ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 12/12/2014

ClinicalTrials.gov ID: NCT02013206

Study Identification

Unique Protocol ID:	MO18660
Brief Title:	A Study of Tarceva (Erlotinib) in Patients With Advanced Non-Small Cell Lung Cancer Naive to Chemotherapy
Official Title:	An Parallel Phase II Study of Tarceva (Erlotinib) in Patients With Advanced Non-small Cell Lung Cancer (Stage IIIB/IV) Not Pre-treated by Chemotherapy Including Dose Escalation to Toxicity in Current and Former Smokers
Secondary IDs:	

Study Status

Record Verification:	December 2014
Overall Status:	Completed
Study Start:	September 2006
Primary Completion:	October 2010 [Actual]
Study Completion:	October 2010 [Actual]

Sponsor/Collaborators

Sponsor:	Hoffmann-La Roche
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? No

	Delayed Posting?
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 14-Jun-2005 Board Name: Ethikkommission der Medizinischen Universität Wien Board Affiliation: Allgemeinen Krankenhauses der Stadt Wien AKH Phone: 43 1 40400-2147 Email: ethik-kom@meduniwien.ac.at
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	Austria: Austrian Federal Office for Safety in Health Care, BASG - AGES.

Study Description

Brief Summary:	This study will evaluate the efficacy and safety of Tarceva in two groups of patients with non-small cell lung cancer who have not been pre-treated with chemotherapy. One group, consisting of patients who have never smoked, will receive Tarceva 150 mg/day, and the other group, consisting of current/former smokers, will receive Tarceva 150 mg/day increasing to a maximum of 300 mg/day. The anticipated time on study treatment is 1-2 years.
Detailed Description:	

Conditions

Conditions:	Non-Small Cell Lung Cancer
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Parallel Assignment
Number of Arms:	2
Masking:	Open Label
Allocation:	Non-Randomized
Endpoint Classification:	Safety/Efficacy Study

Enrollment: 52 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Never Smokers Never Smokers (participants who smoked ≤ 100 cigarettes in entire lifetime or had never smoked cigarettes) received erlotinib [Tarceva] 150 mg orally daily until disease progression or unacceptable toxicity.	Drug: erlotinib [Tarceva] Erlotinib tablets taken orally once daily in the morning. Other Names: • Tarceva
Experimental: Current/Former Smokers Current Smokers (participants who smoked > 100 cigarettes in entire lifetime and either quit smoking < 1 year ago or were currently smoking) or Former Smokers (participants who smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 year ago) received erlotinib [Tarceva] 150 mg orally daily, increasing to a maximum of 300 mg orally daily until disease progression or unacceptable toxicity.	Drug: erlotinib [Tarceva] Erlotinib tablets taken orally once daily in the morning. Other Names: • Tarceva

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- adult patients, >=18 years of age;
- histologically documented advanced non-small cell lung cancer (stage IIIB/IV);
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2;
- no previous chemotherapy.

Exclusion Criteria:

- previous therapy which acts on Epidermal Growth Factor Receptor (EGFR) axis;
- clinical evidence of brain metastasis;
- any unstable systemic disease;
- unable to take oral medication;

- any significant ophthalmological abnormality.

Contacts/Locations

Study Officials: Clinical Trials
Study Chair
Hoffmann-La Roche

Locations: Italy
Milano, Italy, 20162

Rozzano, Italy, 20089

Spain
Barcelona, Spain, 08035

France
Marseille, France, 13274

Netherlands
Maastricht, Netherlands, 6229 HX

Germany
Hamburg, Germany, 22045

Spain
Madrid, Spain, 28041

United Kingdom
Manchester, United Kingdom, M2O 4BX

France
Villejuif, France, 94805

Spain
Barcelona, Spain, 08907

Netherlands
Amsterdam, Netherlands, 1105 AZ

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
Current/Former Smokers	Current Smokers (participants who smoked > 100 cigarettes in entire lifetime and either quit smoking < 1 year ago or were currently smoking) or Former Smokers (participants who smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 year ago) received erlotinib [Tarceva] 150 mg orally daily, increasing to a maximum of 300 mg orally daily until disease progression or unacceptable toxicity.
Never Smokers	Never Smokers (participants who smoked ≤ 100 cigarettes in entire lifetime or had never smoked cigarettes) received erlotinib [Tarceva] 150 mg orally daily until disease progression or unacceptable toxicity.

Overall Study

	Current/Former Smokers	Never Smokers
Started	29	23
Received Study Drug	26	23
Completed	2 [1]	1
Not Completed	27	22
Progressive disease (PD)	14	17
Symptomatic deterioration	3	1
Adverse Event	1	0
Patient refusal	2	0
Patient non-compliance	1	0
Death	1	2
Other reasons off treatment	5	2

[1] 3 Patients were on-going at clinical cut-off. Not Completed=patients who discontinued treatment.

Baseline Characteristics

Reporting Groups

	Description
Current/Former Smokers	Current Smokers (participants who smoked > 100 cigarettes in entire lifetime and either quit smoking < 1 year ago or were currently smoking) or Former Smokers (participants who smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 year ago) received erlotinib [Tarceva] 150 mg orally daily, increasing to a maximum of 300 mg orally daily until disease progression or unacceptable toxicity.
Never Smokers	Never Smokers (participants who smoked ≤ 100 cigarettes in entire lifetime or had never smoked cigarettes) received erlotinib [Tarceva] 150 mg orally daily until disease progression or unacceptable toxicity.

Baseline Measures

	Current/Former Smokers	Never Smokers	Total
Number of Participants	29	23	52
Age, Continuous [units: years] Mean (Full Range)	64 (38 to 83)	66 (42 to 88)	65 (38 to 88)
Gender, Male/Female [units: participants]			
Female	15	19	34
Male	14	4	18

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Non-Progression Rate (NPR) at 8 Weeks
Measure Description	Non-Progressive Rate (NPR) was defined as the percentage of participants without progression (had stable disease (SD) or better) based on (Response Evaluation Criteria in Solid Tumours (RECIST) criteria 8 weeks after start of treatment. Diagnosis of Progressive Disease (PD) was made by objective criteria (RECIST criteria) on the target lesion(s), or by documenting, with Computerised Tomography/Magnetic Resonance Imaging (CT/MRI) scans, the presence of newly occurring lesion(s) arising outside the scanned areas of the target lesions. PD required at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Time Frame	Week 8
Safety Issue?	No

Analysis Population Description

Intent-to-Treat Population included all registered participants.

Reporting Groups

	Description
Current/Former Smokers	Current Smokers (participants who smoked > 100 cigarettes in entire lifetime and either quit smoking < 1 year ago or were currently smoking) or Former Smokers (participants who smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 year ago) received erlotinib [Tarceva] 150 mg orally daily, increasing to a maximum of 300 mg orally daily until disease progression or unacceptable toxicity.
Never Smokers	Never Smokers (participants who smoked ≤ 100 cigarettes in entire lifetime or had never smoked cigarettes) received erlotinib [Tarceva] 150 mg orally daily until disease progression or unacceptable toxicity.

Measured Values

	Current/Former Smokers	Never Smokers
Number of Participants Analyzed	29	23
Non-Progression Rate (NPR) at 8 Weeks [units: percentage of participants] Number (95% Confidence Interval)	41.4 (23.5 to 61.1)	65.2 (42.7 to 83.6)

2. Secondary Outcome Measure:

Measure Title	Objective Response Rate
Measure Description	Objective response rate was defined as the percentage of participants with Complete Response (CR) or Partial Response (PR) by Response Evaluation Criteria in Solid Tumours (RECIST). The best overall response was the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment depended on the achievement of both measurement and confirmation criteria. To be assigned the status of PR or CR, changes in tumour measurements were to be confirmed by repeated assessments no less than 4 weeks after the criteria for response were first met. CR was defined as the disappearance of all target lesions; for non-target lesions disappearance of lesions and normal tumour marker levels. PR was defined as at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, using as reference the Baseline sum LD.
Time Frame	Up to 2 years
Safety Issue?	No

Analysis Population Description

Intent-to-Treat Population included all registered participants.

Reporting Groups

	Description
Current/Former Smokers	Current Smokers (participants who smoked > 100 cigarettes in entire lifetime and either quit smoking < 1 year ago or were currently smoking) or Former Smokers (participants who smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 year ago) received erlotinib [Tarceva] 150 mg orally daily, increasing to a maximum of 300 mg orally daily until disease progression or unacceptable toxicity.
Never Smokers	Never Smokers (participants who smoked ≤ 100 cigarettes in entire lifetime or had never smoked cigarettes) received erlotinib [Tarceva] 150 mg orally daily until disease progression or unacceptable toxicity.

Measured Values

	Current/Former Smokers	Never Smokers
Number of Participants Analyzed	29	23
Objective Response Rate [units: percentage of participants] Number (95% Confidence Interval)	17 (5.9 to 35.8)	35 (16.4 to 57.3)

3. Secondary Outcome Measure:

Measure Title	Disease Control Rate
Measure Description	Disease Control Rate was defined as the percentage of participants with Complete Response (CR), Partial Response (PR) or Stable Disease (SD) by Response Evaluation Criteria in Solid Tumours (RECIST). CR was defined as the disappearance of all target lesions; for non-target lesions disappearance of lesions and normal tumour marker levels. PR was defined as at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, using as reference the Baseline sum LD. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started; for non-target lesions persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Time Frame	Up to 2 years
Safety Issue?	No

Analysis Population Description

Intent-to-Treat Population included all registered participants.

Reporting Groups

	Description
Current/Former Smokers	Current Smokers (participants who smoked > 100 cigarettes in entire lifetime and either quit smoking < 1 year ago or were currently smoking) or Former Smokers (participants who smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 year ago) received erlotinib [Tarceva] 150 mg orally daily, increasing to a maximum of 300 mg orally daily until disease progression or unacceptable toxicity.
Never Smokers	Never Smokers (participants who smoked ≤ 100 cigarettes in entire lifetime or had never smoked cigarettes) received erlotinib [Tarceva] 150 mg orally daily until disease progression or unacceptable toxicity.

Measured Values

	Current/Former Smokers	Never Smokers
Number of Participants Analyzed	29	23
Disease Control Rate [units: percentage of participants] Number (95% Confidence Interval)	41 (23.5 to 61.1)	65 (42.7 to 83.6)

4. Secondary Outcome Measure:

Measure Title	Duration of Response
Measure Description	Duration of overall response was defined as the time in months from Complete Response (CR) or Partial Response (PR) by Response Evaluation Criteria in Solid Tumours (RECIST) until the first date Progressive Disease (PD) was objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started) or until the date of death. CR was defined as the disappearance of all target lesions; for non-target lesions disappearance of lesions and normal tumour marker levels.PR was defined as at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, using as reference the Baseline sum LD. PD was defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Time Frame	Up to 2 years
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-Treat (ITT) Population, that included all participants, with CR or PR. Patients still responding to treatment at the time of analysis were treated as censored observations for duration of response on the date of the last tumour assessment.

Reporting Groups

	Description
Current/Former Smokers	Current Smokers (participants who smoked > 100 cigarettes in entire lifetime and either quit smoking < 1 year ago or were currently smoking) or Former Smokers (participants who smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 year ago) received erlotinib [Tarceva] 150 mg orally daily, increasing to a maximum of 300 mg orally daily until disease progression or unacceptable toxicity.
Never Smokers	Never Smokers (participants who smoked ≤ 100 cigarettes in entire lifetime or had never smoked cigarettes) received erlotinib [Tarceva] 150 mg orally daily until disease progression or unacceptable toxicity.

Measured Values

	Current/Former Smokers	Never Smokers
Number of Participants Analyzed	5	8
Duration of Response [units: months] Median (95% Confidence Interval)	13.1 (4.6 to 13.1)	5.7 (4.0 to NA) [1]

[1] 95% Confidence Interval Upper limit was not estimated due to the small number of participants.

