



## Clinical trial results:

**Multicentre, randomized, controlled open-label study over 24 weeks comparing metformin/vildagliptin + basal insulin versus metformin/sulphonylurea + basal insulin therapy in type 2 diabetes patients initiating insulin after a dual therapy by metformin/sulphonylurea**

### Summary

EudraCT number	2012-005183-94
Trial protocol	FR
Global end of trial date	23 February 2015

### Results information

Result version number	v1 (current)
This version publication date	09 July 2016
First version publication date	09 July 2016

### Trial information

#### Trial identification

Sponsor protocol code	CLAF237AFR07
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01871558
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH 4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 February 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to determine the proportion of patients presenting no episode of symptomatic hypoglycaemia during the 24 weeks of randomized treatment in each treatment arm (in association with basal insulin).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 June 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	France: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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	21
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Eligible patients were randomized in a 1:1 ratio between the vildagliptin arm (Vildagliptin 50 mg 2 tablets/day) + metformin and SU/or glinide arm + metformin (control treatment).

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Metformin/vildagliptin + Basal Insulin

Arm description:

Randomized patient will receive Vildagliptin 50 mg twice daily (b.i.d) + continued therapy with Metformin, + start of Basal Insulin up-titrated as per usual algorithms primarily based on FPG

Arm type	Experimental
Investigational medicinal product name	Vildagliptin
Investigational medicinal product code	LAF237
Other name	Galvus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg b.i.d

<b>Arm title</b>	SU+metformin + Basal Insulin
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Arm description:

Randomized patient will remain on their previous dual therapy by SU+metformin, which will be kept unchanged, + start of Basal Insulin up-titrated as per usual algorithms primarily based on FPG

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

Dosage and administration details:

SU+metformin + Basal Insulin

<b>Number of subjects in period 1</b>	<b>Metformin/vildagliptin + Basal Insulin</b>	<b>SU+metformin + Basal Insulin</b>
Started	21	21
Completed	18	19
Not completed	3	2
Consent withdrawn by subject	2	-
Other reason	-	1
antidiabetic drug prematurely stopped	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Metformin/vildagliptin + Basal Insulin
Reporting group description:	
Randomized patient will receive Vildagliptin 50 mg twice daily (b.i.d) + continued therapy with Metformin, + start of Basal Insulin up-titrated as per usual algorithms primarily based on FPG	
Reporting group title	SU+metformin + Basal Insulin
Reporting group description:	
Randomized patient will remain on their previous dual therapy by SU+metformin, which will be kept unchanged, + start of Basal Insulin up-titrated as per usual algorithms primarily based on FPG	

Reporting group values	Metformin/vildagliptin + Basal Insulin	SU+metformin + Basal Insulin	Total
Number of subjects	21	21	42
Age categorical			
Units: Subjects			
Adults (18-64 years)	12	9	21
From 65-84 years	9	12	21
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	60.6	66.8	
standard deviation	± 12.52	± 7.8	-
Gender, Male/Female			
Units: participants			
Female	10	8	18
Male	11	13	24

## End points

### End points reporting groups

Reporting group title	Metformin/vildagliptin + Basal Insulin
Reporting group description: Randomized patient will receive Vildagliptin 50 mg twice daily (b.i.d) + continued therapy with Metformin, + start of Basal Insulin up-titrated as per usual algorithms primarily based on FPG	
Reporting group title	SU+metformin + Basal Insulin
Reporting group description: Randomized patient will remain on their previous dual therapy by SU+metformin, which will be kept unchanged, + start of Basal Insulin up-titrated as per usual algorithms primarily based on FPG	

### Primary: Percentage of patients who reported at least one symptomatic hypoglycemic event during the 24 week randomized period in both treatment arms

End point title	Percentage of patients who reported at least one symptomatic hypoglycemic event during the 24 week randomized period in both treatment arms
End point description:	
End point type	Primary
End point timeframe: 24 weeks	

End point values	Metformin/vildagliptin + Basal Insulin	SU+metformin + Basal Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: percent of participants				
number (not applicable)	22.2	45		

### Statistical analyses

Statistical analysis title	Primary Stats
Comparison groups	Metformin/vildagliptin + Basal Insulin v SU+metformin + Basal Insulin
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.139
Method	Chi-squared

### Secondary: Percentage of patients reaching their glycemic target without

## hypoglycemic events

End point title	Percentage of patients reaching their glycemic target without hypoglycemic events
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End point description:

Glycemic target is defined as Glycated hemoglobin(HbA1c)  $\leq$  7%

End point type	Secondary
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End point timeframe:

24 weeks

End point values	Metformin/vildagliptin + Basal Insulin	SU+metformin + Basal Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: percent of participants				
number (not applicable)	44.4	47.4		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in HbA1c to week 24 in both treatment arms

End point title	Change from baseline in HbA1c to week 24 in both treatment arms
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Metformin/vildagliptin + Basal Insulin	SU+metformin + Basal Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: HbA1c percent				
arithmetic mean (standard deviation)				
baseline	8.2 ( $\pm$ 0.56)	8.2 ( $\pm$ 0.42)		
week 24	7.2 ( $\pm$ 0.71)	7.4 ( $\pm$ 0.89)		

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Change from baseline in body weight in both treatment arms**

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End point title	Change from baseline in body weight in both treatment arms
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Week 24

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End point values	Metformin/vildagliptin + Basal Insulin	SU+metformin + Basal Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: kg				
arithmetic mean (standard deviation)	-0.3 ( $\pm$ 2.51)	1.4 ( $\pm$ 2.61)		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Mean daily insulin dose at Week 24**

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End point title	Mean daily insulin dose at Week 24
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End point description:

End point type	Secondary
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End point timeframe:

Week 24

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End point values	Metformin/vildagliptin + Basal Insulin	SU+metformin + Basal Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: (U/d)				
arithmetic mean (standard deviation)	33 ( $\pm$ 23.08)	19.8 ( $\pm$ 13.83)		

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**Statistical analyses**

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No statistical analyses for this end point



**Secondary: Percentage of patients with severe and confirmed hypoglycemic events**

End point title	Percentage of patients with severe and confirmed hypoglycemic events
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End point description:

Severe hypoglycemic events (and number of events) , defined as events requiring assistance of a third party, and with confirmed hypoglycemic events (and number of events) defined as events with concomitant self monitoring of blood glucose (SMBG) < 70 mg/dL

End point type	Secondary
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End point timeframe:

24 weeks

End point values	Metformin/vildagliptin + Basal Insulin	SU+metformin + Basal Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percent participants				
number (not applicable)	0	0		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: percent of participants that reach therapeutic goal (HbA1c ≤ 7%) at Week 24 without any hypoglycaemic episode (symptomatic or not) and without any weight gain (variation ≥3% compared to baseline)**

End point title	percent of participants that reach therapeutic goal (HbA1c ≤ 7%) at Week 24 without any hypoglycaemic episode (symptomatic or not) and without any weight gain (variation ≥3% compared to baseline)
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End point description:

HbA1c ≤ 7% without any hypoglycaemic episode (symptomatic or not) and without any weight gain

End point type	Secondary
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End point timeframe:

week 24

End point values	Metformin/vildagliptin + Basal Insulin	SU+metformin + Basal Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: percent of participants				
number (not applicable)	27.8	21.1		

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	Metformin/vildagliptin + Basal Insulin
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Reporting group description:

Randomized patient will receive Vildagliptin 50 mg twice daily (b.i.d) + continued therapy with Metformin, + start of Basal Insulin up-titrated as per usual algorithms primarily based on FPG

Reporting group title	SU+metformin + Basal Insulin
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Reporting group description:

Randomized patient will remain on their previous dual therapy by SU+metformin, which will be kept unchanged, + start of Basal Insulin up-titrated as per usual algorithms primarily based on FPG

Serious adverse events	Metformin/vildagliptin + Basal Insulin	SU+metformin + Basal Insulin	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Metformin/vildagliptin + Basal Insulin	SU+metformin + Basal Insulin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 21 (19.05%)	10 / 21 (47.62%)	
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 21 (4.76%) 1	
Surgical and medical procedures Cataract operation subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 21 (4.76%) 1	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)  Parkinson's disease subjects affected / exposed occurrences (all)  Sciatica subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0  0 / 21 (0.00%) 0  0 / 21 (0.00%) 0  0 / 21 (0.00%) 0	1 / 21 (4.76%) 1  1 / 21 (4.76%) 1  1 / 21 (4.76%) 1  1 / 21 (4.76%) 1	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)  Injection site pain subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0  0 / 21 (0.00%) 0	1 / 21 (4.76%) 1  1 / 21 (4.76%) 1	
Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all)  Visual impairment subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0  0 / 21 (0.00%) 0	1 / 21 (4.76%) 1  1 / 21 (4.76%) 1	
Gastrointestinal disorders			

Dyspepsia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	2 / 21 (9.52%) 2	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 21 (4.76%) 1	
Renal and urinary disorders Renal colic subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	0 / 21 (0.00%) 0	
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 21 (4.76%) 1	
Infections and infestations Tooth abscess subjects affected / exposed occurrences (all)  Urinary tract infection subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1  1 / 21 (4.76%) 1	0 / 21 (0.00%) 0  1 / 21 (4.76%) 1	
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 21 (4.76%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2013	The time required for the dual therapy by metformin + SU (or glinides) before enrolling
13 June 2014	This statistical amendment aimed in turning the ADDONIS study into an exploratory pilot

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported