Clinical trial results:
Multicenter, Open-Label, Long-Term Safety and Efficacy Study of the Fixed Dose Combination of Nifedipine Gastrointestinal Therapeutic System and Candesartan Cilexetil in Adult Subjects With Moderate to Severe Essential Hypertension

Summary

EudraCT number	2012-004515-32
Trial protocol	DE GB PL
Global end of trial date	01 May 2014

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	20 June 2015

Trial information

Trial identification

Sponsor protocol code	BAY98-7106/14801

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01788358
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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	01 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the long-term safety and tolerability of Fixed Dose Combination (FDC) of Nifedipine Gastrointestinal Therapeutic System (GITS) / candesartan cilexetil (primarily the highest dose) once daily in subjects with moderate to severe essential hypertension.

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: -

Actual start date of recruitment	14 February 2013
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	Germany: 48
Country: Number of subjects enrolled	United States: 277
Country: Number of subjects enrolled	United Kingdom: 98
Country: Number of subjects enrolled	Canada: 85
Worldwide total number of subjects	508
EEA total number of subjects	146

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)	346
From 65 to 84 years	162
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 70 study centers between 14 February 2013 (first subject first visit) and 1 May 2014 (last subject last visit).

Pre-assignment

Screening details:

Of 753 subjects screened, 245 subjects were not enrolled, due to screen failure for 215 subjects, consent withdrawal by 23 subjects, protocol violation by 5 subjects, 1 subject was lost to follow-up and recruitment stopped for 1 subject. Remaining 508 subjects were enrolled and received at least 1 treatment with study drug.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)

Arm description:

Subjects received nifedipine GITS/candesartan cilexetil FDC (BAY98-7106) tablet orally, once daily in the morning of Visit 1 (Week 0) for 28 or 52 weeks. The starting dose (30/8 milligram [mg] or 30/16 mg) was determined based on local practice and clinical judgment by the investigator. Based on the experience of symptomatic and asymptomatic hypotension, peripheral edema or significant tolerability, the doses were up-titrated to the highest target dose (60/32 mg).

Arm type	Experimental
Investigational medicinal product name	Nifedipine gastrointestinal therapeutic system (GITS)/Candesartan cilexetil fixed dose combination (FDC)
Investigational medicinal product code	BAY98-7106
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received nifedipine GITS/candesartan cilexetil FDC (BAY98-7106) tablet orally, once daily in the morning of Visit 1 (Week 0) for 28 or 52 weeks. The starting dose (30/8 mg or 30/16 mg) was determined based on local practice and clinical judgment by the investigator. Based on the experience of symptomatic and asymptomatic hypotension, peripheral edema or significant tolerability, the doses were up-titrated to the highest target dose (60/32 mg).

Number of subjects in period 1	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)
Started	508
Treated	508
Completed Week 28	417
Entered Extension to Week 52	200 [1]
Completed Week 52	193 [2]

Completed	410
Not completed	98
Consent withdrawn by subject	26
Logistical difficulties	1
Protocol violation	3
Adverse event	51
Unspecified	11
Lost to follow-up	5
Lack of efficacy	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: As planned, only the first 200 subjects who completed Week 28 visit, continued treatment up to 52 weeks. Hence, the number of subjects at this milestone seems inconsistent with the number of subjects in the arm.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Of the first 200 subjects who entered Week 52 visit, 193 completed and the remaining 7 subjects did not complete due to consent withdrawal by 2 subjects, 1 subject lost to follow up and 4 subjects due to other reasons. Hence, the number of subjects at this milestone seems inconsistent with the number of subjects in the arm.

Baseline characteristics

Reporting groups	
Reporting group title	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)
Reporting group description:	
Subjects received nifedipine GITS/candesartan cilexetil FDC (BAY98-7106) tablet orally, once daily in the morning of Visit 1 (Week 0) for 28 or 52 weeks. The starting dose (30/8 milligram [mg] or 30/16 mg) was determined based on local practice and clinical judgment by the investigator. Based on the experience of symptomatic and asymptomatic hypotension, peripheral edema or significant tolerability, the doses were up-titrated to the highest target dose (60/32 mg).	

Reporting group values	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)	Total	
Number of subjects	508	508	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 59 ± 10.2	 -	
Gender categorical Units: Subjects			
Female Male	186 322	186 322	
Systolic blood pressure Units: millimeter of mercury (mmHg) arithmetic mean standard deviation	 170.7 ± 8.9	 -	
Diastolic blood pressure Units: mmHg arithmetic mean standard deviation	 95.6 ± 10.4	 -	

End points

End points reporting groups

Reporting group title	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)

Reporting group description:

Subjects received nifedipine GITS/candesartan cilexetil FDC (BAY98-7106) tablet orally, once daily in the morning of Visit 1 (Week 0) for 28 or 52 weeks. The starting dose (30/8 milligram [mg] or 30/16 mg) was determined based on local practice and clinical judgment by the investigator. Based on the experience of symptomatic and asymptomatic hypotension, peripheral edema or significant tolerability, the doses were up-titrated to the highest target dose (60/32 mg).

