Clinical trial results:
Proof-of-concept, multi-center, randomized, double-blind, placebo-controlled, two-way crossover study to investigate the effect strength of BAY 2586116 on the apnea-hypopnea-index after repetitive nasal doses compared to placebo in 80 valid participants with moderate to severe obstructive sleep apnea

Summary

EudraCT number	2020-000520-19
Trial protocol	DE
Global end of trial date	11 November 2021

Results information

Result version number	v1 (current)
This version publication date	15 November 2022
First version publication date	15 November 2022

Trial information

Trial identification

Sponsor protocol code	BAY2586116/20849

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04713826
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Bayer Clinical Trials Contact, Bayer AG, +49 30300139003, clinical-trials-contact@bayer.com
Scientific contact	Bayer Clinical Trials Contact, Bayer AG, +49 30300139003, 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	11 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect strength of BAY2586116 on obstructive sleep apnea (OSA) severity after repetitive doses compared to placebo

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	03 March 2021
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	Germany: 62
Country: Number of subjects enrolled	Switzerland: 31
Worldwide total number of subjects	93
EEA total number of subjects	62

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)	63

From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 3 centers, 2 centers in Germany and 1 center in Switzerland with first subject first visit on 03-Mar-2021 and last subject last visit on 13-Sep-2021

Pre-assignment

Screening details:

120 subjects were screened, 93 subjects were randomized, 47 subjects to BAY2586116–Placebo intervention sequence and 46 to Placebo-BAY2586116 intervention sequence. 2 of these subjects didn’t receive treatment as planned, 1 received BAY2586116 twice and 1 received placebo twice. All 93 randomized subjects received at least 1 dose of study drug.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BAY2586116 160ug (nasal spray) - Placebo

Arm description:

Subjects received multiple daily doses of 160 µg BAY2586116 nasal spray first in treatment period 1, and matching placebo in treatment period 2

Arm type	Experimental
Investigational medicinal product name	BAY2586116
Investigational medicinal product code	BAY2586116
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

160 µg BAY2586116 nasally. Applied once per night for 6 days (+ 1 optional day) and 1 single dose prior to overnight polysomnography (PSG).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Placebo nasally. Applied once per night for 6 days (+ 1 optional day) and 1 single dose prior to overnight PSG.

Arm title	Placebo - BAY2586116 160ug (nasal spray)

Arm description:

Subjects received matching placebo first in treatment period 1, and multiple daily doses of 160 µg BAY2586116 nasal spray in treatment period 2

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

Dosage and administration details:

Placebo nasally. Applied once per night for 6 days (+ 1 optional day) and 1 single dose prior to overnight PSG.

Investigational medicinal product name	BAY2586116
Investigational medicinal product code	BAY2586116
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

160 µg BAY2586116 nasally. Applied once per night for 6 days (+ 1 optional day) and 1 single dose prior to overnight PSG.

Arm title	BAY2586116 160ug (nasal spray)-BAY2586116 160ug (nasal spray)

Arm description:

Subject received multiple daily doses of 160 µg BAY2586116 nasal spray first in treatment period 1, and then multiple daily doses of 160 µg BAY2586116 nasal spray in treatment period 2 by mistake

Arm type	Experimental
Investigational medicinal product name	BAY2586116
Investigational medicinal product code	BAY2586116
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

160 µg BAY2586116 nasally. Applied once per night for 6 days (+ 1 optional day) and 1 single dose prior to overnight PSG.

Arm title	Placebo - Placebo

Arm description:

Subject received matching placebo first in treatment period 1, and then matching placebo in treatment period 2 by mistake

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

Dosage and administration details:

Placebo nasally. Applied once per night for 6 days (+ 1 optional day) and 1 single dose prior to overnight PSG.

Number of subjects in period 1	BAY2586116 160ug (nasal spray) - Placebo	Placebo - BAY2586116 160ug (nasal spray)	BAY2586116 160ug (nasal spray)- BAY2586116 160ug (nasal spray)
Started	46	45	1
Completed	46	44	1
Not completed	0	1	0
Adverse event, non-fatal	-	1	-

