Clinical trial results:
Randomized, multi-center, double-blind, placebo-controlled, group-comparison study to investigate safety, tolerability and pharmacodynamics of BAY2253651 after administration of a single nasal dose in 60 subjects with obstructive sleep apnea and open exploratory evaluation of safety and local tolerability of repeated doses in patients

Summary

EudraCT number	2017-001851-29
Trial protocol	GB
Global end of trial date	23 May 2019

Results information

Result version number	v1 (current)
This version publication date	04 June 2020
First version publication date	04 June 2020

Trial information

Trial identification

Sponsor protocol code	BAY2253651/19038

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03603678
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-trialscontact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trialscontact@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	23 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate changes of apnoea-hypopnoea-index (AHI) within 4 hours after a single dose administration of BAY2253651.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all 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:

Placebo

Actual start date of recruitment	13 August 2018
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	Switzerland: 30
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	34
EEA total number of subjects	4

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)	17
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at two study centers in Switzerland and United Kingdom, between 13-Aug-2018 2018 (first subject first visit) and 23-May-2019 (study termination).

Pre-assignment

Screening details:

Overall, 168 subjects were screened at the two study centers in Switzerland and United Kingdom. 134 subjects failed screening. 34 subjects were randomized with recurring OSA of moderate to severe degree.

Period 1

Period 1 title	Study Part A
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A single dose BAY2253651

Arm description:

Subjects received single dose 100 µg (500 µg/ml * 200 µl) BAY2253651 intranasally

Arm type	Experimental
Investigational medicinal product name	BAY2253651
Investigational medicinal product code	BAY2253651
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Nasal use

Dosage and administration details:

Subjects received single dose 100 µg (500 µg/ml * 200 µl) BAY2253651 intranasally

Arm title	Part A single dose Placebo

Arm description:

Subjects received single dose matching Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Nasal use

Dosage and administration details:

Subjects received single dose matching Placebo

Number of subjects in period 1	Part A single dose BAY2253651	Part A single dose Placebo
Started	17	17
Completed	16	15
Not completed	1	2
Criteria for analysis set not fulfilled	1	2

Period 2

Period 2 title	Study Part B
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Single arm, open label

Arms

Arm title	Part B multiple dose BAY2253651

Arm description:

5 days with repetitive once daily doses of 100µg intra-nasally before bed rest

Arm type	Experimental
Investigational medicinal product name	BAY2253651
Investigational medicinal product code	BAY2253651
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Nasal use

Dosage and administration details:

Subjects received multiple dose
100 µg (500 µg/ml * 200 µl)
BAY2253651 intranasally once
daily on 5 consecutive nights

Number of subjects in period 2[1]	Part B multiple dose BAY2253651
Started	10
Completed	6
Not completed	4
Criteria for analysis set not fulfilled	4

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Per Protocol Set - Part B included subjects of the Per Protocol Set Part A who additionally had dosed him/herself on at least 4 of the 5 consecutive nights with 100µg BAY 2253651 intranasally only

Baseline characteristics

Reporting groups	
Reporting group title	Part A single dose BAY2253651
Reporting group description:	
Subjects received single dose 100 µg (500 µg/ml * 200 µl) BAY2253651 intranasally	
Reporting group title	Part A single dose Placebo
Reporting group description:	
Subjects received single dose matching Placebo	

Reporting group values	Part A single dose BAY2253651	Part A single dose Placebo	Total
Number of subjects	17	17	34
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	12	17
From 65-84 years	12	5	17
85 years and over	0	0	0
Age Continuous Units: years			
median	59.0	70.0	
full range (min-max)	46.0 to 70.0	57.0 to 75.0	-
Gender Categorical Units: Subjects			
Female	3	9	12
Male	14	8	22

Subject analysis sets	
Subject analysis set title	Study part A: Per Protocol Set (PPS) - BAY2253651
Subject analysis set type	Per protocol
Subject analysis set description:	
PPS included all subjects: • received at least one dose of study drug • had a valid AHI by PSG in a sleep laboratory on the third and fourth night of CPAP withdrawal and • did not have an important deviation from the protocol or validity finding having an impact on the primary PD variable.	
Subject analysis set title	Study part A: Per Protocol Set (PPS) - Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
PPS included all subjects: • received at least one dose of study drug • had a valid AHI by PSG in a sleep laboratory on the third and fourth night of CPAP withdrawal	

and
• did not have an important deviation from the protocol or validity finding having an impact on the primary PD variable.

Subject analysis set title	Study part B: Per Protocol Set (PPS) - BAY2253651
Subject analysis set type	Per protocol

Subject analysis set description:

Per Protocol Set - Part B included all subjects of the Per Protocol Set who additionally:
- participated in part B and
- had dosed him/herself on at least 4 of the 5 consecutive nights with 100µg BAY 2253651 intranasally

Reporting group values	Study part A: Per Protocol Set (PPS) - BAY2253651	Study part A: Per Protocol Set (PPS) - Placebo	Study part B: Per Protocol Set (PPS) - BAY2253651
Number of subjects	16	15	6
Age Categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	4	4
From 65-84 years	5	11	2
85 years and over	0	0	0
Age Continuous			
Units: years			
median	58.6	68.2	63.0
full range (min-max)	46.0 to 70.0	57.0 to 75.0	54 to 75
Gender Categorical			
Units: Subjects			
Female	3	7	2
Male	13	8	4

End points

End points reporting groups

Reporting group title	Part A single dose BAY2253651
Reporting group description:	
Subjects received single dose 100 µg (500 µg/ml * 200 µl) BAY2253651 intranasally	
Reporting group title	Part A single dose Placebo
Reporting group description:	
Subjects received single dose matching Placebo	
Reporting group title	Part B multiple dose BAY2253651
Reporting group description:	
5 days with repetitive once daily doses of 100µg intra-nasally before bed rest	
Subject analysis set title	Study part A: Per Protocol Set (PPS) - BAY2253651
Subject analysis set type	Per protocol
Subject analysis set description:	
PPS included all subjects: • received at least one dose of study drug • had a valid AHI by PSG in a sleep laboratory on the third and fourth night of CPAP withdrawal and • did not have an important deviation from the protocol or validity finding having an impact on the primary PD variable.	
Subject analysis set title	Study part A: Per Protocol Set (PPS) - Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
PPS included all subjects: • received at least one dose of study drug • had a valid AHI by PSG in a sleep laboratory on the third and fourth night of CPAP withdrawal and • did not have an important deviation from the protocol or validity finding having an impact on the primary PD variable.	
Subject analysis set title	Study part B: Per Protocol Set (PPS) - BAY2253651
Subject analysis set type	Per protocol
Subject analysis set description:	
Per Protocol Set - Part B included all subjects of the Per Protocol Set who additionally: - participated in part B and - had dosed him/herself on at least 4 of the 5 consecutive nights with 100µg BAY 2253651 intranasally	

Primary: The rate of the responders: changes of apnoea-hypopnoea-index (AHI)

End point title	The rate of the responders: changes of apnoea-hypopnoea-index (AHI)[1]
End point description:	
A responder is defined by the reduction of the AHI (over 0-4h) from baseline by ≥ 50% after a single dose administration of BAY2253651	
End point type	Primary
End point timeframe:	
Apnoea-hypopnoe-index (AHI) (over 0-4h) obtained by polysomnography (PSG) at Visits 1 and 2	

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: Descriptive statistics were done, no inferential statistical analyses were planned for this endpoint.

End point values	Study part A: Per Protocol Set (PPS) - BAY2253651	Study part A: Per Protocol Set (PPS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	15		
Units: Percentage				
number (not applicable)				
Reduction of AHI (0-4h) from baseline by >=50%	6.3	6.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number and severity of treatment emergent adverse events (TEAEs) - Part A

End point title	Number and severity of treatment emergent adverse events (TEAEs) - Part A

End point description:

SAF

End point type	Secondary

End point timeframe:

From the start of study medication administration up to 2 days after the end of treatment with study medication

End point values	Part A single dose BAY2253651	Part A single dose Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: Subjects				
Any AE	12	9		
Intensity for any AE: mild	11	8		
Intensity for any AE: moderate	1	0		
Any study drug related AE	11	8		
Intensity for study drug related AE: mild	11	7		
Intensity for study drug related AE: severe	0	1		
Any AE related to protocol procedures	1	1		
Any AE leading to discontinuation of study drug	0	0		
Any SAE	0	0		
Study drug related SAEs	0	0		
SAE related to protocol procedures	0	0		
SAE leading to discontinuation of study drug	0	0		
AE with the outcome death	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number and severity of treatment emergent adverse events (TEAEs) - Part B

End point title	Number and severity of treatment emergent adverse events (TEAEs) - Part B

End point description:

SAF

End point type	Secondary

End point timeframe:

From the start of study medication administration up to 2 days after the end of treatment with study medication

End point values	Part B multiple dose BAY2253651			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Subjects				
Any AE	5			
Intensity for any AE: mild	5			
Any BAY 2253651 related AE	5			
Intensity for BAY 2253651 related AE: mild	5			
Any AE related to protocol procedures	0			
Any AE leading to discontinuation of BAY 2253651	0			
Any SAE	0			
BAY 2253651 related SAEs	0			
SAE related to protocol procedures	0			
SAE leading to discontinuation of BAY 2253651	0			
AE with the outcome death	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study treatment up to 2 days after end of treatment with study medication	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	BAY2253651 Part A
Reporting group description: -	
Reporting group title	Placebo Part A
Reporting group description: -	
Reporting group title	BAY2253651 Part B
Reporting group description: -	

Serious adverse events	BAY2253651 Part A	Placebo Part A	BAY2253651 Part B
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	BAY2253651 Part A	Placebo Part A	BAY2253651 Part B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 17 (70.59%)	9 / 17 (52.94%)	5 / 10 (50.00%)
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	7 / 17 (41.18%)	2 / 17 (11.76%)	3 / 10 (30.00%)
occurrences (all)	7	2	3
Head discomfort			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			

Application site pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Thirst			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	1 / 17 (5.88%)	2 / 17 (11.76%)	2 / 10 (20.00%)
occurrences (all)	1	2	2
Glossitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Glossodynia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dry throat			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Nasal congestion			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nasal dryness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 10 (0.00%)
occurrences (all)	0	1	0

Throat irritation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Throat tightness			
subjects affected / exposed	2 / 17 (11.76%)	0 / 17 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Intranasal paraesthesia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Laryngeal discomfort			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pharyngeal hypoaesthesia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pharyngeal paraesthesia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Skin discomfort			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 10 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2018	Amendment 1, dated 06 Aug 2018 was issued to incorporate modifications requested by the British Competent Authority (MHRA). All changes were implemented prior to study start: • Clarification of study inclusion criteria for adequate contraception • Inclusion of non-REM AHI for Polysomnography exploratory objectives and analysis • Standardization of blood pressure measurement • Updated Short Form Health Survey (SF-36, Version 2) • Removal of IxRS from drug accountability processes
10 December 2018	Amendment 2, dated 10 Dec 2018 was implemented to include the following modifications: • Combining Visit 4 (Part A) and Visit 5 (Part B) study activities • Clarification of estimated AHI count procedures • Revised ODI screening range (Part A) • Manual adjustment of screening oximetry data • Repeat of non-evaluable CPAP assessments • Extension of screening phase from 6 to 12 weeks • Revised scheduling of assessments conducted at Screening Visit 2 and Visit 2 • Addition of criteria for evaluating PSG assessment at Visit 2

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 May 2019	Study termination	-

Notes:

Limitations and caveats

None reported