Subject analysis set title	Modified intention-to-treat analysis set (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT set (N=508) included all the subjects enrolled into the open-label treatment period and took at least one unit of the study medication.

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

SAF (N=508) was the same as the mITT analysis set which was defined as all the subjects enrolled into the open-label treatment period and took at least one unit of the study medication.

Primary: Number of Subjects With All Treatment-emergent Adverse Events (TEAEs) and Drug-related TEAEs up to Week 28

End point title	Number of Subjects With All Treatment-emergent Adverse Events (TEAEs) and Drug-related TEAEs up to Week 28[1]

End point description:

An adverse event (AE) is any untoward medical occurrence (that is, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. AEs were considered to be treatment-emergent if they had started or worsened after first application of study medication.

End point type	Primary

End point timeframe:

From the time of first study drug administration up to Week 28

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 performed.

End point values	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)			
Subject group type	Reporting group			
Number of subjects analysed	508[2]			
Units: Subjects				
All TEAEs	390			
Drug-related TEAEs	230			

Notes:

[2] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) of Special Interest up to Week 28

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) of Special Interest up to Week 28[3]

End point description:

An AE is any untoward medical occurrence (that is, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. AEs were considered to be treatment-emergent if they had started or worsened after first application of study medication. TEAEs of special interest included the incidence of symptomatic hypotension and the incidence and severity of vasodilatory adverse events (such as oedema, headache, and flushing). Only subjects who had TEAEs of special interest as mild, moderate or severe were reported.

End point type	Primary

End point timeframe:

From the time of first study drug administration up to Week 28

Notes:

[3] - 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 performed.

End point values	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)			
Subject group type	Reporting group			
Number of subjects analysed	508[4]			
Units: Subjects				
Oedema (mild)	124			
Oedema (moderate)	54			
Oedema (severe)	7			
Headache (mild)	31			
Headache (moderate)	15			
Flushing (mild)	3			
Symptomatic hypotension (mild)	4			

Notes:

[4] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With All Treatment-emergent Adverse Events (TEAEs) and Drug-related TEAEs up to Week 52/End of Study (EOS)

End point title	Number of Subjects With All Treatment-emergent Adverse Events (TEAEs) and Drug-related TEAEs up to Week 52/End of Study (EOS)[5]

End point description:

An AE is any untoward medical occurrence (that is, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. AEs were considered to be treatment-emergent if they had started or worsened after first application of study medication.

End point type	Primary

End point timeframe:

From the time of first study drug administration up to Week 52/EOS

Notes:

[5] - 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 performed.

End point values	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)			
Subject group type	Reporting group			
Number of subjects analysed	508[6]			
Units: Subjects				
All TEAEs	404			
Drug-related TEAEs	238			

Notes:

[6] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) of Special Interest up to Week 52/End of Study (EOS)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) of Special Interest up to Week 52/End of Study (EOS)[7]

End point description:

An AE is any untoward medical occurrence (that is, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. AEs were considered to be treatment-emergent if they had started or worsened after first application of study medication. TEAEs of special interest included the incidence of symptomatic hypotension and the incidence and severity of vasodilatory adverse events (such as oedema, headache, and flushing). Only subjects who had TEAEs of special interest as mild, moderate or severe were reported.

End point type	Primary

End point timeframe:

From the time of study treatment up to Week 52/EOS

Notes:

[7] - 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 performed.

End point values	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)			
Subject group type	Reporting group			
Number of subjects analysed	508[8]			
Units: Subjects				
Oedema (mild)	131			
Oedema (moderate)	56			
Oedema(severe)	7			
Headache (mild)	31			
Headache (moderate)	17			

Flushing (mild)	3			
Symptomatic hypotension (mild)	4			

Notes:

[8] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Relevant Changes in Laboratory Parameters

End point title	Number of Subjects With Clinically Relevant Changes in Laboratory Parameters

End point description:

Laboratory evaluations of blood and urine samples were performed, including hematology (hematocrit, hemoglobin, red blood cells count, white blood cells count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets), blood chemistry (sodium, potassium, chloride, bicarbonate, uric acid, total protein, albumin, calcium, blood urea nitrogen, creatinine, aspartate transaminase, alanine transaminase, lactate dehydrogenase, gamma glutamyl transferase, alkaline phosphatase, creatine kinase, total bilirubin, direct bilirubin, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, fasting glucose), urinalysis (pH, blood, specific gravity, glucose, protein, cells/sediment). A laboratory test abnormality considered clinically relevant, for example, causing withdrawal by subject, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, were reported as AEs.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52/EOS

End point values	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)			
Subject group type	Reporting group			
Number of subjects analysed	508[9]			
Units: Subjects	0			

Notes:

[9] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Mean Seated Systolic Blood Pressure (MSSBP) At Weeks 28 And 52

End point title	Change From Baseline In Mean Seated Systolic Blood Pressure (MSSBP) At Weeks 28 And 52

End point description:

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 28 and 52

End point values	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)			
Subject group type	Reporting group			
Number of subjects analysed	508[10]			
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline	170.7 (± 8.9)			
Change at Week 28	-30.4 (± 17.7)			
Change at Week 52	-30.1 (± 18.4)			

Notes:

[10] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Seated Diastolic Blood Pressure (MSDBP) at Weeks 28 and 52

End point title	Change From Baseline in Mean Seated Diastolic Blood Pressure (MSDBP) at Weeks 28 and 52

End point description:

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 28 and 52

End point values	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)			
Subject group type	Reporting group			
Number of subjects analysed	508[11]			
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline	95.6 (± 10.4)			
Change at Week 28	-12.7 (± 10.6)			
Change at Week 52	-12.8 (± 10.7)			

Notes:

[11] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Pressure Control Rate at Weeks 28 and 52

End point title	Blood Pressure Control Rate at Weeks 28 and 52

End point description:

Control rate was defined as the percentage of subjects that reached a predetermined blood pressure (BP) target of BP less than (<) 140/90 mmHg.

End point type	Secondary

End point timeframe:

Weeks 28 and 52

End point values	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)			
Subject group type	Reporting group			
Number of subjects analysed	508[12]			
Units: percentage of subjects				
number (not applicable)				
Week 28	51.4			
Week 52	51.6			

Notes:

[12] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Pressure Response Rate at Weeks 28 and 52

End point title	Blood Pressure Response Rate at Weeks 28 and 52

End point description:

Response rate was defined as the percentage of subjects who achieved a systolic blood pressure response (MSSBP of <140 mmHg or a reduction of MSSBP of more than (>) 20 mmHg from baseline value), or a diastolic blood pressure response (MSDBP of <90 mmHg or a reduction of MSDBP of >10 mmHg from baseline value).

End point type	Secondary

End point timeframe:

Weeks 28 and 52

End point values	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)			
Subject group type	Reporting group			
Number of subjects analysed	508[13]			
Units: percentage of subjects				
number (not applicable)				
Week 28	86.6			
Week 52	86.2			

Notes:

[13] - mITT

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs were collected from the time of first study drug administration up to 7 days after Week 52/EOS

Adverse event reporting additional description:

One death reported under SAE happened approximately 6 months after the subject had completed the study, not related to the treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)

Reporting group description:

Subjects received nifedipine GITS/candesartan cilexetil FDC (BAY98-7106) tablet orally, once daily in the morning of Visit 1 (Week 0) for 28 or 52 weeks. The starting dose (30/8 mg or 30/16 mg) was determined based on local practice and clinical judgment by the investigator. Based on the experience of symptomatic and asymptomatic hypotension, peripheral edema or significant tolerability, the doses were up-titrated to the highest target dose (60/32 mg).

Serious adverse events	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 508 (2.95%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Prostate cancer			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Aplastic anaemia			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Chronic sinusitis			
subjects affected / exposed	1 / 508 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Nifedipine GITS/Candesartan Cilexetil FDC (BAY98-7106)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	279 / 508 (54.92%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	47 / 508 (9.25%)		
occurrences (all)	55		
Headache			

subjects affected / exposed	47 / 508 (9.25%)		
occurrences (all)	60		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 508 (3.54%)		
occurrences (all)	20		
Oedema			
subjects affected / exposed	55 / 508 (10.83%)		
occurrences (all)	80		
Oedema peripheral			
subjects affected / exposed	150 / 508 (29.53%)		
occurrences (all)	239		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	27 / 508 (5.31%)		
occurrences (all)	30		
Upper respiratory tract infection			
subjects affected / exposed	25 / 508 (4.92%)		
occurrences (all)	29		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2013	This amendment was globally implemented to mainly address questions and comments from regulatory agencies at a scientific advice meeting. This amendment included the addition of blood pressure measurement, updates to the statistical analysis method, updates on pharmacokinetic analysis information, and several clarifications on the renal impairment and estimated glomerular filtration rate calculation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported