This Summary of Clinical Study Report is provided for patients and healthcare professionals to demonstrate the transparency efforts of the Menarini Group. This document is not intended to replace the advice of a healthcare professional and can't be considered as a recommendation. Patients must always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document can not be considered as prescribing advice.

The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

2. Synopsis

Clinical Study Report Synopsis: Study Guid/05/Met-GDM/001

Title of Study: Assessment of effects of a 12-month treatment with Metformin on insulin action and secretion in women with prior gestational diabetes mellitus (GDM)	
Investigator(s): This multicentre/study included 11 principal investigators	
Study Centre(s): This study was conducted at 11 study centres in Italy	
Publication(s) Based on the Study: None at this time	
Length of Study: 34 months Date first subject enrolled: 13 November 2006 Date last subject completed: 04 September 2009	**Phase of Development:** III
Objectives: The primary objective of the study was to assess the effects of a 12-month treatment with Metformin on insulin action and secretion in women with prior GDM and impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). Whole body insulin sensitivity index (ISI-Matsuda) at endpoint was the primary efficacy variable of the study. The secondary objective of the study was to assess the effects of Metformin on HOMA-Index, beta-index, fasting plasma glucose (FPG), glucose tolerance, HbA_{1c}, physio-pathologic (phenotype) and immunologic features associated with previous GDM and with its outcome.	
Study Design: This was a double blind, multicentre, randomised, placebo-controlled, parallel group study design. Seven visits at the clinic were scheduled: visit 1 (study entry, follow-up in post-partum from 10 to 36 months after delivery), visit 2 (baseline and start of the treatment phase, once the results of the laboratory tests are available), visit 3 (after 3 months of test treatment), visit 4 (after 6 months of test treatment), visit 5 (after 9 months of test treatment), visit 6 (final visit after 12 months of test treatment) and visit 7 (follow-up for safety 1 month after the end of the treatment phase). A maximum 7-day window was allowed for the scheduled days of visits 3-7.	
Number of Subjects: Planned: 96; Randomized: 38; Completed: 32	
Diagnosis and Main Criteria for Inclusion: Female subjects aged ≥ 18 and ≤ 45 years; Caucasian race; history of prior GDM during pregnancy; altered Glucose Regulation (IFG or IGT) confirmed at the first post-partum follow-up; female of childbearing potential had to use effective contraceptive measures for at least 1 month prior to the entry into the study and should have continued to use the same contraceptive method during the overall study period; written informed consent obtained.	
Test Product, Dose, and Mode of Administration: Metformin hydrochloride film coated tablets 850 mg (Metformin hydrochloride 500 mg for the first 15 days of treatment), one tablet twice daily, soon after the mail meals (lunch and dinner).	
Duration of Treatment: 12 months	
Reference Therapy, Dose, and Mode of Administration: Placebo coated tablets, one tablet twice daily, soon after the mail meals (lunch and dinner).	
Variables: **<u>Efficacy</u>:** Whole body insulin sensitivity index (ISI) was the primary variable of the study. The secondary efficacy variables of the study were: • Glucidic parameters: FPG, HbA_{1c}, insulin, C-peptide on fasting and after oral glucose tolerance test (OGTT); homeostasis model assessment (HOMA index); • Lipid parameters: triglycerides, total cholesterol, LDL-cholesterol, HDL cholesterol; • Markers: high sensitivity C-reactive protein, homocysteine, adiponectine; • Although not scheduled in the study protocol, the oral glucose insulin sensitivity (OGIS) index was also calculated.	

Safety:

The safety variables of the study were:

- Adverse events (AEs) and adverse drug reactions (ADRs);
- Vital signs (heart rate and blood pressure);
- Laboratory tests (routine haematology and blood chemistry). Routine haematology included assessment of red blood cells (RBCs), haemoglobin (Hb), haematocrit (Hct), white blood cells (WBCs) with formula, platelets. Routine blood chemistry included assessment of creatinine, blood urea nitrogen (BUN), AST, ALT, γ-GT and electrolytes (sodium, potassium, chloride).

Methods:

Statistical:

The following populations were considered for data analysis:

- Intent-to-treat population (ITT), which included all randomised subjects who received at least one dose of study medication and with post-baseline efficacy data. The efficacy analysis was performed in this population.
- Safety population, which included all randomized subjects who took at least one dose of study medication. The safety analysis was performed in this population.

The primary efficacy variable (ISI-Matsuda) was analysed within treatment by calculating the 95% confidence interval (CI) for the mean change from baseline to the final visit after 12 months of treatment. The comparison between groups of primary efficacy variable was performed by using an ANOVA model. Variables measured at each clinic visit (e.g. FPG, HbA_{1c} or lipid parameters) were analysed within treatment by calculating the 95% CI for the mean change from baseline at any time point (when measured).

Adverse Events were coded using MedDRA dictionary, version 11.0. The System Organ Class (SOC) and Preferred Term (PT) were used for tabulation. The number and percentage of subjects experiencing adverse event, adverse drug reactions, serious adverse events and AEs leading to withdrawal were summarized within each group and overall. All AE data were presented in the data listings. Vital signs (heart rate and blood pressure) were summarized at each visit within both groups using descriptive statistics. Laboratory parameters were listed by subject and treatment group.

Summary:

Subject disposition:

Due to the insufficient enrolment rate, the sponsor decided to terminate the enrolment before the target was reached. A total of 38 subjects were randomised: 18 were included in the Metformin group and 20 in the Placebo group. A total of 6 subjects (15.8% of randomised) discontinued prematurely from the study: 3 subjects (16.7%) in the Metformin group and 3 (15%) in the Placebo group.

Efficacy results:

ISI-Matsuda:

A small non-significant increase from baseline to month 12 was observed in the Metformin group, compared to a small non-significant decrease in the Placebo group. The mean changes from baseline to month 12 were 1.61 ± 2.98 (95% CI: -0.52 to 3.74) in the Metformin group and -1.04 ± 3.81 (95% CI: -3.60 to 1.52) in the Placebo group. The comparison between groups in the ANOVA model did not show statistically significant differences ($p = 0.733$).

OGIS index:

A non-significant increase from baseline to month 12 was observed in the Metformin group, compared to no substantial changes in the Placebo group. The mean changes from baseline to month 12 were 48.4 ± 88.6 (95% CI: -19.7 to 11.5) in the Metformin group and -6.06 ± 87.0 (95% CI: -68.3 to 56.1) in the Placebo group. The comparison between groups in the ANOVA model did not show statistically significant differences ($p = 0.124$).

HOMA index:

The mean HOMA index decreased from baseline to month 12 in a non-statistically significant extent in the Metformin group, compared to a small and non significant increase in the Placebo group. The mean changes from baseline to month 12 were -0.47 ± 1.62 (95% CI: -1.63 to 0.69) in the Metformin group and 0.22 ± 0.68 (95% CI: -0.23 to 0.68) in the placebo group.

FPG:

Mean FPG concentration slightly decreased from baseline to any post-baseline time point in the Metformin group (in a non-statistically significant extent), compared to a small increase from baseline to any post-baseline time point (which was significant at month 9) in the placebo group. The mean changes from baseline to month 12 were -1.47 ± 12.1 mg/dL (95% CI: -8.2 to 5.2) in the Metformin group and 3.06 ± 12.7 mg/dL (95% CI: -3.7 to 9.8) in the placebo group.

HbA1c:

Mean HbA1c levels slightly decreased from baseline to month 6 and month 12 in the Metformin group (in a non-statistically significant extent), compared to a small non significant increase from baseline to month 6 and month 12 in the placebo group. The mean changes from baseline to month 12 were -0.09 ± 0.27 % (95% CI: -0.24 to 0.07) and 0.28 ± 0.64 % (95% CI: -0.06 to 0.62) in the placebo group.

Lipid parameters:

The results of lipid parameters did not show substantial changes from baseline up to month 12 in both the Metformin and the placebo group in mean levels of total cholesterol, HDL- and LDL-cholesterol, while mean triglycerides levels increased from baseline to any time point in the Metformin group, compared to decreases from baseline in the placebo group. The mean changes of triglycerides levels from baseline to month 12 were 7.6 ± 38.7 mg/dL (95% CI: -13.8 to 29.0) in the Metformin group and -36.1 ± 39.4 mg/dL (95% CI: -56.4 to -15.9) in the placebo group.

Markers:

There were no substantial differences between Metformin and placebo in changes from baseline to month 12 of adiponectine (non-significant increase in both groups) and C-reactive protein (non-significant decrease in both groups), while the increase from baseline to month 12 of mean homocysteine levels was statistically significant only in the Metformin group.

Safety results:

Adverse events:

The total number of adverse events reported was 9 in the Metformin group and 7 in the Placebo group, and were reported in 5 (31.3%) and 5 (26.3%) subjects, respectively in the two groups.

The most frequent adverse events were '*diarrhoea*' (2 subjects [12.5%] in the Metformin group) and '*influenza*' (2 subjects [12.5%] in the Metformin group). None of the other adverse events was reported in more than one subject in either group. The total number of drug-related adverse events recorded was 2, both in the Metformin group. They were reported in 2 subjects (12.5%), and both consisted of diarrhoea. One serious adverse event occurred in one subject in the Metformin group. The event consisted of '*cholelithiasis*' and was reported by subject 08002. This event was of severe intensity and was considered as not related with study drug.

Vital signs:

In both treatment groups, there were no important changes in mean values of systolic and diastolic blood pressure, and heart rate, from baseline to any time point.

Conclusions:

- Due to the premature study interruption because of insufficient enrolment rate, the number of evaluable subjects was lower than scheduled. Therefore, no definitive conclusions can be drawn from the results of this study;
- Despite the small sample size, the one-year treatment with Metformin of women with prior GDM and impaired glucose tolerance or impaired fasting glucose was associated with a small non-significant increase from baseline in primary variable ISI-Matsuda. This effect was confirmed by the results of OGIS index and HOMA index;
- Treatment with Metformin was associated with a decrease from baseline of FPG and HbA1c levels.
- Metformin given at conventional doses was well tolerated with no unexpected safety concerns;
- Although inconclusive, the promising results of this study may warrant further investigation.