Clinical trial results:
A randomised, double blind phase I/II trial to investigate efficacy, immunogenicity and safety of intradermally administered BI 1361849 (CV9202) plus afatinib versus placebo plus afatinib as first-line treatment for patients with stage IV adenocarcinoma of the lung harbouring common EGFR mutations.

Summary

EudraCT number	2015-001477-41
Trial protocol	ES DE
Global end of trial date	20 June 2016

Results information

Result version number	v1 (current)
This version publication date	06 January 2019
First version publication date	06 January 2019
Summary attachment (see zip file)	Statement (1373.1_Statement_Eudract.pdf)

Trial information

Trial identification

Sponsor protocol code	1373.1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 June 2016
Global end of trial reached?	Yes
Global end of trial date	20 June 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy, immunogenicity and safety of BI 1361849 (CV9202) in combination with afatinib as first-line treatment for patients with metastatic non-small cell lung cancer (NSCLC) (stage IV) harbouring common Epidermal Growth Factor Receptor (EGFR) mutations.

Phase I: To confirm feasibility and safety of the combination of BI 1361849 (CV9202) with afatinib, and to assess immunological responses of BI 1361849 (CV9202) in combination with afatinib in comparison to placebo plus afatinib.

Phase II (analyses will cover all randomised patients, i.e. will also include all patients randomised during the phase I part of the trial): To assess efficacy, immunogenicity and safety of BI 1361849 (CV9202) in combination with afatinib in comparison to placebo plus afatinib.

Protection of trial subjects:

No patient entered the study, therefore no results data available. 99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants entering the trial. 199998 number entered in population of trial subjects is "Not applicable", the number is added to match the count in the participant flow which we get after adding the NA value "99999" for each treatment arm.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 199998
Worldwide total number of subjects	199998
EEA total number of subjects	199998

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	199998
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No patient was entered in the trial.

Pre-assignment

Screening details:

All patients were planned to be screened for eligibility to participate in the trial. Patients had to attend specialist sites which would then ensure that they (the patients) met all inclusion/exclusion criteria. Patients were not to be entered to the trial if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Placebo-controlled, double blind, randomised, parallel design

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 1361849 (CV9202) in combination with afatinib

Arm description:

Patients were to be administered with BI 1361849 (CV9202) 0.32 milligram (mg) via intradermal injection per each of 6 components (i.e. 1.92 mg in total) per vaccination time point on day 1 of weeks 1, 2, 3, 5, 7, 9, 12, 15, 18, 21, 24, and continued thereafter every 6 weeks; 2 injections per component resulting in 12 intradermal injections per vaccination visit distributed over 4 different body sites (upper arms, thighs) with afatinib: 40 mg once daily orally (dose can be reduced to 30 mg and 20 mg daily)

Arm type	Experimental
Investigational medicinal product name	BI 1361849
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Patients were to be administered with BI 1361849 (CV9202) 0.32 milligram (mg) via intradermal injection per each of 6 components (i.e. 1.92 mg in total) per vaccination time point on day 1 of weeks 1, 2, 3, 5, 7, 9, 12, 15, 18, 21, 24, and continued thereafter every 6 weeks; 2 injections per component resulting in 12 intradermal injections per vaccination visit distributed over 4 different body sites (upper arms, thighs)

Investigational medicinal product name	afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to be administered with afatinib 40 mg once daily orally (dose can be reduced to 30 mg and 20 mg daily)

Arm title	Placebo matching BI 1361849 (CV9202) in combination with afati

Arm description:

Patients were to be administered with placebo matching BI 1361849 (CV9202) via intradermal injection per each of 6 components per vaccination time point on day 1 of weeks 1, 2, 3, 5, 7, 9, 12, 15, 18, 21,

24, and continued thereafter every 6 weeks; 2 injections per component resulting in 12 intradermal injections per vaccination visit distributed over 4 different body sites (upper arms, thighs) with afatinib: 40 mg once daily orally (dose can be reduced to 30 mg and 20 mg daily)

Arm type	Placebo
Investigational medicinal product name	Placebo matching BI 1361849
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Patients were to be administered with placebo matching BI 1361849 (CV9202) via intradermal injection per each of 6 components per vaccination time point on day 1 of weeks 1, 2, 3, 5, 7, 9, 12, 15, 18, 21, 24, and continued thereafter every 6 weeks; 2 injections per component resulting in 12 intradermal injections per vaccination visit distributed over 4 different body sites (upper arms, thighs)

Investigational medicinal product name	afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to be administered with afatinib 40 mg once daily orally (dose can be reduced to 30 mg and 20 mg daily)

Number of subjects in period 1	BI 1361849 (CV9202) in combination with afatinib	Placebo matching BI 1361849 (CV9202) in combination with afati
Started	99999	99999
Completed	99999	99999

Baseline characteristics

Reporting groups	
Reporting group title	BI 1361849 (CV9202) in combination with afatinib
Reporting group description:	
Patients were to be administered with BI 1361849 (CV9202) 0.32 milligram (mg) via intradermal injection per each of 6 components (i.e. 1.92 mg in total) per vaccination time point on day 1 of weeks 1, 2, 3, 5, 7, 9, 12, 15, 18, 21, 24, and continued thereafter every 6 weeks; 2 injections per component resulting in 12 intradermal injections per vaccination visit distributed over 4 different body sites (upper arms, thighs) with afatinib: 40 mg once daily orally (dose can be reduced to 30 mg and 20 mg daily)	
Reporting group title	Placebo matching BI 1361849 (CV9202) in combination with afati
Reporting group description:	
Patients were to be administered with placebo matching BI 1361849 (CV9202) via intradermal injection per each of 6 components per vaccination time point on day 1 of weeks 1, 2, 3, 5, 7, 9, 12, 15, 18, 21, 24, and continued thereafter every 6 weeks; 2 injections per component resulting in 12 intradermal injections per vaccination visit distributed over 4 different body sites (upper arms, thighs) with afatinib: 40 mg once daily orally (dose can be reduced to 30 mg and 20 mg daily)	

Reporting group values	BI 1361849 (CV9202) in combination with afatinib	Placebo matching BI 1361849 (CV9202) in combination with afati	Total
Number of subjects	99999	99999	199998
Age categorical Units: Subjects			
Age continuous			
Treated set (TS); that is, all participants who received at least one dose of study medication. 99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants entered in the trial.			
Units: years			
arithmetic mean	0	0	
standard deviation	± 0	± 0	-
Gender categorical			
Treated set (TS); that is, all participants who received at least one dose of study medication. 99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants entered in the trial.			
Units: Subjects			
Female	0	0	0
Male	99999	99999	199998

End points

End points reporting groups

Reporting group title	BI 1361849 (CV9202) in combination with afatinib

Reporting group description:

Patients were to be administered with BI 1361849 (CV9202) 0.32 milligram (mg) via intradermal injection per each of 6 components (i.e. 1.92 mg in total) per vaccination time point on day 1 of weeks 1, 2, 3, 5, 7, 9, 12, 15, 18, 21, 24, and continued thereafter every 6 weeks; 2 injections per component resulting in 12 intradermal injections per vaccination visit distributed over 4 different body sites (upper arms, thighs) with afatinib: 40 mg once daily orally (dose can be reduced to 30 mg and 20 mg daily)

Reporting group title	Placebo matching BI 1361849 (CV9202) in combination with afati

Reporting group description:

Patients were to be administered with placebo matching BI 1361849 (CV9202) via intradermal injection per each of 6 components per vaccination time point on day 1 of weeks 1, 2, 3, 5, 7, 9, 12, 15, 18, 21, 24, and continued thereafter every 6 weeks; 2 injections per component resulting in 12 intradermal injections per vaccination visit distributed over 4 different body sites (upper arms, thighs) with afatinib: 40 mg once daily orally (dose can be reduced to 30 mg and 20 mg daily)

Primary: Progression free survival (PFS)

End point title	Progression free survival (PFS)[1]

End point description:

Progression free survival (PFS), defined as time (days) from the date of randomisation to the date of progression or to the date of death, whichever occurs first. This will be centrally adjudicated by independent review according to Response Evaluation Criteria In Solid Tumors Criteria (RECIST 1.1). 99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants entered in the trial.

End point type	Primary

End point timeframe:

From the date of randomisation to the date of progression or to the date of death

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No participant entered in the trial hence results are not available.

End point values	BI 1361849 (CV9202) in combination with afatinib	Placebo matching BI 1361849 (CV9202) in combination with afati		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99999[2]	99999[3]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[2] - Treated Set

[3] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (OS), defined as time (days) from the date of randomisation to the date of death. 99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants entered in the trial.

End point type	Secondary

End point timeframe:

From the date of randomisation to the date of death.

End point values	BI 1361849 (CV9202) in combination with afatinib	Placebo matching BI 1361849 (CV9202) in combination with afati		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99999[4]	99999[5]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[4] - Treated Set

[5] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: PFS status at 52 weeks after randomisation by central independent review based on RECIST 1.1

End point title	PFS status at 52 weeks after randomisation by central independent review based on RECIST 1.1

End point description:

Progression free survival (PFS) status at 52 weeks, defined as time (days) from the date of randomisation to the date of progression or to the date of death or week 52, whichever occurs first. This will be centrally adjudicated by independent review according to Response Evaluation Criteria In Solid Tumors Criteria (RECIST 1.1). 99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants entered in the trial.

End point type	Secondary

End point timeframe:

At 52 weeks after randomisation

End point values	BI 1361849 (CV9202) in combination with afatinib	Placebo matching BI 1361849 (CV9202) in combination with afati		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99999[6]	99999[7]		

Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[6] - Treated Set

[7] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival 2 (PFS2)

End point title	Progression free survival 2 (PFS2)

End point description:

PFS2, defined as time (days) from randomisation to either death or disease progression by investigator assessment occurring after initiation of 1st subsequent post trial systemic therapy. 99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants entered in the trial.

End point type	Secondary

End point timeframe:

From randomisation to either death or disease progression by investigator assessment occurring after initiation of 1st subsequent post trial systemic therapy

End point values	BI 1361849 (CV9202) in combination with afatinib	Placebo matching BI 1361849 (CV9202) in combination with afati		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99999[8]	99999[9]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[8] - Treated Set

[9] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Immune response status

End point title	Immune response status

End point description:

A planned total amount of approx. 330 ml blood will be taken within a planned time of week 13 in all 120 patients for the purpose of immunomonitoring at time points before start of treatment (C1V1) as well as at planned time points week 6 (C2V1) and week 13 (C3V2) after the first vaccination. Patients are considered to show an immune response against BI 1361849 (CV9202) if at least one of the two post-baseline time points, week 6 and 13, show assay positivity for at least one of the assessments by Intracellular Cytokine Staining (ICS), Enzyme-linked immunosorbent spot (ELISpot) or Enzyme-linked immunosorbent assay (ELISA) for at least one of the six antigens. 99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants entered in the trial.

End point type	Secondary

End point timeframe:

Week 6 and 13

End point values	BI 1361849 (CV9202) in combination with afatinib	Placebo matching BI 1361849 (CV9202) in combination with afati		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99999[10]	99999[11]		
Units: Participants	99999	99999		

Notes:

[10] - Treated Set

[11] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Symptomatic progression

End point title	Symptomatic progression

End point description:

Symptomatic progression, defined as time (days) from randomisation to an increase of at least 10 points from baseline for one or more of cough (Q1, QLQ-LC13), dyspnoea (Q3-5, QLQ-LC13) or chest pain (Q10, QLQLC13) based on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung cancer specific supplementary module (EORTC QLQ-LC13). 99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants entered in the trial.

End point type	Secondary

End point timeframe:

From randomisation to an increase of at least 10 points from baseline for one or one or more of cough (Q1, QLQ-LC13), dyspnea (Q3-5, QLQ-LC13) or chest pain (Q10, QLQ-LC13)

End point values	BI 1361849 (CV9202) in combination with afatinib	Placebo matching BI 1361849 (CV9202) in combination with afati		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99999[12]	99999[13]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[12] - Treated Set

[13] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation of vaccination by 13 weeks after randomisation due to an adverse event or patient refusal to continue taking medication

End point title	Discontinuation of vaccination by 13 weeks after randomisation due to an adverse event or patient refusal to continue taking medication

End point description:

Discontinuation of vaccination by 13 weeks after randomisation due to an adverse event or patient refusal to continue taking medication. This was planned to analyse at the primary analysis, planned at 52 weeks after the last patient has been randomised. It was planned to analyse separately for all randomised patients from phase I, and all randomised patients across both phase I and phase II portions of the trial. 99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants entered in the trial.

End point type	Secondary

End point timeframe:

At 52 weeks after the last patient has been randomised

End point values	BI 1361849 (CV9202) in combination with afatinib	Placebo matching BI 1361849 (CV9202) in combination with afati		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99999[14]	99999[15]		
Units: Participants	99999	99999		

Notes:

[14] - Treated Set

[15] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation of vaccination by 24 weeks after randomisation due to an adverse event or patient refusal to continue taking medication

End point title	Discontinuation of vaccination by 24 weeks after randomisation due to an adverse event or patient refusal to continue taking medication

End point description:

Discontinuation of vaccination by 24 weeks after randomisation due to an adverse event or patient refusal to continue taking medication. This was planned to analyse at the primary analysis, planned at 52 weeks after the last patient has been randomised. 99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants entered in the trial.

End point type	Secondary

End point timeframe:

At 52 weeks after the last patient has been randomized

End point values	BI 1361849 (CV9202) in combination with afatinib	Placebo matching BI 1361849 (CV9202) in combination with afati		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99999[16]	99999[17]		
Units: Participants	99999	99999		

Notes:

[16] - Treated Set

[17] - Treated Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All adverse events occurring after first intake of treatment until end of the follow up period.

Adverse event reporting additional description:

99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants enrolled in the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	0

Frequency threshold for reporting non-serious adverse events: 5 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No participant entered in the trial hence results are not available.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2015	Administrative changes, corrections, clarifications and re-wording , Added missed vital signs at week 13, Added Electrocardiogram (ECG) at time points before start of treatment and change frequency of ECG from every second course to every course, Added clarification on Peripheral Blood Mononuclear Cells blood collection, Specified that pneumonitis will be ruled out with a high-resolution chest Computed tomography (CT) rather than x-ray/low dose CT, Removed bands and change to perform Prothrombin Time or International Normalised Ratio in safety laboratory parameters and Added Data Monitoring Committee review of safety data after the first 20 patients have been treated before originally planned review after the first 40 patients have been treated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This trial was discontinued with no participants enrolled in the trial.

Notes: