 0 / 0	4 (10) / 5 / 2	0 (0) / 0 / 0
Eye disorders	0 (0) / 0 / 0	3 (6) / 3 / 2	2 (5) / 2 / 2	1 (3) / 1 / 0
_____Dry eye	0 (0) / 0 / 0	3 (6) / 3 / 2	2 (5) / 2 / 2	1 (3) / 1 / 0
Psychiatric disorders	2 (5) / 2 / 2	0 (0) / 0 / 0	2 (5) / 4 / 3	0 (0) / 0 / 0
_____Insomnia	2 (5) / 2 / 2	0 (0) / 0 / 0	2 (5) / 4 / 3	0 (0) / 0 / 0
Cardiac disorders	0 (0) / 0 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0	2 (5) / 2 / 0
_____Palpitations	0 (0) / 0 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0	2 (5) / 2 / 0
Ear and labyrinth disorders	0 (0) / 0 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0	2 (5) / 2 / 0
_____Vertigo	0 (0) / 0 / 0	0 (0) / 0 / 0	0 (0) / 0 / 0	2 (5) / 2 / 0

More Information: Global Substantial Protocol Amendments

Amendment Number / Date	Description
Version 1/ 08 Aug 2007	Original Protocol
Version 2 (Amendment 1)/ 12 Nov 2007	Collection of additional blood samples for PK analysis
Version 8 (Amendment 7) and Addendum 4/ 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
Version 8 Addendum 6/ 12 Feb 2010	Correction to schedule of procedures