Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-008494-59	
Name of active ingredient: Linagliptin (BI 1356) + metformin (free combination)		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 10 NOV 2011	**Trial No. / U No.:** 1218.52 / U11-1782-01	**Dates of trial:** 30 JUN 2009 - 16 JUN 2011	**Date of revision:** Not applicable

Title of trial:	A Phase III randomised, double-blind parallel group extension study to investigate the safety and efficacy of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg versus monotherapy with metformin 1000 mg twice daily over 54 weeks in type 2 diabetic patients previously completing the double-blind part of study 1218.46
Coordinating Investigator:	[redacted]
Trial sites:	Multinational trial conducted in 101 centres in 14 countries worldwide (Canada, Croatia, Estonia, France, Germany, India, Lithuania, Mexico, Netherlands, Romania, Russia, Sweden, Tunisia, and Ukraine)
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The objective was to investigate the safety and efficacy of linagliptin (2.5 mg) plus metformin (500 mg or 1000 mg) twice daily (b.i.d.) versus monotherapy with metformin 1000 mg b.i.d. given for 54 weeks (lina 2.5 + met 500, lina 2.5 + met 1000, and met 1000 respectively). The met 1000 treatment group was added in an amendment to the protocol.
Methodology:	This was a multicentre, randomised, double-blind, parallel-group extension study. A 54-week double-blind treatment period was followed by a 1-week follow-up period. The treatment period comprised a 2-week titration period followed by 52 weeks of treatment. Patients randomised to lina 2.5 + met 500, lina 2.5 + met 1000, or met 1000 in the preceding trial, 1218.46, were to continue the same trial medication in this extension trial. Patients randomised to 500 mg metformin b.i.d., linagliptin 5 mg q.d., or placebo in trial 1218.46 were to be randomised to one of the 3 treatment groups in this extension trial.

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Name of finished product: Not applicable		**EudraCT No.:** 2008-008494-59	
Name of active ingredient: Linagliptin (BI 1356) + metformin (free combination)		**Page:** 2 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 10 NOV 2011	**Trial No. / U No.:** 1218.52 / U11-1782-01	**Dates of trial:** 30 JUN 2009 - 16 JUN 2011	**Date of revision:** Not applicable

No. of subjects:	
planned:	entered: 700
actual:	enrolled: 567 Treatment Linagliptin 2.5 mg + metformin 500 mg b.i.d. (lina 2.5 + met 500): entered: 225 treated: 225 analysed: 225 Treatment Linagliptin 2.5 mg + metformin 1000 mg b.i.d. (lina 2.5 + met 1000): entered: 171 treated: 171 analysed: 171 Treatment Metformin 1000 mg b.i.d. (met 1000): entered: 171 treated: 170 analysed: 170 Note: no primary efficacy endpoint was defined for this study. Instead, safety and efficacy were assessed through descriptive analyses.
Diagnosis and main criteria for inclusion:	Patients with type 2 diabetes mellitus (T2DM) who had completed trial 1218.46 and were not being treated with rescue medication, who signed informed consent, were eligible to participate in this extension trial.
Test product:	Free combination of linagliptin + metformin, tablets (lina 2.5 + met 500 and lina 2.5 + met 1000)
dose:	Linagliptin 2.5 mg + metformin 500 mg twice daily (lina 2.5 + met 500) or Linagliptin 2.5 mg + metformin 1000 mg twice daily (lina 2.5 + met 1000) Patients randomised to lina 2.5 + met 1000 who had not previously been treated with a dose of 1000 mg metformin in trial 1218.46 were treated with a lower dose of metformin (i.e. linagliptin 2.5 mg + metformin 500 mg twice daily) for the first 2 weeks of the treatment period.
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6

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Name of finished product: Not applicable		**EudraCT No.:** 2008-008494-59	
Name of active ingredient: Linagliptin (BI 1356) + metformin (free combination)		**Page:** 3 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 10 NOV 2011	**Trial No. / U No.:** 1218.52 / U11-1782-01	**Dates of trial:** 30 JUN 2009 - 16 JUN 2011	**Date of revision:** Not applicable

Reference therapy:	Metformin (met 1000), tablets
dose:	1000 mg twice daily Patients who had not previously been treated with metformin 1000 mg in trial 1218.46 were treated for the first 2 weeks with a lower dose of metformin (i.e. 500 mg twice daily).
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6
Duration of treatment:	54 weeks, comprising a 2-week titration period followed by 52 weeks of treatment and, thereafter, a 1-week follow-up period.
Criteria for evaluation:	
Efficacy:	There was no primary endpoint in a statistical sense in this study. All efficacy endpoints were secondary or other endpoints, including the change from baseline in glycosylated haemoglobin (HbA_{1c}) by visit over time and the occurrence of a treat to target response that was an HbA_{1c} under treatment of <7.0% (or <6.5%) or a relative efficacy response (HbA_{1c} lowering by at least 0.5% from baseline) after 54 weeks of treatment. The change from baseline in fasting plasma glucose (FPG) after 54 weeks of treatment and over time, the use of rescue therapy, and the change in body weight and waist circumference from baseline to Week 54.
Safety:	Safety endpoints were the incidence and intensity of adverse events (AEs), withdrawals due to AEs, clinically relevant new or worsening findings in physical examination, 12-lead ECG, vital signs, and clinical laboratory parameters.
Statistical methods:	Two interim analyses were planned for this trial to provide data required at the time of regulatory submissions due within the course of this study. For the first interim analysis [U10-2442-01], all data were analysed for visits that occurred on or before the cut-off date of 08 June 2010. For the second interim analysis [U11-1145-01], all data were analysed for visits that occurred on or before the cut-off date of 15 October 2010. This final report includes data obtained up to study completion.

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Name of finished product: Not applicable		**EudraCT No.:** 2008-008494-59	
Name of active ingredient: Linagliptin (BI 1356) + metformin (free combination)		**Page:** 4 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 10 NOV 2011	**Trial No. / U No.:** 1218.52 / U11-1782-01	**Dates of trial:** 30 JUN 2009 - 16 JUN 2011	**Date of revision:** Not applicable

Statistical methods (continued):

No inferential analyses were planned or performed for efficacy or safety data. All safety and efficacy data were summarised using descriptive statistics for patients in the Treated set (TS). Changes in HbA_{1c} over time were also analysed for the Full Analysis Set (FAS) completers. Changes in HbA_{1c} and FPG were additionally analysed for subsets of patients who switched and did not switch study medication from the previous study 1218.46. For patients who continued in the same treatment group as in the previous study 1218.46, additional analyses of changes in HbA_{1c} and FPG since baseline (Visit 3) of that study were also performed. Time to first use of rescue medication and time to the first onset of hypoglycaemia were estimated by the Kaplan-Meier method. Safety data was additionally summarised for patients who switched study medication from the previous study.

SUMMARY – CONCLUSIONS:

Efficacy results:

The reasons for premature discontinuation were comparable across the 3 treatment groups. Of the 111 patients (19.6%) who had discontinued the trial, the most common reason for discontinuation was due to an AE (36 patients, 6.4%). Two patients were unblinded during the conduct of the trial due to AEs (anaemia and acute myocardial infarction, each for 1 patient).

The demographic characteristics were comparable across the treatment groups. Overall, the mean age was 55.8 years; the majority of patients (78.3%) were aged <65 years. More than half the patients (54.8%) were male and more than half (65.2%) were White. Mean BMI was 29.0 kg/m^2 at baseline and most patients (39.2%) had a BMI of ≥30 kg/m^2 or 25 to <30 kg/m^2 (38.5%). Most patients had been diagnosed with T2DM ≤1 year (40.6%) or >1 to ≤5 years (37.6%). Baseline characteristics for patients who did not switch treatments between the previous trial and the extension trial (the Non-Switched Set; NONS) and for those who switched treatment (the Switched Set; SWS) were generally comparable with the TS.

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Name of active ingredient: Linagliptin (BI 1356) + metformin (free combination)		**Page:** 5 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 10 NOV 2011	**Trial No. / U No.:** 1218.52 / U11-1782-01	**Dates of trial:** 30 JUN 2009 - 16 JUN 2011	**Date of revision:** Not applicable

Efficacy results (continued):

HbA_{1c} over time: The decrease in HbA_{1c} from Visit 1 of this study to Week 54 was more marked in the lina 2.5 + met 1000 (-0.24% [SD: 0.91%]) and lina 2.5 + met 500 (-0.28% [SD: 0.86%]) groups than in the met 1000 treatment group (-0.06% [SD: 0.77%]). For the SWS patients, the mean change in HbA_{1c} from baseline to Week 54 was more marked in the lina 2.5 + met 1000 group (-0.96% [SD: 1.05%]) than in the lina 2.5 + met 500 (-0.63% [SD: 0.83%]) and the met 1000 (-0.42% [SD: 0.76%]) groups. For the NONS patients, the mean reduction in HbA_{1c} from baseline of the previous trial to baseline of the current trial was greater in the lina 2.5 + met 1000 group than in the other 2 groups. For the NONS, the reduction in HbA_{1c} achieved by the end of trial 1218.46 (i.e. at baseline of this extension trial) was maintained in this extension trial in all 3 treatment groups.

HbA_{1c} response: The frequency of patients achieved target HbA_{1c} levels of <7.0% at Week 54 was higher for the lina 2.5 + met 1000 group (56.8%) than for the lina 2.5 + met 500 (42.9%) and met 1000 (50.5%) treatment groups. The frequencies of responders using the more stringent target of <6.5% HbA_{1c} followed a similar pattern (met 1000: 21.8%; lina 2.5 + met 500: 21.8%; lina 2.5 + met 1000: 34.7%).

FPG: The mean reduction in FPG from baseline to Week 54 was greater in the lina 2.5 + met 1000 (-9.82 mg/dL [SD: 31.83 mg/dL]) and lina 2.5 + met 500 (-7.24 mg/dL [SD: 36.27 mg/dL]) groups than in the met 1000 group (-6.02 mg/dL [SD: 29.25 mg/dL]). For the SWS, the mean reduction in FPG from baseline to Week 54 was greater in the lina 2.5 + met 1000 group (-34.38 mg/dL [SD: 30.94 mg/dL]) than in the lina 2.5 + met 500 (-13.74 mg/dL [SD: 38.95 mg/dL]) and met 1000 (-14.63 mg/dL [SD: 25.45 mg/dL]) groups. For the NONS, the mean reduction in FPG from baseline of the previous trial to baseline of the current trial was greater in the lina 2.5 + met 1000 group than in the other 2 groups. The reduction in FPG achieved by the end of trial 1218.46 (i.e. at baseline of this extension trial) was maintained in this extension trial for all 3 treatment groups in the NONS.

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Name of finished product: Not applicable		**EudraCT No.:** 2008-008494-59	
Name of active ingredient: Linagliptin (BI 1356) + metformin (free combination)		**Page:** 6 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 10 NOV 2011	**Trial No. / U No.:** 1218.52 / U11-1782-01	**Dates of trial:** 30 JUN 2009 - 16 JUN 2011	**Date of revision:** Not applicable

Efficacy results (continued):	**Use of rescue medication:** The incidence of rescue medication was lower for the lina 2.5 + met 1000 treatment group (14.0%) than for lina + met 500 (27.6%) and met 1000 (24.7%) treatment groups. The mean time to first use was later in the lina 2.5 + met 1000 group (165.3 days) than in the lina 2.5 + met 500 (121.9 days) and met 1000 (118.9 days) treatment groups. **Body weight and waist circumference:** There were no clinically meaningful differences in the mean change in body weight from baseline to either Week 18 or Week 54 for any of the treatment groups. There were also no clinically meaningful differences in the mean change in waist circumference from baseline to Week 54 for any of the treatment groups.
Safety results:	The mean duration of exposure was comparable across the 3 treatment groups (341 to 344 days). More than 80% of patients in each treatment group had been treated with trial medication for at least 42 weeks (met 1000: 84.1%; lina 2.5 + met 500: 84.9%; lina 2.5 + met 1000: 87.1%). For the SWS, the mean duration of exposure was comparable with the TS. The overall incidence of treatment-emergent AEs was comparable across treatment groups (met 1000: 72.9%; lina 2.5 + met 500: 66.2%; lina 2.5 + met 1000: 77.2%). The incidence of drug-related AEs was higher in the met 1000 and lina 2.5 + met 1000 groups than in the lina 2.5 + met 500 group (met 1000: 15.9%; lina 2.5 + met 500: 8.4%; lina 2.5 + met 1000: 14.0%). Severe AEs were reported infrequently in all treatment groups (2.4% of met 1000 patients, 3.1% of lina 2.5 + met 500 patients, and 2.9% of lina 2.5 + met 1000 patients). The frequencies of AEs by SOC as well as by preferred term were generally comparable in the 3 treatment groups within most SOCs and for most preferred terms. The SOC with the highest incidence of AEs was infections and infestations (met 1000: 27.6%; lina 2.5 + met 500: 30.2%; lina 2.5 + met 1000: 25.7%), followed by metabolism and nutrition disorders (met 1000: 25.9%; lina 2.5 + met 500: 28.9%; lina 2.5 + met 1000: 26.3%), investigations (met 1000: 18.2%; lina 2.5 + met 500: 15.1%; lina 2.5 + met 1000: 17.5%), and gastrointestinal disorders (met 1000: 14.1%; lina 2.5 + met 500: 16.0%; lina 2.5 + met 1000: 18.1%).

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Name of active ingredient: Linagliptin (BI 1356) + metformin (free combination)		**Page:** 7 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 10 NOV 2011	**Trial No. / U No.:** 1218.52 / U11-1782-01	**Dates of trial:** 30 JUN 2009 - 16 JUN 2011	**Date of revision:** Not applicable

Safety results (continued):

The most frequent AEs by preferred term were hyperglycaemia (met 1000: 11.8%; lina 2.5 + met 500: 12.9%; lina 2.5 + met 1000: 6.4%) and worsening diabetes mellitus (met 1000: 8.2%; lina 2.5 + met 500: 8.0%; lina 2.5 + met 1000: 9.9%).

The incidences of SAEs, 'other significant' AEs (based on ICH E3), and of AEs leading to discontinuation were low and comparable across the 3 treatment groups.

In total, SAEs during the treatment period were reported for 33 patients, including 7 patients (4.1%) on met 1000, 12 patients (5.3%) on lina 2.5 + met 500, and 14 patients (8.2%) on lina 2.5 + met 1000. Four patients (2 patients in the lina 2.5 + met 500 group and 1 each in the met 1000 and line 2.5 + met 1000 groups) were reported to have died during the trial.

Four patients had immediately life-threatening SAEs: 1 cerebrovascular accident (met 1000 group), 2 acute myocardial infarctions (1 in the met 1000 group and 1 in the lina 2.5 + met 500 group), and cardiogenic shock and supraventricular tachycardia (both in a single patient in the lina 2.5 + met 1000 group). The cardiogenic shock and supraventricular tachycardia were considered as drug-related by the investigator. No other SAEs were considered to be drug-related.

The most frequent SAEs according to SOC were cardiac disorders (met 1000: 1.2%, lina 2.5 + met 500: 1.8%; lina 2.5 + met 1000: 2.3%).

The incidence of investigator-defined hypoglycaemia was low and comparable across treatment groups: hypoglycaemic episodes were reported for 2.9% of met 1000 patients, 4.9% of lina 2.5 + met 500 patients, and 6.4% of lina 2.5 + met 1000 patients. The majority of patients reported only a single episode of hypoglycaemia; none were severe. No patients had an investigator-defined hypoglycaemic event while on rescue medication. The median time to onset of the first hypoglycaemic AE was 55 days for the met 1000 group, 116 days for the lina 2.5 + met 500 group, and 57 days for the lina 2.5 + met 1000 group.

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Name of active ingredient: Linagliptin (BI 1356) + metformin (free combination)		**Page:** 8 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 10 NOV 2011	**Trial No. / U No.:** 1218.52 / U11-1782-01	**Dates of trial:** 30 JUN 2009 - 16 JUN 2011	**Date of revision:** Not applicable

Safety results (continued):	Pre-specified significant AEs and AEs of special interest were hepatic AEs, renal AEs, hypersensitivity reactions, severe cutaneous adverse reaction, and pancreatitis. No severe cutaneous adverse reactions or cases of pancreatitis were reported. Hepatic AEs were uncommon and the incidences were comparable across treatment groups, reported for 13 patients in the met 1000 group (7.6%), 11 patients in the lina 2.5 + met 500 group (4.9%), and 11 patients in the lina 2.5 + met 1000 group (6.4%). Three patients were reported with hypersensitivity reactions (bronchospasm for 1 patient in the met 1000 group and urticaria for 2 patients in the lina 2.5 + met 1000 group). Renal failure was reported for 1 patient in the met 1000 group and for 1 patient in the lina 2.5 + met 1000 group. There were no clinically meaningful or unexpected changes in any laboratory variables or in vital signs during this trial in any treatment group. There was no indication that patients who switched treatments between trial 1218.46 and this extension trial had a markedly different AE profile compared with patients in the TS.
Conclusions:	The objectives of this trial were the analyses of safety and efficacy of the 3 treatments. The safety profiles of the 2 treatment groups with free combinations of linagliptin 2.5 mg plus either 500 mg or 1000 mg metformin b.i.d. were comparable with the metformin monotherapy treatment group (1000 mg metformin b.i.d.). All trial medications were safe and well tolerated, including in patients who had switched treatments between trial 1218.46 and this extension trial. The analysis of efficacy was a secondary objective of this trial. The baseline efficacy values for HbA_{1c} and FPG were maintained or improved in the 3 treatment groups over the duration of this trial. For patients who continued trial medication unchanged from the preceding trial 1218.46 (i.e. for patients in the NONS), the reductions in HbA_{1c} and FPG achieved at the end of the preceding trial were maintained in each of the 3 treatment groups of this extension trial.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The primary endpoint of this trial was a safety endpoint.

Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

Safety endpoints were:

- the incidence and intensity of adverse events (AEs)
- frequency of patients with adverse events occurring with incidence in preferred term greater than 2 %
- withdrawals due to AEs

The appended tables provide additional results of patient dispostion and secondary endpoints as summarized below.

Results for	**presented in**
Patient Disposition	Table 15.1.1: 1
AE Summary (primary endpoint)	Table 15.3.2.1: 1
Frequency [N (%)] of patients with adverse events occurring with incidence in preferred term greater than 2 % (primary endpoint)	Table 15.3.2.1: 3
Percentage of patients with HbA1c lowering by 0.5% up to week 54 (secondary endpoint)	Table 15.2.2.1: 5
The change in HbA1c from baseline by visit over time up to week 54 (secondary endpoint)*	Table 15.2.2.1: 6
The change in FPG from baseline by visit over time up to week 54 (secondary endpoint)*	Table 15.2.2.2: 2

*The mean visit value minus the mean baseline value does not equal the mean change from baseline for successive visits over time in these analyses. This is due to variation in the data and the different numbers of evaluable patients at each visit compared to baseline.

Table 15.1.1: 1 Disposition of patients entering the extension trial - SCR

	M1000 N (%)	L2.5+M500 N (%)	L2.5+M1000 N (%)	Total N (%)
Entered				567
Randomised	171	225	171	567
Not treated	1	0	0	1
Treated *	170 (100.0)	225 (100.0)	171 (100.0)	566 (100.0)
Not prematurely discontinued trial medication	134 (78.8)	179 (79.6)	142 (83.0)	455 (80.4)
Prematurely discontinued trial medication	36 (21.2)	46 (20.4)	29 (17.0)	111 (19.6)
Adverse events	12 (7.1)	13 (5.8)	11 (6.4)	36 (6.4)
AE study dis. worse	2 (1.2)	1 (0.4)	1 (0.6)	4 (0.7)
AE other dis. worse	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
AE other	10 (5.9)	12 (5.3)	9 (5.3)	31 (5.5)
Lack of efficacy #	9 (5.3)	15 (6.7)	3 (1.8)	27 (4.8)
Non compl. protocol	4 (2.4)	1 (0.4)	2 (1.2)	7 (1.2)
Lost to follow-up	1 (0.6)	2 (0.9)	2 (1.2)	5 (0.9)
Refused cont. medic.	6 (3.5)	8 (3.6)	4 (2.3)	18 (3.2)
Other	4 (2.4)	7 (3.1)	7 (4.1)	18 (3.2)

* In all tables 'treated' refers to treatment with randomised study drug
# Includes patients discontinued due to hyperglycemia

Table 15.3.2.1: 1 Adverse event overall summary - TS

Treatment analysis: Drug stop + 7 days (by trt, post trt)

	M1000 N (%)	L2.5+M500 N (%)	L2.5+M1000 N (%)	Post-treat N (%)
Number of patients	170 (100.0)	225 (100.0)	171 (100.0)	566 (100.0)
Patients with any AE	124 (72.9)	149 (66.2)	132 (77.2)	14 (2.5)
Patients with severe AEs	4 (2.4)	7 (3.1)	5 (2.9)	1 (0.2)
Patients with investigator defined drug-related AEs	27 (15.9)	19 (8.4)	24 (14.0)	3 (0.5)
Patients with other significant AEs (according to ICH E3)	6 (3.5)	3 (1.3)	2 (1.2)	0 (0.0)
Patients with AEs leading to discontinuation of trial drug	10 (5.9)	11 (4.9)	9 (5.3)	0 (0.0)
Patients with significant AEs (pre-specified events)	12 (7.1)	19 (8.4)	14 (8.2)	3 (0.5)
Patients with serious AEs	7 (4.1)	12 (5.3)	14 (8.2)	0 (0.0)
Fatal	1 (0.6)	2 (0.9)	1 (0.6)	0 (0.0)
Imm life-threatening	2 (1.2)	1 (0.4)	1 (0.6)	0 (0.0)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Req.hospitalisation	5 (2.9)	11 (4.9)	13 (7.6)	0 (0.0)
Prol.hospitalisation	2 (1.2)	1 (0.4)	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Other	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 14.0

Table 15.3.2.1: 3 Frequency [N (%)] of patients with adverse events occurring with incidence in preferred term greater than 2 % by treatment, primary system organ class and preferred term - TS

Treatment analysis: Drug stop + 7 days (by trt, no post trt)

System organ class/ Preferred term	M1000 N (%)	L2.5+M500 N (%)	L2.5+M1000 N (%)
Number of patients	170 (100.0)	225 (100.0)	171 (100.0)
Total with adverse events	124 (72.9)	149 (66.2)	132 (77.2)
Blood and lymphatic system disorders	7 (4.1)	7 (3.1)	7 (4.1)
Anaemia	4 (2.4)	5 (2.2)	5 (2.9)
Gastrointestinal disorders	24 (14.1)	36 (16.0)	31 (18.1)
Diarrhoea	4 (2.4)	8 (3.6)	12 (7.0)
Gastritis	4 (2.4)	3 (1.3)	6 (3.5)
Vomiting	1 (0.6)	4 (1.8)	4 (2.3)
General disorders and administration site conditions	13 (7.6)	13 (5.8)	11 (6.4)
Pyrexia	3 (1.8)	5 (2.2)	4 (2.3)
Hepatobiliary disorders	5 (2.9)	6 (2.7)	5 (2.9)
Hepatic steatosis	4 (2.4)	4 (1.8)	2 (1.2)
Infections and infestations	47 (27.6)	68 (30.2)	44 (25.7)
Asymptomatic bacteriuria	0 (0.0)	1 (0.4)	5 (2.9)
Bronchitis	6 (3.5)	7 (3.1)	1 (0.6)
Gastroenteritis	0 (0.0)	6 (2.7)	2 (1.2)
Influenza	6 (3.5)	11 (4.9)	3 (1.8)
Nasopharyngitis	9 (5.3)	9 (4.0)	12 (7.0)
Rhinitis	0 (0.0)	5 (2.2)	1 (0.6)
Upper respiratory tract infection	6 (3.5)	5 (2.2)	4 (2.3)
Urinary tract infection	4 (2.4)	9 (4.0)	10 (5.8)

Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 14.0

Total AEs includes all AEs whereas PTs are if >2% in any treatment

Table 15.3.2.1: 3 Frequency [N (%)] of patients with adverse events occurring with incidence in preferred term greater than 2 % by treatment, primary system organ class and preferred term - TS

Treatment analysis: Drug stop + 7 days (by trt, no post trt)

System organ class/ Preferred term	M1000 N (%)	L2.5+M500 N (%)	L2.5+M1000 N (%)
Investigations	31 (18.2)	34 (15.1)	30 (17.5)
Alanine aminotransferase increased	4 (2.4)	4 (1.8)	3 (1.8)
Blood amylase increased	3 (1.8)	0 (0.0)	5 (2.9)
Blood creatine phosphokinase increased	6 (3.5)	1 (0.4)	3 (1.8)
Gamma-glutamyltransferase increased	2 (1.2)	0 (0.0)	4 (2.3)
Glomerular filtration rate decreased	6 (3.5)	14 (6.2)	11 (6.4)
Glycosylated haemoglobin increased	9 (5.3)	12 (5.3)	4 (2.3)
Metabolism and nutrition disorders	44 (25.9)	65 (28.9)	45 (26.3)
Diabetes mellitus	14 (8.2)	18 (8.0)	17 (9.9)
Hyperglycaemia	20 (11.8)	29 (12.9)	11 (6.4)
Hypoglycaemia	4 (2.4)	11 (4.9)	11 (6.4)
Musculoskeletal and connective tissue disorders	21 (12.4)	25 (11.1)	23 (13.5)
Arthralgia	8 (4.7)	5 (2.2)	3 (1.8)
Back pain	4 (2.4)	7 (3.1)	7 (4.1)
Osteoarthritis	4 (2.4)	1 (0.4)	2 (1.2)
Spinal osteoarthritis	0 (0.0)	1 (0.4)	4 (2.3)
Nervous system disorders	16 (9.4)	18 (8.0)	10 (5.8)
Headache	4 (2.4)	6 (2.7)	1 (0.6)
Paraesthesia	4 (2.4)	2 (0.9)	2 (1.2)

Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 14.0

Total AEs includes all AEs whereas PTs are if >2% in any treatment

Table 15.3.2.1: 3 Frequency [N (%)] of patients with adverse events occurring with incidence in preferred term greater than 2 % by treatment, primary system organ class and preferred term - TS

Treatment analysis: Drug stop + 7 days (by trt, no post trt)

System organ class/ Preferred term	M1000 N (%)	L2.5+M500 N (%)	L2.5+M1000 N (%)
Renal and urinary disorders	14 (8.2)	5 (2.2)	7 (4.1)
Haematuria	4 (2.4)	3 (1.3)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	7 (4.1)	7 (3.1)	8 (4.7)
Cough	0 (0.0)	2 (0.9)	5 (2.9)
Vascular disorders	10 (5.9)	11 (4.9)	14 (8.2)
Hypertension	9 (5.3)	8 (3.6)	10 (5.8)

Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 14.0

Total AEs includes all AEs whereas PTs are if >2% in any treatment

Table 15.2.2.1: 5 Number of patients with a reduction in HbA1c of at least 0.5% over time - TS (OC)

	M1000	L2.5+M500	L2.5+M1000
Week 6			
HbA1c<0.5% [N (%)]			
N(non-missing)	157 (100.0)	207 (100.0)	166 (100.0)
No	140 (89.2)	143 (69.1)	126 (75.9)
Yes	17 (10.8)	64 (30.9)	40 (24.1)
Week 18			
HbA1c<0.5% [N (%)]			
N(non-missing)	136 (100.0)	184 (100.0)	147 (100.0)
No	108 (79.4)	114 (62.0)	99 (67.3)
Yes	28 (20.6)	70 (38.0)	48 (32.7)
Week 30			
HbA1c<0.5% [N (%)]			
N(non-missing)	121 (100.0)	165 (100.0)	134 (100.0)
No	87 (71.9)	95 (57.6)	91 (67.9)
Yes	34 (28.1)	70 (42.4)	43 (32.1)
Week 42			
HbA1c<0.5% [N (%)]			
N(non-missing)	110 (100.0)	152 (100.0)	127 (100.0)
No	77 (70.0)	99 (65.1)	85 (66.9)
Yes	33 (30.0)	53 (34.9)	42 (33.1)
Week 54			
HbA1c<0.5% [N (%)]			
N(non-missing)	98 (100.0)	132 (100.0)	117 (100.0)
No	71 (72.4)	83 (62.9)	81 (69.2)
Yes	27 (27.6)	49 (37.1)	36 (30.8)

Source data: Appendix 16.2, Listing 6.1.3

Table 15.2.2.1: 6 Descriptive statistics of HbA1c (%) and change from visit 1 1218.52 over time - NONS (OC)

	M1000 (N=109)						L2.5+M500 (N=113)					
	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Observed case												
Visit 1 1218.52	105	7.31	0.88	5.4	7.30	9.3	113	7.34	0.96	5.2	7.30	10.7
Week 6	106	7.27	0.91	5.4	7.25	10.6	104	7.29	0.91	5.8	7.20	10.7
Week 18	94	7.22	0.87	5.3	7.25	10.2	93	7.21	0.94	5.6	7.10	10.0
Week 30	85	7.15	0.93	5.4	7.20	11.4	81	7.04	0.90	5.4	7.00	10.5
Week 42	78	7.10	0.85	5.4	7.00	10.0	73	7.07	0.80	5.5	7.00	9.3
Week 54	69	7.08	0.80	5.4	7.00	9.1	66	7.14	0.89	5.3	7.20	10.5
Change from Visit 1 1218.52 at week 6	102	0.01	0.36	-0.9	0.00	1.5	104	0.00	0.43	-1.6	0.00	1.8
Change from Visit 1 1218.52 at week 18	90	0.04	0.53	-1.1	0.00	1.8	93	0.03	0.68	-2.0	-0.10	2.5
Change from Visit 1 1218.52 at week 30	81	0.06	0.84	-2.0	0.00	4.3	81	-0.08	0.67	-2.0	-0.10	2.6
Change from Visit 1 1218.52 at week 42	74	0.03	0.76	-1.7	0.00	2.4	73	-0.01	0.61	-2.2	0.00	1.5
Change from Visit 1 1218.52 at week 54	66	0.12	0.72	-1.6	0.10	2.9	66	0.08	0.74	-2.1	-0.10	2.8

Table 15.2.2.1: 6 Descriptive statistics of HbA1c (%) and change from visit 1 1218.52 over time - NONS (OC)

	L2.5+M1000 (N=111)					
	N	Mean	SD	Min	Median	Max
Observed case						
Visit 1 1218.52	111	6.93	0.85	5.0	6.70	9.9
Week 6	108	6.88	0.82	5.0	6.75	8.8
Week 18	95	6.95	0.90	5.2	6.70	10.9
Week 30	87	6.77	0.77	5.2	6.60	9.5
Week 42	84	6.80	0.82	5.2	6.70	10.3
Week 54	78	6.84	0.76	5.3	6.85	8.8
Change from Visit 1 1218.52 at week 6	108	-0.03	0.44	-2.4	0.00	1.7
Change from Visit 1 1218.52 at week 18	95	0.06	0.56	-2.7	0.10	2.3
Change from Visit 1 1218.52 at week 30	87	-0.01	0.48	-1.3	-0.10	1.3
Change from Visit 1 1218.52 at week 42	84	0.09	0.57	-1.5	0.10	2.3
Change from Visit 1 1218.52 at week 54	78	0.13	0.54	-1.4	0.10	1.6

Table 15.2.2.2: 2 Descriptive statistics of FPG (mg/dL) and change from visit 1 1218.52 over time - NONS (OC)

	M1000 (N=109)						L2.5+M500 (N=113)					
	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Observed case												
Visit 1 1218.52	105	151.95	38.50	79.0	144.00	267.0	107	159.57	43.77	97.0	148.00	306.0
Week 2	107	148.74	38.40	86.0	140.00	317.0	106	156.85	37.45	92.0	153.00	263.0
Week 6	101	151.03	39.79	76.0	140.00	317.0	98	149.43	31.11	88.0	143.00	241.0
Week 18	93	147.52	33.81	97.0	139.00	285.0	92	148.76	34.82	97.0	142.00	238.0
Week 30	80	142.98	34.41	86.0	135.00	306.0	77	142.71	30.80	86.0	140.00	218.0
Week 42	71	143.06	28.96	103.0	137.00	232.0	73	147.55	29.42	95.0	140.00	220.0
Week 54	65	141.29	26.97	94.0	137.00	238.0	66	144.66	34.00	83.0	139.00	245.0
Change from Visit 1 1218.52 at week 2	104	-2.75	28.70	-151.0	-4.00	99.0	101	-3.08	27.66	-149.0	0.00	88.0
Change from Visit 1 1218.52 at week 6	98	0.98	31.32	-104.0	0.00	103.0	93	-3.96	20.55	-76.0	-4.00	49.0
Change from Visit 1 1218.52 at week 18	90	0.00	36.26	-151.0	4.55	134.0	87	-1.61	28.37	-110.0	-2.00	90.0
Change from Visit 1 1218.52 at week 30	78	-1.56	46.30	-170.0	-0.50	160.0	74	-5.58	30.56	-112.0	-5.00	85.0
Change from Visit 1 1218.52 at week 42	69	-2.49	31.49	-124.0	0.00	56.0	71	-0.13	32.35	-103.0	4.00	117.0
Change from Visit 1 1218.52 at week 54	63	-1.92	30.23	-112.0	-5.00	81.0	64	-0.35	32.06	-124.0	-1.50	83.0

Table 15.2.2.2: 2 Descriptive statistics of FPG (mg/dL) and change from visit 1 1218.52 over time - NONS (OC)

	L2.5+M1000 (N=111)					
	N	Mean	SD	Min	Median	Max
Observed case						
Visit 1 1218.52	107	142.82	28.13	94.0	137.00	250.0
Week 2	107	140.04	29.76	90.0	133.00	240.0
Week 6	105	140.21	30.67	54.0	133.00	252.0
Week 18	93	138.09	29.99	95.0	133.00	258.0
Week 30	86	133.27	22.19	88.0	130.00	202.0
Week 42	85	138.28	30.93	99.0	131.00	277.0
Week 54	79	140.22	28.92	101.0	135.00	254.0
Change from Visit 1 1218.52 at week 2	105	-2.77	21.60	-100.0	-4.00	52.0
Change from Visit 1 1218.52 at week 6	103	-1.94	26.37	-100.0	-2.00	104.0
Change from Visit 1 1218.52 at week 18	91	-2.86	24.37	-69.0	-7.00	104.0
Change from Visit 1 1218.52 at week 30	84	-6.13	22.13	-74.0	-5.50	55.0
Change from Visit 1 1218.52 at week 42	83	-2.18	23.76	-58.0	-4.00	81.0
Change from Visit 1 1218.52 at week 54	78	1.83	25.01	-42.0	0.00	70.0