5. Secondary Outcome Measure:

Measure Title	Time to Progression
Measure Description	Time to progression was defined as the time from start of treatment until the first date criteria for Progressive Disease (PD) was met (taking as reference the smallest measurements recorded since the treatment started). Diagnosis of PD was made by objective criteria (RECIST criteria) on the target lesion(s), or by documenting, with Computerised Tomography/Magnetic Resonance Imaging (CT/MRI) scans, the presence of newly occurring lesion(s) arising outside the scanned areas of the target lesions. PD required at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Time Frame	Up to 2 years
Safety Issue?	No

Analysis Population Description

Safety Population included all registered patients who received at least 1 dose of study treatment and had at least 1 safety follow-up. Patients without PD at the time of analysis were censored on the date of the last tumour assessment. Patients without PD who received a second anti-cancer therapy were censored prior to start of new therapy.

Reporting Groups

	Description
Current/Former Smokers	Current Smokers (participants who smoked > 100 cigarettes in entire lifetime and either quit smoking < 1 year ago or were currently smoking) or Former Smokers (participants who smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 year ago) received erlotinib [Tarceva] 150 mg orally daily, increasing to a maximum of 300 mg orally daily until disease progression or unacceptable toxicity.
Never Smokers	Never Smokers (participants who smoked ≤ 100 cigarettes in entire lifetime or had never smoked cigarettes) received erlotinib [Tarceva] 150 mg orally daily until disease progression or unacceptable toxicity.

Measured Values

	Current/Former Smokers	Never Smokers
Number of Participants Analyzed	26	23
Time to Progression [units: months] Median (95% Confidence Interval)	1.9 (1.0 to 5.6)	5.5 (3.4 to 7.3)

6. Secondary Outcome Measure:

Measure Title	Progression-Free Survival
Measure Description	Progression-Free Survival (PFS) was defined as the time in months from the start of treatment until the first date criteria for Progressive Disease (PD) were met (taking as reference the smallest measurements recorded since the treatment started), or the date of death for any reason in the absence of PD. Diagnosis of PD was made by objective criteria (RECIST criteria) on the target lesion(s), or by documenting, with Computerised Tomography/Magnetic Resonance Imaging (CT/MRI) scans, the presence of newly occurring lesion(s) arising outside the scanned areas of the target lesions.
Time Frame	Up to 2 years
Safety Issue?	No

Analysis Population Description

Safety Population included all registered participants who received at least one study treatment and had at least one safety follow-up. Patients without PD at the time of analysis were censored on the date of the last tumour assessment. Patients without PD who received a second anti-cancer therapy were censored prior to start of new therapy.

Reporting Groups

	Description
Current/Former Smokers	Current Smokers (participants who smoked > 100 cigarettes in entire lifetime and either quit smoking < 1 year ago or were currently smoking) or Former Smokers (participants who smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 year ago) received erlotinib [Tarceva] 150 mg orally daily, increasing to a maximum of 300 mg orally daily until disease progression or unacceptable toxicity.
Never Smokers	Never Smokers (participants who smoked ≤ 100 cigarettes in entire lifetime or had never smoked cigarettes) received erlotinib [Tarceva] 150 mg orally daily until disease progression or unacceptable toxicity.

Measured Values

	Current/Former Smokers	Never Smokers
Number of Participants Analyzed	26	23
Progression-Free Survival [units: months] Median (95% Confidence Interval)	1.9 (1.0 to 5.6)	4.1 (3.4 to 5.7)

7. Secondary Outcome Measure:

Measure Title	Overall Survival
Measure Description	Overall survival was defined as the time in months from the start of treatment to the date of death irrespective of the cause of death.
Time Frame	Up to 2 years
Safety Issue?	No

Analysis Population Description

Safety Population included all participants with at least one study treatment and had at least one safety follow-up. Patients who had not died at the time of the final analysis were censored at the date of last contact.

Reporting Groups

	Description
Current/Former Smokers	Current Smokers (participants who smoked > 100 cigarettes in entire lifetime and either quit smoking < 1 year ago or were currently smoking) or Former Smokers (participants who smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 year ago) received erlotinib [Tarceva] 150 mg orally daily, increasing to a maximum of 300 mg orally daily until disease progression or unacceptable toxicity.
Never Smokers	Never Smokers (participants who smoked ≤ 100 cigarettes in entire lifetime or had never smoked cigarettes) received erlotinib [Tarceva] 150 mg orally daily until disease progression or unacceptable toxicity.

Measured Values

	Current/Former Smokers	Never Smokers
Number of Participants Analyzed	26	23
Overall Survival [units: months] Median (95% Confidence Interval)	9.9 (5.6 to 14.0)	13.9 (8.9 to 18.0)

8. Secondary Outcome Measure:

Measure Title	Safety: Number of Participants With Adverse Events (AE) and Serious Adverse Events (SAE)
Measure Description	An AE was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study and laboratory or clinical tests that resulted in a change in treatment or discontinuation from study drug were reported as adverse events. A SAE was any experience that: resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect or was medically significant.
Time Frame	Up to 2 years
Safety Issue?	No

Analysis Population Description

Safety Population included all registered participant who received at least one study treatment and had at least one safety follow-up.

Reporting Groups

	Description
Current/Former Smokers	Current Smokers (participants who smoked > 100 cigarettes in entire lifetime and either quit smoking < 1 year ago or were currently smoking) or Former Smokers (participants who smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 year ago) received erlotinib [Tarceva] 150 mg orally daily, increasing to a maximum of 300 mg orally daily until disease progression or unacceptable toxicity.
Never Smokers	Never Smokers (participants who smoked ≤ 100 cigarettes in entire lifetime or had never smoked cigarettes) received erlotinib [Tarceva] 150 mg orally daily until disease progression or unacceptable toxicity.

Measured Values

	Current/Former Smokers	Never Smokers
Number of Participants Analyzed	26	23
Safety: Number of Participants With Adverse Events (AE) and Serious Adverse Events (SAE)		

	Current/Former Smokers	Never Smokers
[units: participants]		
Adverse Events	26	23
Serious Adverse Events	14	7

Reported Adverse Events

Time Frame	Up to 2 Years
Additional Description	[Not specified]

Reporting Groups

	Description
Current/Former Smokers	Current Smokers (participants who smoked > 100 cigarettes in entire lifetime and either quit smoking < 1 year ago or were currently smoking) or Former Smokers (participants who smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 year ago) received erlotinib [Tarceva] 150 mg orally daily, increasing to a maximum of 300 mg orally daily until disease progression or unacceptable toxicity.
Never Smokers	Never Smokers (participants who smoked ≤ 100 cigarettes in entire lifetime or had never smoked cigarettes) received erlotinib [Tarceva] 150 mg orally daily until disease progression or unacceptable toxicity.

Serious Adverse Events

	Current/Former Smokers	Never Smokers
	Affected/At Risk (%)	Affected/At Risk (%)
Total	14/26 (53.85%)	7/23 (30.43%)
Blood and lymphatic system disorders		
Neutropenia [A] †	1/26 (3.85%)	0/23 (0%)
Cardiac disorders		
Cardiac arrest [A] †	0/26 (0%)	1/23 (4.35%)
Gastrointestinal disorders		
Abdominal pain [A] †	1/26 (3.85%)	1/23 (4.35%)

	Current/Former Smokers	Never Smokers
	Affected/At Risk (%)	Affected/At Risk (%)
Intestinal obstruction [A] †	1/26 (3.85%)	0/23 (0%)
Vomiting [A] †	1/26 (3.85%)	0/23 (0%)
General disorders		
Oedema peripheral [A] †	1/26 (3.85%)	0/23 (0%)
Performance status decreased [A] †	1/26 (3.85%)	0/23 (0%)
Infections and infestations		
Abscess [A] †	0/26 (0%)	1/23 (4.35%)
Pneumonia [A] †	2/26 (7.69%)	0/23 (0%)
Pseudomonas infection [A] †	1/26 (3.85%)	0/23 (0%)
Urinary tract infection [A] †	0/26 (0%)	1/23 (4.35%)
Injury, poisoning and procedural complications		
Femur fracture [A] †	0/26 (0%)	1/23 (4.35%)
Investigations		
Biopsy muscle [A] †	0/26 (0%)	1/23 (4.35%)
Musculoskeletal and connective tissue disorders		
Back pain [A] †	1/26 (3.85%)	0/23 (0%)
Pain in extremity [A] †	1/26 (3.85%)	0/23 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumour necrosis [A] †	1/26 (3.85%)	0/23 (0%)
Nervous system disorders		
Cerebral ischaemia [A] †	1/26 (3.85%)	0/23 (0%)
Transient ischaemic attack [A] †	1/26 (3.85%)	0/23 (0%)
Renal and urinary disorders		

	Current/Former Smokers	Never Smokers
	Affected/At Risk (%)	Affected/At Risk (%)
Anuria [A] †	1/26 (3.85%)	0/23 (0%)
Reproductive system and breast disorders		
Ovarian disorder [A] †	1/26 (3.85%)	0/23 (0%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea [A] †	2/26 (7.69%)	2/23 (8.7%)
Pulmonary embolism [A] †	0/26 (0%)	2/23 (8.7%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 11.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 4%

	Current/Former Smokers	Never Smokers
	Affected/At Risk (%)	Affected/At Risk (%)
Total	26/26 (100%)	23/23 (100%)
Blood and lymphatic system disorders		
Anaemia [A] †	4/26 (15.38%)	1/23 (4.35%)
Leukopenia [A] †	2/26 (7.69%)	0/23 (0%)
Cardiac disorders		
Tachycardia [A] †	2/26 (7.69%)	2/23 (8.7%)
Congenital, familial and genetic disorders		
Trichomegaly [A] †	0/26 (0%)	2/23 (8.7%)
Ear and labyrinth disorders		
Vertigo [A] †	2/26 (7.69%)	1/23 (4.35%)
Endocrine disorders		
Hypothyroidism [A] †	0/26 (0%)	2/23 (8.7%)
Eye disorders		

	Current/Former Smokers	Never Smokers
	Affected/At Risk (%)	Affected/At Risk (%)
Blepharitis [A] †	1/26 (3.85%)	1/23 (4.35%)
Conjunctivitis [A] †	2/26 (7.69%)	0/23 (0%)
Dry Eye [A] †	2/26 (7.69%)	2/23 (8.7%)
Growth of eyelashes [A] †	2/26 (7.69%)	0/23 (0%)
Gastrointestinal disorders		
Abdominal pain [A] †	6/26 (23.08%)	3/23 (13.04%)
Abdominal pain upper [A] †	3/26 (11.54%)	2/23 (8.7%)
Constipation [A] †	2/26 (7.69%)	3/23 (13.04%)
Diarrhoea [A] †	14/26 (53.85%)	11/23 (47.83%)
Dysphagia [A] †	4/26 (15.38%)	1/23 (4.35%)
Nausea [A] †	10/26 (38.46%)	11/23 (47.83%)
Vomiting [A] †	5/26 (19.23%)	4/23 (17.39%)
General disorders		
Asthenia [A] †	8/26 (30.77%)	8/23 (34.78%)
Chest pain [A] †	5/26 (19.23%)	3/23 (13.04%)
Fatigue [A] †	4/26 (15.38%)	4/23 (17.39%)
Mucosal dryness [A] †	1/26 (3.85%)	1/23 (4.35%)
Mucosal inflammation [A] †	3/26 (11.54%)	3/23 (13.04%)
Oedema [A] †	2/26 (7.69%)	1/23 (4.35%)
Oedema peripheral [A] †	1/26 (3.85%)	2/23 (8.7%)
Pyrexia [A] †	7/26 (26.92%)	3/23 (13.04%)
Xerosis [A] †	2/26 (7.69%)	3/23 (13.04%)

	Current/Former Smokers	Never Smokers
	Affected/At Risk (%)	Affected/At Risk (%)
Hepatobiliary disorders		
Hepatobiliary disorders [A] †	2/26 (7.69%)	0/23 (0%)
Infections and infestations		
Bronchitis [A] †	0/26 (0%)	2/23 (8.7%)
Lower respiratory tract infection [A] †	0/26 (0%)	2/23 (8.7%)
Paronychia [A] †	2/26 (7.69%)	3/23 (13.04%)
Pneumonia [A] †	2/26 (7.69%)	0/23 (0%)
Respiratory tract infection [A] †	2/26 (7.69%)	0/23 (0%)
Subcutaneous abscess [A] †	1/26 (3.85%)	1/23 (4.35%)
Injury, poisoning and procedural complications		
Injury, poisoning and procedural complication [A] †	1/26 (3.85%)	2/23 (8.7%)
Investigations		
Alanine aminotransferase increased [A] †	2/26 (7.69%)	0/23 (0%)
Blood alkaline phosphatase increased [A] †	2/26 (7.69%)	0/23 (0%)
Blood bilirubin increased [A] †	1/26 (3.85%)	1/23 (4.35%)
Weight decreased [A] †	8/26 (30.77%)	7/23 (30.43%)
Metabolism and nutrition disorders		
Anorexia [A] †	8/26 (30.77%)	12/23 (52.17%)
Hypokalaemia [A] †	2/26 (7.69%)	0/23 (0%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	4/26 (15.38%)	4/23 (17.39%)
Back pain [A] †	2/26 (7.69%)	3/23 (13.04%)

	Current/Former Smokers	Never Smokers
	Affected/At Risk (%)	Affected/At Risk (%)
Muscle spasms [A] †	2/26 (7.69%)	1/23 (4.35%)
Muscular weakness [A] †	1/26 (3.85%)	1/23 (4.35%)
Musculoskeletal pain [A] †	1/26 (3.85%)	2/23 (8.7%)
Pain in extremity [A] †	2/26 (7.69%)	2/23 (8.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumour pain [A] †	2/26 (7.69%)	0/23 (0%)
Nervous system disorders		
Dysgeusia [A] †	2/26 (7.69%)	1/23 (4.35%)
Headache [A] †	3/26 (11.54%)	1/23 (4.35%)
Lethargy [A] †	1/26 (3.85%)	1/23 (4.35%)
Psychiatric disorders		
Anxiety [A] †	2/26 (7.69%)	3/23 (13.04%)
Insomnia [A] †	2/26 (7.69%)	0/23 (0%)
Renal and urinary disorders		
Dysuria [A] †	3/26 (11.54%)	0/23 (0%)
Reproductive system and breast disorders		
Reproductive system and breast disorders [A] †	3/26 (11.54%)	3/23 (13.04%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] †	4/26 (15.38%)	7/23 (30.43%)
Dyspnoea [A] †	8/26 (30.77%)	5/23 (21.74%)
Haemoptysis [A] †	2/26 (7.69%)	1/23 (4.35%)
Pharyngolaryngeal pain [A] †	1/26 (3.85%)	1/23 (4.35%)

	Current/Former Smokers	Never Smokers
	Affected/At Risk (%)	Affected/At Risk (%)
Productive cough [A] †	1/26 (3.85%)	1/23 (4.35%)
Pulmonary embolism [A] †	0/26 (0%)	2/23 (8.7%)
Skin and subcutaneous tissue disorders		
Alopecia [A] †	5/26 (19.23%)	8/23 (34.78%)
Dry skin [A] †	6/26 (23.08%)	4/23 (17.39%)
Pruritus [A] †	5/26 (19.23%)	4/23 (17.39%)
Rash [A] †	19/26 (73.08%)	19/23 (82.61%)
Skin exfoliation [A] †	1/26 (3.85%)	1/23 (4.35%)
Skin fissures [A] †	3/26 (11.54%)	1/23 (4.35%)
Skin toxicity [A] †	1/26 (3.85%)	1/23 (4.35%)
Surgical and medical procedures		
Surgical and medical procedures [A] †	0/26 (0%)	2/23 (8.7%)
Vascular disorders		
Hypertension [A] †	2/26 (7.69%)	1/23 (4.35%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 11.0

Limitations and Caveats

Treatment was ongoing for 3 patients at the time of the Clinical Study Report (CSR) cut-off. In the addendum to the CSR, there were no findings for these 3 patients that deviated from those observed in the original report.

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

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