Number of subjects in period 1	Placebo - Placebo
Started	1

Completed	1
Not completed	0
Adverse event, non-fatal	-

Baseline characteristics

Reporting groups	
Reporting group title	BAY2586116 160ug (nasal spray) - Placebo
Reporting group description:	
Subjects received multiple daily doses of 160 µg BAY2586116 nasal spray first in treatment period 1, and matching placebo in treatment period 2	
Reporting group title	Placebo - BAY2586116 160ug (nasal spray)
Reporting group description:	
Subjects received matching placebo first in treatment period 1, and multiple daily doses of 160 µg BAY2586116 nasal spray in treatment period 2	
Reporting group title	BAY2586116 160ug (nasal spray)-BAY2586116 160ug (nasal spray)
Reporting group description:	
Subject received multiple daily doses of 160 µg BAY2586116 nasal spray first in treatment period 1, and then multiple daily doses of 160 µg BAY2586116 nasal spray in treatment period 2 by mistake	
Reporting group title	Placebo - Placebo
Reporting group description:	
Subject received matching placebo first in treatment period 1, and then matching placebo in treatment period 2 by mistake	

Reporting group values	BAY2586116 160ug (nasal spray) - Placebo	Placebo - BAY2586116 160ug (nasal spray)	BAY2586116 160ug (nasal spray)-BAY2586116 160ug (nasal spray)
Number of subjects	46	45	1
Age categorical Units: Subjects			
Adults (18-64 years)	30	33	0
From 65-84 years	16	12	1
Gender categorical Units: Subjects			
Female	10	13	0
Male	36	32	1
Baseline AHI Group			
AHI: apnea-hypopnea index			
Units: Subjects			
Baseline AHI <15	3	4	0
Baseline AHI 15-30 (moderate OSA)	18	17	0
Baseline AHI >30 (severe OSA)	24	23	1
Missing baseline AHI	1	1	0

Reporting group values	Placebo - Placebo	Total	
Number of subjects	1	93	
Age categorical Units: Subjects			
Adults (18-64 years)	0	63	
From 65-84 years	1	30	
Gender categorical Units: Subjects			
Female	0	23	

Male	1	70	

Baseline AHI Group			
AHI: apnea-hypopnea index			
Units: Subjects			
Baseline AHI <15	0	7	
Baseline AHI 15-30 (moderate OSA)	0	35	
Baseline AHI >30 (severe OSA)	1	49	
Missing baseline AHI	0	2	

End points

End points reporting groups

Reporting group title	BAY2586116 160ug (nasal spray) - Placebo
Reporting group description:	
Subjects received multiple daily doses of 160 µg BAY2586116 nasal spray first in treatment period 1, and matching placebo in treatment period 2	
Reporting group title	Placebo - BAY2586116 160ug (nasal spray)
Reporting group description:	
Subjects received matching placebo first in treatment period 1, and multiple daily doses of 160 µg BAY2586116 nasal spray in treatment period 2	
Reporting group title	BAY2586116 160ug (nasal spray)-BAY2586116 160ug (nasal spray)
Reporting group description:	
Subject received multiple daily doses of 160 µg BAY2586116 nasal spray first in treatment period 1, and then multiple daily doses of 160 µg BAY2586116 nasal spray in treatment period 2 by mistake	
Reporting group title	Placebo - Placebo
Reporting group description:	
Subject received matching placebo first in treatment period 1, and then matching placebo in treatment period 2 by mistake	
Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects randomly assigned to study intervention and who took at least 1 dose of study intervention. Subjects were analyzed according to the intervention they actually received.	
Subject analysis set title	Efficacy Analysis Set (EAS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who had valid AHI by PSG in sleep laboratory in all three nights and took at least 80% of the study medication in each period.	
Subject analysis set title	BAY2586116
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who received BAY2586116	
Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who received placebo	

Primary: Responder rates for BAY2586116 and placebo

End point title	Responder rates for BAY2586116 and placebo
End point description:	
A response was defined as reduction of AHI from baseline by ≥50%	
End point type	Primary
End point timeframe:	
At day -1, and day 7 in Period 1, and day 7 in Period 2	

End point values	BAY2586116	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84[1]	84[2]		
Units: percentage				
number (not applicable)	11.9	8.3		

Notes:

[1] - EAS

[2] - EAS

Statistical analyses

Statistical analysis title	Difference in responder rates between treatment

Statistical analysis description:

Success criterion: Prob(Responder rate "Placebo"<Responder rate "BAY 2586116" | data) ≥ 95%.
Responder rates were compared using a Bayesian logistic regression. The posterior probability Prob(Responder rate "Placebo"<Responder rate "BAY 2586116" | data) = 80.54%, estimated difference in responder rates and 90% credible intervals were presented.
Erroneously, database auto calculates the total number of subjects for the selected arms. Number of subjects evaluated in this analysis was 84.

Comparison groups	Placebo v BAY2586116
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.13
upper limit	0.05

Secondary: Number of subjects with at least one treatment-emergent adverse event (TEAE) and maximum severity of TEAEs per subject

End point title	Number of subjects with at least one treatment-emergent adverse event (TEAE) and maximum severity of TEAEs per subject

End point description:

An adverse event (AE) was any untoward medical occurrence in a patient or clinical study subject whether or not considered related to the study intervention
AEs were considered to be treatment-emergent if they started or worsened after first application of study intervention in each period up to 2 days after end of treatment in each period with study intervention
An serious adverse event (SAE) was defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening
c. Requires inpatient hospitalization or prolongation of existing hospitalization
d. Results in persistent disability/incapacity
e. Is a congenital anomaly/birth defect
f. Other situations

End point type	Secondary

End point timeframe:

From first application of study intervention up to 2 days after end of treatment in each period with study intervention

End point values	BAY2586116	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92[3]	92[4]		
Units: subject				
Any AE	18	20		
Maximum intensity for any AE: MILD	16	17		
Maximum intensity for any AE: MODERATE	2	2		
Maximum intensity for any AE: SEVERE	0	1		
Any study drug-related AE	5	8		
Any AE related to procedures required by protocol	5	8		
Any AE leading to discontinuation of study drug	1	0		
Any SAE	0	1		

Notes:

[3] - SAF

[4] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dosing up to 2 days after end of treatment in each period with study intervention. Adverse event reporting for the deaths (all causes) considers all deaths that occurred at any time during the study before the last contact.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	BAY2586116

Reporting group description:

All subjects who received BAY2586116.

Reporting group title	Placebo

Reporting group description:

All subjects who received placebo.

Serious adverse events	BAY2586116	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BAY2586116	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 92 (19.57%)	20 / 92 (21.74%)	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Fatigue			

subjects affected / exposed	0 / 92 (0.00%)	2 / 92 (2.17%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	1 / 92 (1.09%)	2 / 92 (2.17%)	
occurrences (all)	1	2	
Throat irritation			
subjects affected / exposed	3 / 92 (3.26%)	0 / 92 (0.00%)	
occurrences (all)	3	0	
Nasal discomfort			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Pharyngeal hypoaesthesia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 92 (2.17%)	1 / 92 (1.09%)	
occurrences (all)	2	1	
Pharyngeal paraesthesia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Psychiatric disorders			

Initial insomnia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Nightmare			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Panic attack			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Thought blocking			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Inflammatory marker increased			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Post procedural haematuria			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	

Dizziness			
subjects affected / exposed	1 / 92 (1.09%)	2 / 92 (2.17%)	
occurrences (all)	1	2	
Headache			
subjects affected / exposed	2 / 92 (2.17%)	2 / 92 (2.17%)	
occurrences (all)	2	2	
Somnolence			
subjects affected / exposed	3 / 92 (3.26%)	4 / 92 (4.35%)	
occurrences (all)	3	4	
Blood and lymphatic system disorders			
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Eye disorders			
Pupils unequal			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	2 / 92 (2.17%)	1 / 92 (1.09%)	
occurrences (all)	2	1	
Abdominal rigidity			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	1 / 92 (1.09%)	1 / 92 (1.09%)	
occurrences (all)	1	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	

Nausea			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 92 (1.09%)	1 / 92 (1.09%)	
occurrences (all)	1	1	
Hepatobiliary disorders			
Ocular icterus			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Chronic kidney disease			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2021	Amendment 1 dated 26 FEB 2021, was a substantial amendment. It was issued to globally implement changes requested by the German and Swiss Competent Authorities after review of the clinical study protocol and before approval. The amendment included the following key modifications: • The description of the selected study population was changed from "Male and female participants with OSA who are otherwise healthy" to "Male and female participants with OSA" • Exclusion criteria for heart failure, uncontrolled arterial hypertension and chronic obstructive pulmonary disease (COPD) were added • Prohibited medication in concomitant medication was specified • Definitions to exclude disease related findings from laboratory/AE assessment were deleted • Data Monitoring Committee (DMC) was added • Treatable traits were adapted to include traits derived from treatment PSGs • Other treatments of OSA in addition to continuous positive airway pressure (CPAP) for pre-treatment of OSA were included • The timepoints for activities before start of PSG were adapted • The wording of the primary endpoint was changed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported