These results are supplied for informational purposes only. *Prescribing decisions should be made based on the approved package insert in the country of prescription*

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00633425
		Study Code:	HOE490B_4001
Generic drug name:	glimepiride	**Date:**	21 March 2008

Title of the study:	Continuous glucose monitoring in type 2 diabetics inadequately controlled by metformin: analysis of the glucose profile before and after the addition of Glimepiride. HOE 490B_4001		
Investigator(s):	Prof. Bernard Bauduceau Hôpital BEGIN 69 avenue de Paris 94160 ST MANDE FRANCE		
Study centre(s):	National multicentre study (19 centres)		
Publications (reference):			
Study period: Date first patient enrolled: 29 Oct. 2002 Date last patient completed: 21 Oct. 2003		**Phase of development:** IV	
Objectives:	Analyse the glucose profile, based on continuous glucose monitoring by CGMS, in type 2 diabetics inadequately controlled by metformin, before and after the addition of Glimepiride.		
Methodology:	Exploratory, multicentre, open-label, prospective, one-arm study. The study comprises 3 phases: Observation phase (2 weeks), Titration phase (from 1 to 5 weeks), and Maintenance phase (12 weeks). Continuous glucose monitoring by CGMS during the observation and maintenance phases.		
Number of patients:	Planned: 50	Screened: 43	Treated: 32 (74.4%)
Evaluated:	Efficacy: 30 (69.8%) FAS	Safety: tolerability for CGMS: 32 tolerability for the treatment: 32	Pharmacokinetics: 30
Diagnosis and criteria for inclusion:	Men or women aged 35 to 70 years, having given their consent, type 2 diabetics (HBA1c > 6.5%, fasting glycaemia $\geq$ 1.40 g/l) not controlled by Metformin for at least 6 weeks.		

Investigational product: Dose: Administration:	**Glimepiride** The daily dose of Glimepiride was comprised between 1 and 6 mg. Once daily in the morning before or during breakfast	
Duration of treatment: Titration phase (from 1 to 5 weeks), Maintenance phase (12 weeks).		**Duration of observation:** Observation phase (2 weeks), Titration phase (from 1 to 5 weeks), Maintenance phase (12 weeks).
Reference therapy: Dose: Administration:	Metformin hydrochloride For the FAS, all visits combined, the daily metformin dose was comprised between 1700 and 3000 mg 2 to 3 doses per day during or after meals	
Criteria for evaluation:		
Efficacy: and Pharmacodynamics:	**The main efficacy endpoint** is the change in interstitial glucose levels between the observation and maintenance phases: the mean of 24 variations in average hourly glucose readings recorded by CGMS. **Secondary outcome measures**: • Mean interstitial glucose levels during the observation and maintenance phases defined as the mean, per phase, of 24 average hourly glucose readings recorded by CGMS. • Mean nocturnal interstitial glucose levels and change between the observation and maintenance phases, defined as the mean of 7 variations in average hourly nocturnal glucose readings recorded by CGMS between the hours of 11 pm and 6 am. • Daytime interstitial glucose levels and change between the observation and maintenance phases, defined as the mean of 17 variations in average hourly diurnal glucose readings recorded by CGMS between the hours of 6 am and 11 pm. • Area under the curve of glucose readings above 140 mg/dL, recorded by CGMS during the observation and maintenance phases, and change between the two phases. • The excursion time of CGMS interstitial glucose readings above 140 mg/dL, in hours, during the observation and maintenance phases, and change between the two phases. • The monitoring time, in hours, of interstitial glucose and the number of 24-hour glycaemic cycles recorded. • HbA1c and fasting blood glucose levels measured in the observation and maintenance phases, and change between the two phases. **Exploratory outcome measures:** • Glucose levels measured 2 hours (120 minutes) before each meal (breakfast, lunch, dinner) during the first 24 hours, during the observation and maintenance phases, and their change between the two phases; glucose levels measured 2 hours after each meal during the first 24 hours, during the observation and maintenance phases, and their change between the two phases. • Intra-patient variability of interstitial glucose during each of the two phases and change between the two phases. • Instability of mean hourly interstitial glucose levels for recordings between 1 h and 25 h and between 25 h and 49 h after insertion of the CGMS, during the observation and maintenance phases, and change between the two phases.	

Safety:	Tolerability TOLERABILITY RELATED TO THE DIABETE CLINICAL TOLERABILITY BIOLOGICAL TOLERABILITY
Statistical methods:	The main analysis will be the determination of the two-sided 95% confidence interval for the main endpoint. Statistical analyses were performed by Atlanstat using SAS® release 8.2. ANALYTICAL VARIABLES: • INCLUSION VARIABLES o Demographics o Diabetes history • Study monitoring: o Number of patients per population o Final status and reason for early withdrawals, during each phase o Total study duration (days) and duration per phase o Daily dose of Glimepiride (mg) o Daily dosage of metformin (mg) actually taken at each dose o Protocol violations o Previous and/or concomitant treatments, coded according to table WHO DRL 88 • Efficacy – main endpoint • Efficacy – secondary endpoints • Efficacy – exploratory endpoints • Safety

<table>
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<td>Summary:</td>
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For the 24 hour recordings, interstitial glucose levels significantly decreased between the observation and maintenance phases

Table: Means and mean variations in interstitial glucose (mg/dL)
<table>
<tr><th></th><th>Observation phase</th><th>Maintenance phase</th><th>Mean variation</th></tr>
<tr><td>N</td><td>30</td><td>30</td><td>30</td></tr>
<tr><td>Mean</td><td>170.6</td><td>128.0</td><td>-42.6</td></tr>
<tr><td>SD</td><td>35.69</td><td>33.96</td><td>33.35</td></tr>
<tr><td>95% CI</td><td>[157.2–183.9]</td><td>[115.3–140.7]</td><td>[-55.0 – -30.1] *</td></tr>
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* p<0.0001
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<tr>
<td>Efficacy results:
and
Pharmacodynamic results:</td>
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Interstitial glucose levels significantly decreased between the observation and maintenance phases for the hourly nocturnal readings.
Interstitial glucose readings significantly decreased between the observation and maintenance phases for the hourly daytime readings.
The mean hourly variation of the area under the curve located above 140 mg/dL significantly decreased between the observation and maintenance phases. The excursion time in hours for interstitial glucose readings above 140 mg/dL was 16.31 hours (SD=7.368) in the observation phase and 7.38 hours (SD=6.205) in the maintenance phase. The confidence interval of the mean variation between these two phases is [-11.80 – -6.06]. The excursion time therefore significantly decreased between the two phases.
Intra-patient variability significantly decreased between the observation and maintenance phases.
Mean variation in interstitial glucose calculated for glucose readings before and after each meal (one hour before, two hours before and three hours before and two hours after in each case). In each case, for these two time points and for each meal, the mean variations decreased between the observation and maintenance phases.
Analysis of the instability of the hourly averages showed no significant difference between the observation and maintenance phases.
HbA1c levels significantly decreased between the observation and maintenance phases to a mean level < 7%. During the observation phase, 27 patients (93.1%) had HbA1c ≥ 7%, and among these 27 patients, 16 (59.3%) had a level < 7% during the maintenance phase. During the observation phase, 2 patients had HbA1c < 7% and stayed that way during the maintenance phase. A total of 62.1% of patients therefore had HbA1c < 7% during the maintenance phase.
Fasting blood glucose significantly decreased between the observation and maintenance phases.

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Safety results:	• Tolerability related to the diabete: Six patients (18.8%) had symptomatic hypoglycaemia during the study but none of these cases was severe and none was nocturnal. Four patients (13.3%) had at least one interstitial glucose < 60 mg/dL during the observation phase and 11 (36.7%) during the maintenance phase. Two patients (6.7%) had at least one interstitial glucose < 50 mg/dL in the observation phase and 7 (23.3%) in the maintenance phase. • Adverse events (non-CGMS): Nine patients (28.1%) had at least one adverse event including 6 hypoglycaemia, 2 diarrhoea and 2 infections. Five patients (15.6%) had at least one adverse event possibly related to the treatment: 5 hypoglycaemia and 1 diarrhoea. One patient (3.1%) had an adverse event leading to withdrawal of treatment (hypoglycaemia) which was possibly related to the treatment. This AE was serious and medically important. • Adverse events related to CGMS: Three patients (9.4%) had an adverse event related to CGMS including 2 insertion site reactions and 1 skin allergy. These 3 AE were considered to be related to the device, did not result in withdrawal of the sensor, and were not serious.
Date of report:	18 May 2004