Clinical trial results:
A randomized, double-blind, cross-over, placebo-controlled, multi-center, Phase 2a study to assess the safety and efficacy of BAY 2395840 in patients with diabetic neuropathic pain

Summary

EudraCT number	2021-001392-17
Trial protocol	HU CZ ES SK DE
Global end of trial date	21 November 2022

Results information

Result version number	v1 (current)
This version publication date	26 November 2023
First version publication date	26 November 2023

Trial information

Trial identification

Sponsor protocol code	BAY2395840/19636

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05219812
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, +46 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +46 30 300139003, 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	21 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of BAY2395840 on pain associated with diabetic neuropathic pain (DNP) as compared with 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	16 February 2022
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	Czechia: 19
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Slovakia: 20
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	80
EEA total number of subjects	75

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)	33
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 29 centers in 6 countries between 16 FEB 2022 (first participant first visit) and 21 NOV 2022 (last participant last visit).

Pre-assignment

Screening details:

133 subjects were screened in the study, 81 subjects were randomized (1 subject never received treatment). Of those, 52 subjects did not randomize to the study treatment (48 were screening failures, 3 decided not to participate, 1 failed screen due to other reasons).

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	Investigator, Monitor, Data analyst, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Dosage A of BAY2395840 - Placebo

Arm description:

Subjects received dosage A of BAY2395840 in period 1, and received placebo in period 2.

Arm type	Experimental
Investigational medicinal product name	BAY2395840
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage A, tablet, oral administration

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

Dosage and administration details:

once daily, tablet, oral administration

Arm title	Placebo - Dosage A of BAY2395840

Arm description:

Subjects received placebo in period 1, and received dosage A of BAY2395840 in period 2.

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

Dosage and administration details:

once daily, tablet, oral administration

Investigational medicinal product name	BAY2395840
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage A, tablet, oral administration

Number of subjects in period 1	Dosage A of BAY2395840 - Placebo	Placebo - Dosage A of BAY2395840
Started	40	40
Period 1	40	40
Run-in phase	39	39
Period 2	39	39
Completed	37	38
Not completed	3	2
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Dosage A of BAY2395840 - Placebo
Reporting group description:	
Subjects received dosage A of BAY2395840 in period 1, and received placebo in period 2.	
Reporting group title	Placebo - Dosage A of BAY2395840
Reporting group description:	
Subjects received placebo in period 1, and received dosage A of BAY2395840 in period 2.	

Reporting group values	Dosage A of BAY2395840 - Placebo	Placebo - Dosage A of BAY2395840	Total
Number of subjects	40	40	80
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	65.2	64.4	
standard deviation	± 10.5	± 10.6	-
Gender Categorical Units: Subjects			
Female	21	19	40
Male	19	21	40

End points

End points reporting groups

Reporting group title	Dosage A of BAY2395840 - Placebo
Reporting group description:	
Subjects received dosage A of BAY2395840 in period 1, and received placebo in period 2.	
Reporting group title	Placebo - Dosage A of BAY2395840
Reporting group description:	
Subjects received placebo in period 1, and received dosage A of BAY2395840 in period 2.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who took at least one dose of study intervention. Of 81 randomized subjects, 80 subjects (98.8%, 40 per treatment sequence) were valid for SAF since 1 subject never received study intervention.	
Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in FAS without any validity finding impacting interpretation of study results were available. PPS included 78 subjects (39 per treatment sequence) which was 96.3% of all randomized subjects.	
Subject analysis set title	Dosage A of BAY2395840 in PPS
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects treated with BAY2395840 in the PPS. in Group 1 (BAY2395840 - placebo treatment sequence) period 1 and in Group 2 (placebo - BAY2395840 treatment sequence) period 2.	
Subject analysis set title	Placebo in PPS
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects treated with placebo in the PPS. Group 1 (BAY2395840 - placebo treatment sequence) period 2 and in Group 2 (placebo - BAY2395840 treatment sequence) period 1.	
Subject analysis set title	Dosage A of BAY2395840 in SAF
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects treated with BAY2395840 in the SAF. Overall, 80 participants were valid for SAF. 2 participants (1 in Group 1 with BAY2395840 – placebo treatment sequence, 1 in Group 2 with placebo – BAY2395840 treatment sequence) did not enter period 2. Thus, 79 participants were treated with BAY2395840 in the SAF.	
Subject analysis set title	Placebo in SAF
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects treated with placebo in the SAF. Overall, 80 participants were valid for SAF. 2 participants (1 in Group 1 with BAY2395840 – placebo treatment sequence, 1 in Group 2 with placebo – BAY2395840 treatment sequence) did not enter period 2. Thus, 79 participants were treated with placebo in the SAF.	

Primary: Change in weekly mean 24-hour average pain intensity score using the 11-point NRS from baseline to the end of intervention

End point title	Change in weekly mean 24-hour average pain intensity score using the 11-point NRS from baseline to the end of intervention
End point description:	
Subjects were asked to report their average neuropathic pain severity in the past 24 hours using an 11-point NRS with 0 as "no pain" and 10 as "worst imaginable pain". NRS=Pain Numeric Rating Scale	
End point type	Primary
End point timeframe:	
Baseline to end of intervention (in total up to 16 weeks)	

End point values	Dosage A of BAY2395840 in PPS	Placebo in PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76[1]	75[2]		
Units: scores				
arithmetic mean (standard deviation)				
Week 1	-0.33 (± 0.82)	-0.39 (± 0.86)		
Week 2	-0.44 (± 0.98)	-0.75 (± 1.13)		
Week 3	-0.67 (± 1.24)	-1.06 (± 1.30)		
Week 4	-0.93 (± 1.45)	-1.23 (± 1.44)		

Notes:

[1] - PPS

[2] - PPS, the analyzed subjects at Week 1 and 2 were 75, at Week 3 it was 74, and at Week 4 it was 71.

Statistical analyses

Statistical analysis title	ANCOVA for change from baseline in NRS

Statistical analysis description:

At Week 4 in period 1 and period 2, the estimated mean (SE) treatment difference for weekly mean 24-hour average NRS between BAY2395840 and placebo

Comparison groups	Dosage A of BAY2395840 in PPS v Placebo in PPS
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.17
upper limit	0.314
Variability estimate	Standard error of the mean
Dispersion value	0.146

Notes:

[3] - Database auto-calculates total number of subjects erroneously, analysed number of subjects was 78.

Secondary: Number of participants with treatment emergent adverse events

End point title	Number of participants with treatment emergent adverse events

End point description:

An AE was any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention. An SAE was defined as any AE that, at any dose: a. Results in death, b. Was life-threatening, c. Required inpatient hospitalization or prolongation of existing hospitalization, d. Resulted in persistent or significant disability/incapacity, e. Was a congenital anomaly/birth defect, etc. AE=Adverse event SAE=Serious adverse event

End point type	Secondary

End point timeframe:

From start of study intervention to 14 days after last dose (up to 13 weeks)

End point values	Dosage A of BAY2395840 in SAF	Placebo in SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	79[4]	79[5]		
Units: subjects				
Any AE	33	26		
Any SAE	2	2		

Notes:

[4] - SAF

[5] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Neuropathic Pain Symptom Inventory (NPSI) total score from baseline to the end of intervention

End point title	Change in Neuropathic Pain Symptom Inventory (NPSI) total score from baseline to the end of intervention

End point description:

The NPSI contained 12 items, of which five summary pain scores can be calculated: "superficial spontaneous", "deep spontaneous", "paroxysmal pain", "evoked pain", and "paresthesia/ dysesthesia". The total score was sum of the summary scores divided by 100. The 10 descriptive items used to derive the domain summary scores are each rated on an 11-point numeric rating scale (0= "no (symptom)" and 10= "worst (symptom) imaginable"); each item has a recall period of the past 24 hours. The remaining two items report how consistently pain has been present and the number of pain episodes.

End point type	Secondary

End point timeframe:

At visit 2, visit 4, visit 6, visit 8, visit 10 and at visit 12 end of intervention (EOI)

End point values	Dosage A of BAY2395840 in PPS	Placebo in PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[6]	78[7]		
Units: scores				
arithmetic mean (standard deviation)				
Visit 4 / Visit 10	-6.89 (± 10.53)	-5.43 (± 10.56)		
Visit 6 / Visit 12	-7.23 (± 15.10)	-5.30 (± 11.44)		

Notes:

[6] - Per protocol set (PPS)

[7] - Per protocol set (PPS)

Statistical analyses

Statistical analysis title	ANCOVA of change on NPSI

Statistical analysis description:

The mean difference change from baseline in the NPSI total score between BAY2395840 and placebo at Week 4 in period 1 and period 2

Comparison groups	Dosage A of BAY2395840 in PPS v Placebo in PPS
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Mean difference (final values)
Point estimate	-1.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.528
upper limit	1.157
Variability estimate	Standard error of the mean
Dispersion value	1.406

Notes:

[8] - Database auto-calculates total number of subjects erroneously, analysed number of subjects was 78.

Secondary: Change in Patient Global Impression of Severity (PGI-S) score from baseline to the end of intervention

End point title	Change in Patient Global Impression of Severity (PGI-S) score from baseline to the end of intervention

End point description:

Subjects were asked to best describe their diabetic nerve pain symptoms on a 6-point scale in the last week scored as: "none"(1), "very mild"(2), "mild"(3), "moderate"(4), "severe"(5), or "very severe"(6). PGI-S=Patient Global Impression of Severity

End point type	Secondary

End point timeframe:

At visit 2, visit 4, visit 6, visit 8, visit 10 and at visit 12 end of intervention (EOI)

End point values	Dosage A of BAY2395840 in PPS	Placebo in PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[9]	78[10]		
Units: scores				
arithmetic mean (standard deviation)				
Visit 4 / Visit 10	-0.27 (± 0.85)	-0.37 (± 0.83)		
Visit 6 / Visit 12	-0.39 (± 0.88)	-0.43 (± 0.94)		

Notes:

[9] - Per protocol set (PPS)

[10] - Per protocol set (PPS)

Statistical analyses

Statistical analysis title	ANCOVA of change on PGI-S

Statistical analysis description:

The estimated mean (SE) treatment difference based on PGI-S severity score between BAY2395840 and placebo at Week 4 in period 1 and period 2

Comparison groups	Dosage A of BAY2395840 in PPS v Placebo in PPS
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.131
upper limit	0.272
Variability estimate	Standard error of the mean
Dispersion value	0.121

Notes:

[11] - Database auto-calculates total number of subjects erroneously, analysed number of subjects was 78.

Secondary: Number of subjects achieving a ≥30% and a ≥50% reduction in weekly mean 24-hour average pain intensity score (i.e. responder rates using NRS)

End point title	Number of subjects achieving a ≥30% and a ≥50% reduction in weekly mean 24-hour average pain intensity score (i.e. responder rates using NRS)

End point description:

Responder rates using NRS were defined as the proportion of participants with a ≥30% and a ≥50% reduction in weekly mean 24-hour average pain intensity score at Visit 4 in period 1 and Visit 10 in period 2. NRS=Pain Numeric Rating Scale

End point type	Secondary

End point timeframe:

From baseline to end of intervention (in total up to 12 weeks)

End point values	Dosage A of BAY2395840 in PPS	Placebo in PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[12]	78[13]		
Units: subjects				
Achieved >=30% reduction in NRS	24	33		
Achieved >=50% reduction in NRS	10	13		

Notes:

[12] - Per protocol set (PPS)

[13] - Per protocol set (PPS)

Statistical analyses

Statistical analysis title	Marginal responder rates analysis

Statistical analysis description:

Odds ratio for estimated responder rate on weekly mean 24-hour average pain NRS in week 4 between BAY2395840 and placebo among subjects achieving >=50% improvement in pain compared to baseline

Comparison groups	Dosage A of BAY2395840 in PPS v Placebo in PPS

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other[14]
Parameter estimate	Odds ratio (OR)
Point estimate	0.653
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.2681
upper limit	1.5904

Notes:

[14] - Database auto-calculates total number of subjects erroneously, analysed number of subjects was 78.

Statistical analysis title	Marginal responder rates analysis

Statistical analysis description:

Odds ratio for estimated responder rate on weekly mean 24-hour average pain NRS in week 4 between BAY2395840 and placebo among subjects achieving >=30% improvement in pain compared to baseline

Comparison groups	Dosage A of BAY2395840 in PPS v Placebo in PPS
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other[15]
Parameter estimate	Odds ratio (OR)
Point estimate	0.5143
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.2624
upper limit	1.008

Notes:

[15] - Database auto-calculates total number of subjects erroneously, analysed number of subjects was 78.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs started or worsened after application of study intervention and up to 14 days after the last study intervention per period

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo in SAF

Reporting group description:

Subjects treated with matching placebo in the SAF. Overall, 80 participants were valid for SAF. 2 participants (1 in Group 1 with BAY2395840 - placebo treatment sequence, 1 in Group 2 with placebo - BAY2395840 treatment sequence) did not enter period 2. Thus, 79 participants were treated with placebo in the SAF.

Reporting group title	Dosage A of BAY2395840 in SAF

Reporting group description:

Subjects treated with BAY2395840 in the SAF. Overall, 80 participants were valid for SAF. 2 participants (1 in Group 1 with BAY2395840 - placebo treatment sequence, 1 in Group 2 with placebo - BAY2395840 treatment sequence) did not enter period 2. Thus, 79 participants were treated with BAY2395840 in the SAF.

Serious adverse events	Placebo in SAF	Dosage A of BAY2395840 in SAF	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 79 (2.53%)	2 / 79 (2.53%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	0	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	1 / 79 (1.27%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo in SAF	Dosage A of BAY2395840 in SAF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 79 (8.86%)	11 / 79 (13.92%)	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 79 (7.59%)	5 / 79 (6.33%)	
occurrences (all)	14	5	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 79 (0.00%)	4 / 79 (5.06%)	
occurrences (all)	0	4	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 79 (1.27%)	4 / 79 (5.06%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported