Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Secukinumab

Trial Indication(s)

Ankylosing spondylitis

Protocol Number

CAIN457F2305

Protocol Title

A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the 16 week efficacy and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active Ankylosing Spondylitis

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: October 2011 (Actual)
Study Completion Date: December 2014 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

Multicenter, multinational, randomized, double-blind, parallel-group, efficacy and safety

Centers

81 centers in 14 countries: United States(10), Taiwan(2), Turkey(7), Russia(6), Peru(7), Netherlands(2), Mexico(4), Italy(8), United Kingdom(5), France(4), Germany(13), Canada(4), Bulgaria(5), Belgium(4)

Objectives:

The primary objective was to demonstrate that the efficacy of at least one dose of secukinumab at Week 16 is superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS 20 (Assessment of Spondyloarthritis International Society) response.

The secondary objectives were to demonstrate that the efficacy of at least one dose of secukinumab at Week 16 was superior to placebo in patients with active AS based on the following endpoints:

- the proportion of patients achieving an ASAS 40 response
- the change from baseline in high-sensitivity C-reactive protein (hsCRP)
- the proportion of patients achieving an ASAS 5/6 response
- the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- the change from baseline in SF-36 physical component summary (PCS)
- the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL)
- the proportion of patients achieving an ASAS partial remission

Another secondary objective was to evaluate the overall safety and tolerability of secukinumab compared to placebo as assessed by vital signs, clinical laboratory values, and adverse events monitoring.

Test Product (s), Dose(s), and Mode(s) of Administration

Secukinumab 150 mg Powder for Solution for sc injection or iv infusion was provided in glass vials each containing 150 mg secukinumab as lyophilized cake and labeled as AIN457 150 mg. The vials contained a 20% overfill to allow a complete withdrawal of the labeled amount of secukinumab. The 150 mg Powder for Solution was used to prepare both the 75 mg and the 150 mg dose.

Statistical Methods

Statistical analyses of efficacy variables were performed on an intent-to-treat basis, involving all randomized patients who were assigned to study treatment (Full Analysis Set). Baseline characteristics were analyzed for all randomized patients. Safety analyses were performed for all patients who received at least one dose of study treatment (Safety Set).

A sequentially rejective testing strategy was used to evaluate the study hypotheses for the primary and secondary variables while retaining a family-wise type I error of 5%, adjusting for multiplicity across the doses and endpoints. The primary efficacy variable was the response to treatment according to the ASAS 20 criteria at Week 16, defined as an improvement of ≥20% and ≥1 unit on a scale of 10 in at least three of the four main domains and no worsening of ≥20% and ≥1 unit on a scale of 10 in the remaining domain. The testing strategy and the statistical models for ASAS 20 and for all secondary efficacy endpoints at Week 16 were described earlier in the Week 52 CAIN457F2305 CSR.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:
-Male or non-pregnant, non-lactating female patients at least 18 years of age
-Diagnosis of moderate to severe AS with prior documented radiologic evidence (X-ray) fulfilling the Modified New York criteria for AS (1984)
-Patients should have been on NSAIDs with an inadequate response
-Patients who are regularly taking NSAIDs as part of their AS therapy are required to be on a stable dose
-Patients who have been on an anti-TNFα agent (not more than one) must have experienced an inadequate response

Exclusion criteria:
-Chest X-ray with evidence of ongoing infectious or malignant process
-Patients with total ankylosis of the spine
-Patients previously treated with any biological immunomodulating agents except for those targeting TNFα
-Previous treatment with any cell-depleting therapies

Participant Flow Table

Overall Study

	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo
Started	124	125	122
Completed	103	97	90
Not Completed	21	28	32
Death	1	0	1
Withdrawal by Subject	9	5	10
Technical issues	0	1	0
Pregnancy	0	1	0
Physician Decision	1	0	0
Non Compliance with Study Treatment	0	1	1
Lost to Follow-up	1	1	3
Lack of Efficacy	3	8	6
Adverse Event	6	11	11

Baseline Characteristics

	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo	Total
Number of Participants [units: participants]	124	125	122	371
Age Categorical (units: participants)				
<=18 years	0	0	0	0
Between 18 and 65 years	117	122	115	354
>=65 years	7	3	7	17
Gender, Male/Female (units: participants)				
Female	36	41	37	114
Male	88	84	85	257

Summary of Efficacy

Primary Outcome Result(s)

Assessment of SpondyloArthritis International Society / ASAS 20 response

Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo

Number of Participants Analyzed [units: participants]	124	125	122
Assessment of SpondyloArthritis International Society / ASAS 20 response (units: % responders)	59.7	60.8	28.7

Secondary Outcome Result(s)

ASAS 40 response

	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo
Number of Participants Analyzed [units: participants]	124	125	122
ASAS 40 response (units: % responders)	33.1	41.6	13.1

Serum hsCRP

	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo
Number of Participants Analyzed [units:	124	125	122

participants]			
Serum hsCRP (units: ratio) Least Squares Mean ± Standard Error	0.45 ± 1.092	0.4 ± 1.090	0.97 ± 1.095

ASAS 5/6 response

	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo
Number of Participants Analyzed [units: participants]	124	125	122
ASAS 5/6 response (units: % change from baseline)	45.2	48.8	13.1

Bath Ankylosing Spondylitis Disease Activity Index / BASDAI

	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo
Number of Participants Analyzed [units: participants]	124	125	122
Bath Ankylosing Spondylitis Disease Activity Index / BASDAI (units: units on scale)	-2.34	-2.32	-0.59

Physical function component of the short-form health survey / SF-36 PCS

	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo
Number of Participants Analyzed [units: participants]	124	125	122
Physical function component of the short-form health survey / SF-36 PCS (units: units on a scale)	5.64	5.57	0.96

Ankylosing Spondylitis Quality of Life questionnaire / ASQoL

	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo
Number of Participants Analyzed [units: participants]	124	125	122
Ankylosing Spondylitis Quality of Life questionnaire / ASQoL (units: units on a scale)	-3.61	-3.58	-1.04

ASAS partial remission

	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo
Number of Participants Analyzed [units: participants]	124	125	122
ASAS partial remission	16.1	15.2	3.3

(units: % responders)

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

Time Frame	Baseline to week 104
Additional Description	Patients initially randomized to placebo were assessed for ASAS 20 response at Week 16 and switched to active treatment at Week 16 (for placebo non-responders) or at Week 24 (for placebo responders). Blinding was maintained beyond the primary endpoint to ensure reliable efficacy and safety measures.
Source Vocabulary for Table Default	MedDRA
Assessment Type for Table Default	Systematic Assessment

	Any AIN457 75 mg N = 179	Any AIN457 150 mg N = 181	Placebo N = 122
Total participants affected	24 (13.41%)	22 (12.15%)	5 (4.10%)
Blood and lymphatic system disorders			
Abdominal lymphadenopathy	1 (0.56%)	0 (0.00%)	0 (0.00%)
Anaemia	0 (0.00%)	0 (0.00%)	1 (0.82%)
Pancytopenia	1 (0.56%)	0 (0.00%)	0 (0.00%)
Cardiac disorders			
Cardiac failure	1 (0.56%)	0 (0.00%)	0 (0.00%)
Coronary artery stenosis	1 (0.56%)	0 (0.00%)	0 (0.00%)
Myocardial infarction	2 (1.12%)	2 (1.10%)	0 (0.00%)

Ear and labyrinth disorders			
Sudden hearing loss	1 (0.56%)	0 (0.00%)	0 (0.00%)
Vertigo	0 (0.00%)	0 (0.00%)	1 (0.82%)
Endocrine disorders			
Hyperparathyroidism	1 (0.56%)	0 (0.00%)	0 (0.00%)
Eye disorders			
Cataract	1 (0.56%)	1 (0.55%)	0 (0.00%)
Uveitis	0 (0.00%)	1 (0.55%)	0 (0.00%)
Gastrointestinal disorders			
Colitis	1 (0.56%)	0 (0.00%)	0 (0.00%)
Diarrhoea	1 (0.56%)	0 (0.00%)	0 (0.00%)
Epigastric discomfort	1 (0.56%)	0 (0.00%)	0 (0.00%)
Gastritis	0 (0.00%)	1 (0.55%)	0 (0.00%)
Gastrooesophageal reflux disease	0 (0.00%)	1 (0.55%)	0 (0.00%)
Hiatus hernia	1 (0.56%)	0 (0.00%)	0 (0.00%)
Lumbar hernia	1 (0.56%)	0 (0.00%)	0 (0.00%)
Pancreatitis	0 (0.00%)	1 (0.55%)	0 (0.00%)
Pancreatitis acute	0 (0.00%)	1 (0.55%)	0 (0.00%)
Small intestinal obstruction	0 (0.00%)	1 (0.55%)	0 (0.00%)
General disorders and administration site conditions			
Adverse drug reaction	0 (0.00%)	0 (0.00%)	1 (0.82%)

Application site pain	1 (0.56%)	0 (0.00%)	0 (0.00%)
Chest discomfort	1 (0.56%)	0 (0.00%)	0 (0.00%)
Pyrexia	1 (0.56%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders			
Cholelithiasis	2 (1.12%)	0 (0.00%)	0 (0.00%)
Hepatitis toxic	0 (0.00%)	1 (0.55%)	0 (0.00%)
Hepatosplenomegaly	1 (0.56%)	0 (0.00%)	0 (0.00%)
Infections and infestations			
Appendicitis	1 (0.56%)	0 (0.00%)	0 (0.00%)
Helicobacter gastritis	1 (0.56%)	0 (0.00%)	0 (0.00%)
Pneumonia	1 (0.56%)	0 (0.00%)	0 (0.00%)
Pyelonephritis acute	0 (0.00%)	1 (0.55%)	0 (0.00%)
Tonsillitis	0 (0.00%)	2 (1.10%)	0 (0.00%)
Injury, poisoning and procedural complications			
Cartilage injury	1 (0.56%)	0 (0.00%)	0 (0.00%)
Cervical vertebral fracture	1 (0.56%)	0 (0.00%)	0 (0.00%)
Craniocerebral injury	1 (0.56%)	0 (0.00%)	0 (0.00%)
Dislocation of vertebra	1 (0.56%)	0 (0.00%)	0 (0.00%)
Injury	0 (0.00%)	1 (0.55%)	0 (0.00%)
Laceration	1 (0.56%)	0 (0.00%)	0 (0.00%)
Lower limb fracture	0 (0.00%)	1 (0.55%)	0 (0.00%)
Postoperative thrombosis	0 (0.00%)	1 (0.55%)	0 (0.00%)

Rib fracture	0 (0.00%)	2 (1.10%)	0 (0.00%)
Spinal fracture	0 (0.00%)	1 (0.55%)	0 (0.00%)
Thoracic vertebral fracture	1 (0.56%)	0 (0.00%)	0 (0.00%)
Tibia fracture	0 (0.00%)	1 (0.55%)	0 (0.00%)
Upper limb fracture	1 (0.56%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders			
Ankylosing spondylitis	0 (0.00%)	3 (1.66%)	0 (0.00%)
Back pain	0 (0.00%)	1 (0.55%)	0 (0.00%)
Rotator cuff syndrome	1 (0.56%)	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma	1 (0.56%)	0 (0.00%)	0 (0.00%)
Bladder transitional cell carcinoma	0 (0.00%)	1 (0.55%)	0 (0.00%)
Breast cancer	0 (0.00%)	1 (0.55%)	0 (0.00%)
Lymphoma	0 (0.00%)	0 (0.00%)	1 (0.82%)
Nervous system disorders			
Brain oedema	1 (0.56%)	0 (0.00%)	0 (0.00%)
Cerebrovascular accident	0 (0.00%)	1 (0.55%)	0 (0.00%)
Generalised tonic-clonic seizure	0 (0.00%)	1 (0.55%)	0 (0.00%)
Hemiparesis	0 (0.00%)	1 (0.55%)	0 (0.00%)
Peripheral sensory	0 (0.00%)	1 (0.55%)	0 (0.00%)

neuropathy			
Subarachnoid haemorrhage	1 (0.56%)	0 (0.00%)	0 (0.00%)
Trigeminal neuralgia	1 (0.56%)	0 (0.00%)	0 (0.00%)
Vocal cord paresis	0 (0.00%)	0 (0.00%)	1 (0.82%)
Pregnancy, puerperium and perinatal conditions			
Abortion incomplete	0 (0.00%)	1 (0.55%)	0 (0.00%)
Psychiatric disorders			
Completed suicide	0 (0.00%)	0 (0.00%)	1 (0.82%)
Depression	0 (0.00%)	0 (0.00%)	1 (0.82%)
Renal and urinary disorders			
Renal colic	0 (0.00%)	1 (0.55%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	1 (0.56%)	0 (0.00%)	0 (0.00%)
Asthma	1 (0.56%)	0 (0.00%)	0 (0.00%)
Chronic obstructive pulmonary disease	1 (0.56%)	0 (0.00%)	0 (0.00%)
Dyspnoea	1 (0.56%)	0 (0.00%)	0 (0.00%)
Nasal septum deviation	1 (0.56%)	0 (0.00%)	0 (0.00%)
Pulmonary fibrosis	1 (0.56%)	0 (0.00%)	0 (0.00%)
Respiratory failure	1 (0.56%)	1 (0.55%)	0 (0.00%)
Vascular disorders			
Peripheral venous disease	1 (0.56%)	0 (0.00%)	0 (0.00%)

Varicose vein	0 (0.00%)	1 (0.55%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Baseline to week 104
Additional Description	Patients initially randomized to placebo were assessed for ASAS 20 response at Week 16 and switched to active treatment at Week 16 (for placebo non-responders) or at Week 24 (for placebo responders). Blinding was maintained beyond the primary endpoint to ensure reliable efficacy and safety measures.
Source Vocabulary for Table Default	MedDRA
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	2%

	Any AIN457 75 mg N = 179	**Any AIN457 150 mg N = 181**	**Placebo N = 122**
Total participants affected	125 (69.83%)	142 (78.45%)	56 (45.90%)
Blood and lymphatic system disorders			
Anaemia	4 (2.23%)	4 (2.21%)	0 (0.00%)
Leukopenia	12 (6.70%)	8 (4.42%)	1 (0.82%)
Lymphadenopathy	6 (3.35%)	3 (1.66%)	0 (0.00%)
Neutropenia	5 (2.79%)	3 (1.66%)	0 (0.00%)
Eye disorders			

Uveitis	4 (2.23%)	7 (3.87%)	2 (1.64%)
Gastrointestinal disorders			
Abdominal pain	3 (1.68%)	9 (4.97%)	0 (0.00%)
Abdominal pain upper	9 (5.03%)	8 (4.42%)	0 (0.00%)
Constipation	4 (2.23%)	4 (2.21%)	2 (1.64%)
Crohn's disease	4 (2.23%)	1 (0.55%)	0 (0.00%)
Diarrhoea	22 (12.29%)	25 (13.81%)	7 (5.74%)
Mouth ulceration	9 (5.03%)	7 (3.87%)	3 (2.46%)
Nausea	9 (5.03%)	10 (5.52%)	2 (1.64%)
Tongue ulceration	1 (0.56%)	4 (2.21%)	0 (0.00%)
General disorders and administration site conditions			
Fatigue	6 (3.35%)	5 (2.76%)	2 (1.64%)
Non-cardiac chest pain	0 (0.00%)	4 (2.21%)	0 (0.00%)
Pyrexia	0 (0.00%)	5 (2.76%)	2 (1.64%)
Infections and infestations			
Acute tonsillitis	5 (2.79%)	3 (1.66%)	0 (0.00%)
Bronchitis	2 (1.12%)	10 (5.52%)	2 (1.64%)
Gastroenteritis	7 (3.91%)	7 (3.87%)	1 (0.82%)
Infection parasitic	4 (2.23%)	1 (0.55%)	0 (0.00%)
Influenza	13 (7.26%)	17 (9.39%)	2 (1.64%)
Nasopharyngitis	35 (19.55%)	44 (24.31%)	9 (7.38%)
Oral herpes	2 (1.12%)	8 (4.42%)	0 (0.00%)
Pharyngitis	12 (6.70%)	21 (11.60%)	1 (0.82%)
Rhinitis	5 (2.79%)	12 (6.63%)	0 (0.00%)

Sinusitis	4 (2.23%)	7 (3.87%)	3 (2.46%)
Tonsillitis	0 (0.00%)	5 (2.76%)	0 (0.00%)
Upper respiratory tract infection	21 (11.73%)	17 (9.39%)	2 (1.64%)
Urinary tract infection	3 (1.68%)	9 (4.97%)	0 (0.00%)
Injury, poisoning and procedural complications			
Fall	5 (2.79%)	4 (2.21%)	0 (0.00%)
Laceration	4 (2.23%)	1 (0.55%)	1 (0.82%)
Wound	4 (2.23%)	6 (3.31%)	0 (0.00%)
Investigations			
Alanine aminotransferase increased	3 (1.68%)	6 (3.31%)	1 (0.82%)
Aspartate aminotransferase increased	1 (0.56%)	4 (2.21%)	1 (0.82%)
Low density lipoprotein increased	1 (0.56%)	5 (2.76%)	1 (0.82%)
Osteoprotegerin decreased	2 (1.12%)	6 (3.31%)	2 (1.64%)
Metabolism and nutrition disorders			
Dyslipidaemia	16 (8.94%)	14 (7.73%)	6 (4.92%)
Hypercholesterolaemia	3 (1.68%)	5 (2.76%)	2 (1.64%)
Hyperglycaemia	0 (0.00%)	4 (2.21%)	1 (0.82%)
Hyperlipidaemia	3 (1.68%)	2 (1.10%)	3 (2.46%)
Musculoskeletal and connective tissue			

disorders			
Ankylosing spondylitis	4 (2.23%)	7 (3.87%)	4 (3.28%)
Arthralgia	11 (6.15%)	13 (7.18%)	4 (3.28%)
Back pain	7 (3.91%)	12 (6.63%)	0 (0.00%)
Muscle contracture	1 (0.56%)	4 (2.21%)	0 (0.00%)
Muscle spasms	3 (1.68%)	4 (2.21%)	0 (0.00%)
Musculoskeletal pain	4 (2.23%)	3 (1.66%)	0 (0.00%)
Neck pain	5 (2.79%)	3 (1.66%)	0 (0.00%)
Osteoporosis	2 (1.12%)	6 (3.31%)	1 (0.82%)
Pain in extremity	6 (3.35%)	5 (2.76%)	2 (1.64%)
Rotator cuff syndrome	4 (2.23%)	1 (0.55%)	0 (0.00%)
Tendonitis	5 (2.79%)	3 (1.66%)	2 (1.64%)
Nervous system disorders			
Dizziness	6 (3.35%)	8 (4.42%)	4 (3.28%)
Headache	20 (11.17%)	22 (12.15%)	7 (5.74%)
Paraesthesia	3 (1.68%)	7 (3.87%)	0 (0.00%)
Psychiatric disorders			
Anxiety	5 (2.79%)	0 (0.00%)	0 (0.00%)
Insomnia	4 (2.23%)	6 (3.31%)	2 (1.64%)
Respiratory, thoracic and mediastinal disorders			
Cough	9 (5.03%)	10 (5.52%)	2 (1.64%)
Dyspnoea	4 (2.23%)	1 (0.55%)	1 (0.82%)
Nasal congestion	4 (2.23%)	2 (1.10%)	1 (0.82%)
Oropharyngeal pain	13 (7.26%)	16 (8.84%)	6 (4.92%)

Rhinorrhoea	4 (2.23%)	3 (1.66%)	0 (0.00%)
Skin and subcutaneous tissue disorders			
Dermatitis	0 (0.00%)	6 (3.31%)	0 (0.00%)
Pruritus	3 (1.68%)	7 (3.87%)	1 (0.82%)
Rash	2 (1.12%)	7 (3.87%)	0 (0.00%)
Urticaria	1 (0.56%)	4 (2.21%)	0 (0.00%)
Vascular disorders			
Hypertension	8 (4.47%)	6 (3.31%)	0 (0.00%)

Other Relevant Findings

Not applicable.

Conclusion:

Secukinumab demonstrated a rapid onset of response and superior efficacy over placebo in the treatment of patients with moderate to severe active ankylosing spondylitis through measures of clinical response, quality of life and markers of inflammation. Both the 150 mg and 75 mg regimens of secukinumab preceded by an intravenous loading regimen of 3 doses of 10 mg/kg gave significantly greater responses than placebo, with respect to the primary endpoint (Assessment of Spondyloarthritis International Society criteria 20) and all secondary endpoints (Assessment of Spondyloarthritis International Society criteria 40, (high sensitivity) C-Reactive Protein, Assessment of Spondyloarthritis International Society criteria 5/6, Bath Ankylosing Spondylitis Disease Activity Index, Medical Outcome Short Form-36 Health Survey, Ankylosing Spondylitis Quality of Life, and Assessment of Spondyloarthritis International Society criteria partial remission) at Week 16.

Secukinumab was efficacious through 104 weeks of treatment in both anti-TNF-α naïve patients and patients who failed prior anti-TNF-α therapy. While the two secukinumab regimens had similar drug exposure and comparable efficacy up to Week 16, patients receiving the 150 mg sc maintenance dose maintained greater response rates in the higher hurdle clinical endpoints, such as Assessment of Spondyloarthritis International Society criteria 40, Assessment of Spondyloarthritis International Society criteria partial remission, Bath Ankylosing Spondylitis Disease Activity

Index 50, and Ankylosing Spondylitis Disease Activity Score-CRP/Erythrocyte Sedimentation Rate inactive disease, compared with patients receiving the 75 mg sc maintenance dose. Secukinumab also demonstrated no structural progression in approximately 80% of patients over 2 years, along with a reduction of inflammatory lesions on Magnetic Resonance Imaging and preservation of hip and femoral neck Bone Mineral Density.

The safety profile of secukinumab at both doses in this study showed no new or unexpected safety signals based on a cumulative exposure of 622.5 patient-years. Infections were more frequent with secukinumab compared to placebo and showed dose dependence in non-serious infections, with the majority consisting of upper respiratory tract infections. Serious infections were rare in both secukinumab dose groups.

Date of Clinical Trial Report

2-Oct-2015