Clinical trial results:
Multi-center phase 2 study to assess the safety, tolerability and early signs of efficacy of tid orally administered BAY63-2521 in adult deltaF508 homozygous Cystic Fibrosis patients

Summary

EudraCT number	2013-004595-35
Trial protocol	GB DE NL BE
Global end of trial date	22 September 2017

Results information

Result version number	v1 (current)
This version publication date	02 September 2018
First version publication date	02 September 2018

Trial information

Trial identification

Sponsor protocol code	BAY63-2521/17020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02170025
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	22 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1) To assess the safety and tolerability versus placebo in adult deltaF508 homozygous Cystic Fibrosis patients not on treatment with Orkambi
2) To assess early signs of efficacy versus placebo in adult deltaF508 homozygous Cystic Fibrosis patients not on treatment with Orkambias observed by change from baseline in sweat chloride content (applicable for part 2 only)

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	21
EEA total number of subjects	11

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	21
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at multiple centers in 7 countries worldwide between 30-Sep-2014 (first subject first visit) and 31-Jan-2017 (last subject last visit).

Pre-assignment

Screening details:

Of 31 participants who were screened, 10 failed screening, 21 were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Riociguat (Adempas, BAY63-2521)

Arm description:

Participants received 0.5 mg BAY63-2521 three times daily (tid) for 14 days. The dose would be increased to 1 mg BAY63-2521 for an additional 14 days, if this was considered safe and tolerable on the basis of the available data for a given patient.

Arm type	Experimental
Investigational medicinal product name	Riociguat (Adempas, BAY63-2521)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 0.5 mg BAY63-2521 three times daily (tid) for 14 days. The dose would be increased to 1 mg BAY63-2521 for an additional 14 days, if this was considered safe and tolerable on the basis of the available data for a given patient.

Arm title	Placebo

Arm description:

Participants received matching placebo tid.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received matching placebo tid.

Number of subjects in period 1	Riociguat (Adempas, BAY63-2521)	Placebo
Started	14	7
Completed	12	7
Not completed	2	0
Adverse Event	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Riociguat (Adempas, BAY63-2521)
Reporting group description:	
Participants received 0.5 mg BAY63-2521 three times daily (tid) for 14 days. The dose would be increased to 1 mg BAY63-2521 for an additional 14 days, if this was considered safe and tolerable on the basis of the available data for a given patient.	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo tid.	

Reporting group values	Riociguat (Adempas, BAY63-2521)	Placebo	Total
Number of subjects	14	7	21
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	27.1	29.1	
standard deviation	± 6.9	± 7.2	-
Gender categorical Units: Subjects			
Female	4	1	5
Male	10	6	16
Sweat chloride content Units: mmol/L			
arithmetic mean	96.33	94.50	
standard deviation	± 17.28	± 12.82	-

End points

End points reporting groups

Reporting group title	Riociguat (Adempas, BAY63-2521)
Reporting group description:	
Participants received 0.5 mg BAY63-2521 three times daily (tid) for 14 days. The dose would be increased to 1 mg BAY63-2521 for an additional 14 days, if this was considered safe and tolerable on the basis of the available data for a given patient.	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo tid.	
Subject analysis set title	Pharmacodynamic analysis set (PDS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacodynamic analysis set (N=16) included patients who received the medication and who had valid sweat chloride data for efficacy analysis.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety analysis set (N=21) included patients who had taken at least one dose of the study medication.	

Primary: Change of sweat chloride content from baseline

End point title	Change of sweat chloride content from baseline
End point description:	
Sweat chloride samples were obtained by using a Macroduct induction and collection device according to standard procedures.	
End point type	Primary
End point timeframe:	
Baseline, at day 14 and day 28 in study part 1	

End point values	Riociguat (Adempas, BAY63-2521)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[1]	7[2]		
Units: mmol/L				
arithmetic mean (standard deviation)				
Change at day 14 in part 1	7.06 (± 10.26)	8.71 (± 8.20)		
Change at day 28 in part 1	3.44 (± 11.04)	9.00 (± 12.71)		

Notes:

[1] - PDS

[2] - PDS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Treatment effect describes the difference in outcomes between 0.5 mg riociguat and placebo on Day 14. This was an exploratory analysis. For sample size determination a probabilistic assessment on predicted point estimates and width of credible intervals was performed.

Comparison groups	Riociguat (Adempas, BAY63-2521) v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Bayesian analysis
Point estimate	-1.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.7
upper limit	6

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Treatment effect describes the difference in outcomes between 1.0 mg riociguat and placebo on Day 28. This was an exploratory analysis. For sample size determination a probabilistic assessment on predicted point estimates and width of credible intervals was performed.

Comparison groups	Riociguat (Adempas, BAY63-2521) v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Bayesian analysis
Point estimate	-5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.4
upper limit	2.4

Secondary: Change of FEV1 from baseline

End point title	Change of FEV1 from baseline

End point description:

Spirometry was performed according to the American Thoracic Society Guidelines 1995 at the time points screening/
baseline, treatment period and follow up.

End point type	Secondary

End point timeframe:

From Baseline to Day 14, Day 28 and Follow-up

End point values	Riociguat (Adempas, BAY63-2521)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[3]	7[4]		
Units: % predicted value				
arithmetic mean (standard deviation)				
Change at day 14	0.86 (± 4.59)	2.00 (± 7.28)		
Change at day 28	-0.79 (± 6.04)	2.43 (± 9.55)		
Change at follow-up visit	-0.46 (± 5.51)	2.63 (± 9.50)		

Notes:

[3] - PDS

[4] - PDS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first treatment until 14 days after last treatment	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo tid	
Reporting group title	Riociguat (Adempas, BAY63-2521)
Reporting group description:	
Participants received 0.5 mg three times daily (tid) BAY63-2521 for 14 days.The dose would be increased to 1 mg BAY63-2521 for an additional 14 days,if this was considered safe and tolerable on the basis of the available data for a given patient.	

Serious adverse events	Placebo	Riociguat (Adempas, BAY63-2521)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	1 / 14 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Riociguat (Adempas, BAY63-2521)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	13 / 14 (92.86%)	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Vessel puncture site bruise			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	3	
Immune system disorders			
Jarisch-Herxheimer reaction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 7 (14.29%)	3 / 14 (21.43%)	
occurrences (all)	1	3	
Sinus congestion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Haemoptysis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Sputum discoloured			
subjects affected / exposed	1 / 7 (14.29%)	2 / 14 (14.29%)	
occurrences (all)	1	3	
Sputum increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 14 (7.14%)	
occurrences (all)	1	2	
Increased viscosity of bronchial secretion			
subjects affected / exposed	2 / 7 (28.57%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Serum ferritin decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Pseudomonas test positive			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Skin injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Face injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 7 (14.29%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	2 / 7 (28.57%)	3 / 14 (21.43%)	
occurrences (all)	4	4	
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Orthostatic intolerance			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Eye disorders			
Eye allergy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	4	
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	3 / 14 (21.43%)	
occurrences (all)	0	3	
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Dyspepsia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	2 / 7 (28.57%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Faecal volume decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Faeces soft			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			

subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	2 / 7 (28.57%)	2 / 14 (14.29%)	
occurrences (all)	2	2	
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 7 (28.57%)	2 / 14 (14.29%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2015	Amendment 5 (dated 15 Apr 2015) to the original clinical study protocol Version 1.0, forming current integrated protocol version 2.0. - A "positive sputum culture for Staphylococcus aureus either currently or within the previous year" was removed as exclusion criterion (part of exclusion criterion 5)
28 September 2015	Amendment 7 (dated 28 Sep 2015) to the integrated protocol version 2.0 (15 Apr 2015) - FEV1 range for inclusion extended from 60-90% predicted (p) to 40 to 100%p - The range of acceptable blood pressure for inclusion was extended (upper limit of SBP from 140 to 160 mmHg, upper limit of DBP from 90 to 100 mmHg. - Removal of two barrier methods as acceptable contraception - Switching 2 site visits into telephone contacts - NPD measurement was made optional (and related exclusion criterion removed) - Removal of determination of reticulocytes - Inclusion of pharmacokinetic (PK) data into DSMB assessment
18 August 2016	Amendment 8 (dated 18 Aug 2016) to protocol version 3.0 (28 Sep 2015) - Shortening of safety monitoring period from 12 to 4 h if DSMB review of the data of Cohort 1 did not reveal any safety concerns - LCI measurement was made optional and LCI as well as NPD were changed from secondary endpoints to additional endpoints - Potential combination of 2 visits on one calendar day in patients not performing LCI or NPD - Removal of upper limit of body mass index as inclusion criterion - Removal of cystatin C from the set of laboratory parameters

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.

Based on multiple factors, the design of part 2 is no longer appropriate. Study was terminated at the end of part 1. No safety concerns were identified.

Notes: