Clinical trial results:
Post-marketing study of Amaryl ® (Glimepiride) in patients with type 2 diabetes to investigate pediatric and adult population pharmacokinetics [multicenter, non-comparative, 12-28 weeks, non-blind titration (0.5-6 mg/day) study].

Summary

EudraCT number	2014-004643-12
Trial protocol	Outside EU/EEA
Global end of trial date	13 May 2008

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	18 July 2015

Trial information

Trial identification

Sponsor protocol code	POP6739

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sanofi-aventis K.K.
Sponsor organisation address	Tokyo Opera City Tower, 3-20-2, Nishi Shinjuku, Shinjuku-ku, Tokyo, Japan, 163-1488
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 August 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 May 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the pharmacokinetics of Amaryl® in pediatric subjects (8 to 16 years of age) with type 2 diabetes in comparison with adults subjects (17 years or older of age) with type 2 diabetes under steady state

Protection of trial subjects:

For paediatric subjects, the parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. For the population with pharmacokinetic analysis a minimum number of blood sampling was performed. A topical anesthesia may have been used to minimize distress and discomfort.
Adult subjects: Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	19 July 2006
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	Japan: 141
Worldwide total number of subjects	141
EEA total number of subjects	0

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)	4
Adolescents (12-17 years)	33
Adults (18-64 years)	61
From 65 to 84 years	42
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 34 sites in Japan. A total of 142 subjects were enrolled between 19 July 2006 and 07 November 2007.

Pre-assignment

Screening details:

Of 142 enrolled subjects, 141 subjects were treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Amaryl - Pediatric

Arm description:

Amaryl in children (8-16 years) for 12-28 weeks.

Arm type	Experimental
Investigational medicinal product name	Glimepiride
Investigational medicinal product code	HOE490
Other name	Amaryl ®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.5 or 1 mg/day (once daily, before or after meal in morning) or 2 to 6 mg/day (once or twice daily, before or after meal in morning or morning and evening).

Arm title	Amaryl - Adult

Arm description:

Amaryl in adults (years >= 17) for 12-28 weeks.

Arm type	Experimental
Investigational medicinal product name	Glimepiride
Investigational medicinal product code	HOE490
Other name	Amaryl ®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.5 or 1 mg/day (once daily, before or after meal in morning) or 2 to 6 mg/day (once or twice daily, before or after meal in morning or morning and evening).

Number of subjects in period 1	Amaryl - Pediatric	Amaryl - Adult
Started	35	106
Completed	32	105
Not completed	3	1
Poor treatment compliance	1	-
Subjects did not Wish to Continue	2	-
Adverse event	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Amaryl - Pediatric
Reporting group description:	
Amaryl in children (8-16 years) for 12-28 weeks.	
Reporting group title	Amaryl - Adult
Reporting group description:	
Amaryl in adults (years >= 17) for 12-28 weeks.	

Reporting group values	Amaryl - Pediatric	Amaryl - Adult	Total
Number of subjects	35	106	141
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	13.4	62.1	
standard deviation	± 1.8	± 12.4	-
Gender categorical Units: Subjects			
Female	17	40	57
Male	18	66	84

End points

End points reporting groups

Reporting group title	Amaryl - Pediatric
Reporting group description:	
Amaryl in children (8-16 years) for 12-28 weeks.	
Reporting group title	Amaryl - Adult
Reporting group description:	
Amaryl in adults (years >= 17) for 12-28 weeks.	

Primary: Apparent Clearance (CL/F)

End point title	Apparent Clearance (CL/F)[1]

End point description:

Apparent clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. Full analysis set/pharmacokinetic (FAS/PK) included all subjects (excluding 4 subjects in pediatric arm and 2 subjects in adult arm of the enrolled subjects) for whom pharmacokinetic parameters were analysed.

End point type	Primary

End point timeframe:

Visit 8 (or one of Visit 2-7) - up to 28 weeks

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: This is a population PK analysis - Statistical analysis results are the estimates obtained from the one-compartment model as are provided in below table

End point values	Amaryl - Pediatric	Amaryl - Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	105		
Units: L/h				
arithmetic mean (standard deviation)	1.79 (± 0.77)	1.64 (± 0.59)		

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Volume of Distribution (Vss /F)

End point title	Apparent Volume of Distribution (Vss /F)[2]

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a study drug. Analysis was performed on FAS/PK population.

End point type	Primary

End point timeframe:

Visit 8 (or one of Visit 2-7) - up to 28 weeks

Notes:

[2] - 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: This is a population PK analysis - Statistical analysis results are the estimates obtained from the one-compartment model as are provided in below table

End point values	Amaryl - Pediatric	Amaryl - Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	105		
Units: litre(s)				
arithmetic mean (standard deviation)	6.84 (± 0.09)	6.83 (± 0.11)		

Statistical analyses

No statistical analyses for this end point

Primary: Half-Life (t1/2)

End point title	Half-Life (t1/2)[3]

End point description:

Half-life is the time measured for the plasma concentration of the drug to decrease by one half. Analysis was performed on FAS/PK population.

End point type	Primary

End point timeframe:

Visit 8 (or one of Visit 2-7) - up to 28 weeks

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: This is a population PK analysis - Statistical analysis results are the estimates obtained from the one-compartment model as are provided in below table

End point values	Amaryl - Pediatric	Amaryl - Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	105		
Units: hours				
arithmetic mean (standard deviation)	3.15 (± 1.38)	3.3 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Hemoglobin A1C (HbA1C) at Endpoints

End point title	Change from Baseline in Hemoglobin A1C (HbA1C) at Endpoints

End point description:

Intent-to-treat (ITT) population included all treated subjects.

End point type	Secondary

End point timeframe:

(Visit 1 -8) - from baseline up to last observation max of 28 weeks

End point values	Amaryl - Pediatric	Amaryl - Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	106		
Units: percentage of Hb				
arithmetic mean (standard deviation)				
Baseline (n= 35, 105)	8.26 (± 1.98)	8.7 (± 1.37)		
Endpoint (n= 35, 106)	7.85 (± 2.04)	7.18 (± 0.85)		
Change from baseline (n= 35, 105)	-0.41 (± 1.9)	-1.5 (± 1.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting plasma glucose (FPG) at Endpoints

End point title	Change from Baseline in Fasting plasma glucose (FPG) at Endpoints

End point description:

Analysis was peformed on ITT population.

End point type	Secondary

End point timeframe:

(Visit 1 -8) - from baseline up to last observation max of 28 weeks

End point values	Amaryl - Pediatric	Amaryl - Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	106		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline	159.6 (± 64)	166.7 (± 37.2)		
Endpoint	155.9 (± 61.3)	134.7 (± 22.6)		
Change from baseline	-3.7 (± 60.6)	-32 (± 34.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Blood Glucose by Self-monitoring of Blood Glucose (SMBG) at Endpoints

End point title	Change from Baseline in Fasting Blood Glucose by Self-monitoring of Blood Glucose (SMBG) at Endpoints

End point description:

Analysis was perfomed on ITT population.

End point type	Secondary

End point timeframe:

(Visit 1 -8) - from baseline up to last observation max of 28 weeks

End point values	Amaryl - Pediatric	Amaryl - Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	106		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline (n= 24, 63)	158.9 (± 69)	156.9 (± 44.4)		
Endpoint (n= 26, 64)	140.8 (± 50)	123.8 (± 26.9)		
Change from baseline (n= 24, 63)	-18.4 (± 70.5)	-32.8 (± 44.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 12-28) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (the time between first and the last administration of the investigational product).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Amaryl - Pediatric

Reporting group description:

Amaryl in children (8-16 years) for 12-28 weeks.

Reporting group title	Amaryl - Adult

Reporting group description:

Amaryl in adult (years >= 17) for 12-28 weeks.

Serious adverse events	Amaryl - Pediatric	Amaryl - Adult	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 35 (2.86%)	0 / 106 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Psychiatric disorders			
Mental Disorder			
subjects affected / exposed	1 / 35 (2.86%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Amaryl - Pediatric	Amaryl - Adult	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 35 (62.86%)	39 / 106 (36.79%)	
Investigations			
Blood Creatine Phosphokinase Increased			

subjects affected / exposed	3 / 35 (8.57%)	1 / 106 (0.94%)	
occurrences (all)	3	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 35 (8.57%)	0 / 106 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 35 (5.71%)	0 / 106 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	2 / 35 (5.71%)	0 / 106 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Rhinitis Allergic			
subjects affected / exposed	3 / 35 (8.57%)	1 / 106 (0.94%)	
occurrences (all)	3	1	
Upper Respiratory Tract Inflammation			
subjects affected / exposed	6 / 35 (17.14%)	5 / 106 (4.72%)	
occurrences (all)	6	5	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	2 / 35 (5.71%)	4 / 106 (3.77%)	
occurrences (all)	2	4	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	3 / 35 (8.57%)	0 / 106 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 35 (8.57%)	13 / 106 (12.26%)	
occurrences (all)	4	17	
Influenza			
subjects affected / exposed	2 / 35 (5.71%)	1 / 106 (0.94%)	
occurrences (all)	2	1	
Metabolism and nutrition disorders			

Hypoglycaemia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	20 / 106 (18.87%) 60	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2007	In this amendment the number of sites (35 sites) was changed to approximately 50 sites.
10 August 2007	Concomitant drugs with precaution to potentiate the hyperglycemic action was changed (that is Ciprofloxacin and Levofloxacin were added) due to amendment of the package insert.
24 August 2007	Minor administrative changes were made due to the changes on the administrative structure.
10 April 2008	Minor administrative changes and editorial changes were made due to the changes on the administrative structure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported