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.:** 2008-000750-13	
Name of active ingredient: Linagliptin		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 31 MAY 2011	**Trial No. / U No.:** 1218.40 / U11-1708-02	**Dates of trial:** 13 AUG 2008 – 29 DEC 2010	**Date of revision:** 08 DEC 2011

Title of trial:	A 78 week open-label extension to trials assessing the safety and efficacy of linagliptin (5 mg) as monotherapy or in combination with other antidiabetic medications in type 2 diabetic patients
Coordinating Investigator:	[redacted]
Trial sites:	Multi-national, multi-centre trial: 231 sites in 32 countries in Europe, North America, South America, and Asia
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The objective of this trial was to investigate safety and tolerability of linagliptin 5 mg during open-label, long-term treatment. An additional objective was to assess the efficacy of linagliptin alone or as concomitant administration with other therapies commonly used in the treatment of type 2 diabetes mellitus (T2DM).
Methodology:	This was an uncontrolled open-label extension trial over 78 weeks for patients with T2DM who continued their treatment from 4 previous trials with either 5 mg linagliptin plus 30 mg pioglitazone as initial combination (1218.15 trial), 5 mg linagliptin alone (1218.16 trial), or in addition to either metformin background therapy (1218.17 trial), or metformin plus sulphonylurea background therapy (1218.18 trial). Patients who received placebo in the previous trials were treated with 5 mg linagliptin in this trial.
No. of patients:	
planned:	entered: 2000

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actual:	enrolled: 2124 Linagliptin 5 mg plus 30 mg pioglitazone (patients from 1218.15): treated: 342 analysed (for primary endpoint): 342 Linagliptin 5 mg (patients from 1218.16): treated: 443 analysed (for primary endpoint): 443 Linagliptin 5 mg plus metformin (patients from 1218.17): treated: 610 analysed (for primary endpoint): 610 Linagliptin 5 mg plus metformin and sulphonylurea (patients from 1218.18): treated: 726 analysed (for primary endpoint): 726
Diagnosis and main criteria for inclusion:	Patients with T2DM who had successfully completed the double-blind studies 1218.15, 1218.16, 1218.17, or 1218.18 irrespective of whether they had been treated with rescue medication.
Test product:	Linagliptin tablet
dose:	5 mg once daily
mode of admin.:	Oral
batch no.:	079205_A-F
Background therapy:	Pioglitazone tablet
dose:	30 mg once daily
mode of admin.:	Oral
batch no.:	B081001788, B081001791, B081005131, and B091001838
Reference therapy:	None
Duration of treatment:	78 weeks plus 1 week follow-up

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Criteria for evaluation:

Efficacy / clinical pharmacology: Efficacy was evaluated as secondary endpoints by change from baseline over time in HbA_{1c} and fasting plasma glucose (FPG), the occurrence of a treat-to-target response (i.e. HbA_{1c} on treatment <7.0% and <6.5%) over time, and a relative efficacy response (i.e. HbA_{1c} lowering by at least 0.5%) over time.

Safety: Incidence and intensity of adverse events (AEs), withdrawal due to AEs, physical examination, 12-lead electrocardiogram (ECG), vital signs, clinical laboratory parameters, and home blood glucose monitoring.

Statistical methods: Descriptive statistics to evaluate the safety and efficacy in patients pre-treated with linagliptin (old lina group) and patients pre-treated with placebo (new lina group) in the preceding trials. The frequency of AEs was also compared with respect to the background antidiabetic therapy (stratification by participation in previous trials).

SUMMARY – CONCLUSIONS:

Efficacy results: Of the 2124 patients enrolled in this study, 2121 were treated with at least 1 dose of study medication. Of the 2121 treated patients, 241 patients (11.4%) discontinued treatment prematurely. Most patients discontinued trial medication due to an AE, refusal to continue with study medication, or other reasons (e.g. personal reasons). Most of the AEs leading to treatment discontinuation were other AEs (i.e. neither related to a worsening of the study disease nor to any other pre-existing disease).

Overall, the demographic data were well balanced between the old lina group (1532 patients who received linagliptin in the preceding trials) and the new lina group (589 patients who received placebo in the preceding trials). The mean age was 57.5 years, 48.2% of the treated patients were female, and the mean BMI was 29.0 kg/m^2. The majority of the treated population comprised either Whites (56.7%) or Asians (42.0%). The condition at Visit 1 of this trial was defined as baseline for all parameters; if any data were not collected at Visit 1, the last available value before Visit 1 was used as baseline. The mean baseline HbA_{1c} (standard deviation, SD) was 7.38% (0.90) in the old lina group and 7.87% (1.04) in the new lina group. The mean baseline FPG (SD) was 151.59 mg/dL (35.32) in the old lina group and 164.31 mg/dL (37.36) in the new lina group.

The overall frequency of patients using concomitant therapy at screening was

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comparable between the old lina (81.9%) and new lina (78.4%) groups. Overall, the most frequently prescribed concomitant therapies at screening were acetylsalicyclic acid, simvastatin, atorvastatin, and amlodipine. Among the concomitant medications which were only initiated after start of this trial, the most frequent new concomitant therapy was paracetamol, followed by diclofenac, acetylsalicyclic acid, amoxicillin, omeprazole, and ipuprofen. All concomitant therapies were used at a similar frequency in both groups. At Visit 1 of this trial, the majority of patients neither had an ongoing antidiabetic treatment therapy (excluding background) nor were treated with rescue medication.

Secondary endpoints

In the old lina group, the HbA_{1c} levels already reduced during the 24 weeks of treatment in the previous trials were largely maintained throughout the present trial (change from baseline at Week 78: 0.12%). In the new lina group, a decrease in HbA_{1c} levels until Week 18 (-0.63%) was observed as expected; thereafter no further reduction in HbA_{1c} levels was noted. At Week 78, a mean change from baseline of -0.49% was noted in the new lina group. From Week 18 to 78, the mean HbA_{1c} values in the new lina group were lower than in the old lina group. When stratified by the preceding trial, the maximum effect of linagliptin on HbA_{1c} levels was noted for patients who had been randomised to placebo in the 1218.16 trial (-0.61% mean change from baseline at Week 78).

Concerning the treat-to-target efficacy response, up until Week 30, the frequency of patients with baseline $HbA_{1c} \geq 7.0\%$ and $HbA_{1c} < 7.0\%$ increased in both groups; thereafter the frequency was relatively stable for both groups. At Week 78, HbA_{1c} levels <7.0% were noted for 23.6% (old lina) and 36.0% (new lina) of patients with baseline $HbA_{1c} \geq 7.0\%$. For all visits, HbA_{1c} levels <7.0% were observed at a higher frequency among patients with baseline levels <8.0% than among patients with higher baselines.

The frequency of patients with baseline $HbA_{1c} \geq 6.5\%$ and $HbA_{1c} < 6.5\%$ increased in both groups until Week 18; moreover, the increase was more pronounced in the new lina group as expected; thereafter, the frequency was relatively stable for both groups. HbA_{1c} levels <6.5% were mostly observed at a higher frequency among patients with baseline levels <8.0% than among patients with higher baselines.

For all visits, the proportions of patients with a reduction in HbA_{1c} levels by at

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	least 0.5% were at least twice as high in the new lina group as in the old lina group. A reduction of at least 0.5% in HbA_{1c} was seen at a higher frequency among patients with baseline HbA_{1c} levels of ≥8.0% than among patients with lower baselines. The change in FPG showed a similar trend in the reduction across visits when compared with the reduction seen for HbA_{1c} over time. In the old lina group, the FPG levels already reduced during the 24 weeks of treatment in the previous trials were largely maintained up to Week 78. As expected, patients in the new lina group had a more pronounced decrease in mean FPG levels over time. The mean change from baseline in FPG at Week 78 for the old lina group was 1.90 mg/dL and for the new lina group -13.64 mg/dL. For all visits, the mean FPG levels in the new lina group were lower than those in the old lina group. Other endpoints A similar proportion of patients required rescue therapy in the old lina (31.7%) and new lina groups (28.4%). In both groups, the most common rescue medication was sulphonylurea (old lina: 10.7%, new lina: 9.3%). No meaningful changes in mean body weight or mean waist circumference were noted for either group. The other endpoints related to safety parameters (changes in lipid parameters and clinical laboratory assessments) are described below.
Safety results:	Exposure The median exposure to linagliptin was 547 days in both groups. The mean exposure was similar in both groups (old lina: 513 days, new lina: 520 days). About 90% patients in both groups were exposed to linagliptin for >66 weeks. Adverse events Overall, 1253 patients (81.8%) in the old lina group and 465 (78.9%) in the new lina group were reported with AEs. Generally, the incidences of AEs in both groups were comparable. The highest overall frequency of AEs (84.2%) was noted in patients from the trial 1218.18 with a double background therapy of metformin and SU, followed by patients with metformin background therapy (81.6%, 1218.17 trial) and patients without antidiabetic background therapy (78.8%, 1218.16 trial). Patients with pioglitazone background therapy (1218.15 trial) were reported with the lowest overall frequency of AEs (76.0%).

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The most frequently reported AE on the system organ class (SOC) level was metabolism and nutrition system disorders (old lina: 42.9%, new lina: 41.8%). Within this class, hyperglycaemia (23.4%) and hypoglycaemia (13.5%) accounted for most of the AEs. The incidence of hyperglycaemia was higher in the old lina group (old lina: 24.5%, new lina: 20.5%) whereas hypoglycaemia was more frequently experienced by patients in the new lina group (old lina: 13.2%, new lina: 14.4%). The second and third most frequently reported SOCs were infections and infestations (old lina: 37.3%, new lina: 39.0%) and musculoskeletal and connective tissue disorders (old lina: 19.8%, new lina: 20.0%). Skin disorders are of particular interest as they have been reported for other DPP-4 inhibitors; in this trial, AEs in the SOC 'skin and subcutaneous tissue disorders' were reported for 7.7% (old lina) and 7.3% (new lina) of patients.

AEs of severe intensity were reported for few patients (old lina: 3.7%, new lina: 3.9%); all other AEs were mild or moderate. Drug-related AEs were reported by 14.4% in the old lina group and 14.1% in the new lina group. On preferred term (PT) level, drug-related hypoglycaemia occurred most frequently (old lina: 6.6%, new lina: 7.6%). The frequency of AEs leading to trial discontinuation was low (old lina: 3.7%, new lina: 2.7%). Only 3 patients (0.1%) discontinued the trial due to hypoglycaemia. No meaningful differences in the incidences of treatment-emergent AEs were observed when AEs were analysed with respect to use of rescue medication.

Investigator-defined hypoglycaemia (hypoglycaemia and other PTs related to symptoms of hypoglycaemia) was reported for 13.6% (old lina) and 14.6% (new lina) of patients. Hypoglycaemic events were most frequently experienced by patients who received a double background therapy of metformin and SU (32.2%, from 1218.18 trial). The frequency of hypoglycaemic events experienced by all other patients was much lower: 7.4% (1218.17, metformin background therapy), 2.5% (1218.16, no background therapy), and 1.5% (1218.15, pioglitazone background therapy). Among the worst hypoglycaemic episodes, 10 patients (4.8%) in the old lina group and 3 (3.5%) in the new lina group were reported with severe hypoglycaemic episodes (required the assistance of another person).

A total of 119 patients (5.6%) were reported with cardiac and cerebrovascular events qualified for adjudication by the Clinical Event Committee (CEC). The

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events confirmed by the CEC comprised transient ischaemic attack (1 patient in the old lina group), non-fatal stroke (old lina: 10 patients, 0.7%, new lina: 2, 0.3%), non-fatal myocardial infarction (MI) (old lina: 4, 0.3%, new lina: 10, 1.7%), other myocardial ischaemia (old lina: 18, 1.2%, new lina: 10, 1.7%), and cardiovascular death (old lina: 3, 0.2%, new lina: 1, 0.2%). Of the 12 patients with non-fatal stroke, 11 patients had an ischaemic stroke and 1 had a haemorrhagic stroke. Of the 14 patients confirmed to have experienced non-fatal MIs, 3 had a STEMI (ST segment elevation MI), 9 had a NSTEMI (non-ST segment elevation MI), and 3 not assessable. Of the 28 patients with other myocardial ischaemia, 19 were adjudicated with stable angina and 9 with unstable angina. In total, 35 patients (old lina: 22, 1.4%, new lina: 13, 2.2%) were reported with cardiovascular death, MI, stroke or hospitalisation due to unstable angina. Incidence rates of confirmed cardiac and cerebrovascular events for both treatment groups were low in general (rate of CV death, MI, stroke or hospitalisation due to unstable angina per 1000 years at risk was 10.14 for old lina and 15.42 for new lina) and even slightly lower in the old lina group.

Throughout the trial, 10 patients were known to have died. All 10 deaths were considered not related to study drug intake. Of these, 8 died during the treatment period: the causes of death were cardiac tamponade, malignant lung neoplasm, sudden cardiac death, pneumonia, cardio-respiratory arrest, pulmonary embolism, acute MI, and infectious, polypous and ulcerous endocarditis of aortic valve. Two patients died during the post-treatment period due to cardio-respiratory arrest and metastatic pulmonary adenocarcinoma. Serious adverse events occurred in 10.3% (old lina) and 8.8% (new lina) of patients. On PT level, the most frequently reported serious adverse events (overall incidence of 0.3- 0.4%) were MI, angina pectoris, unstable angina, chest pain, and prostate cancer.

The overall frequency of patients reported with significant AEs based on SMQs (Standardised MedDRA Queries; comprised renal and hepatic AEs, hypersensitivity reactions, severe cutaneous adverse reactions, and pancreatitis) was low. Renal AEs were reported by 1.4% of patients (old lina: 1.3%, new lina: 1.7%), hepatic AEs by 1.2% of patients (old lina: 1.4%, new lina: 0.8%), hypersensitivity reactions by 0.5% of patients in either group, pancreatitis by 0.2% of patients (all in the old lina group), and no severe cutaneous adverse reaction was reported. Other significant AEs (as defined by ICH E3) were

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	reported at a low frequency (old lina: 1.9%, new lina: 1.7%). Laboratory parameters For most laboratory parameters, mean values at baseline and last value on treatment were within the reference ranges and the mean changes from baseline to last value on treatment were small. Mean values of glucose and triglycerides were above the reference ranges both at baseline and last value on treatment. The observed shifts in laboratory values were not clinically significant. Shifts of values from low/normal to high were most frequently observed for glucose (60.9% of treated patients) and triglycerides (21.4%). Possibly clinically significant abnormalities were most frequently reported for increased triglycerides (20.5% of treated patients), potassium (8.8%), and uric acid (8.2%). No potential Hy's law cases were reported. Vital signs The changes in systolic and diastolic blood pressure and pulse rate observed during the course of this trial were minimal and not clinically relevant.
Conclusions:	In this open-label extension study, patients with T2DM were treated with 5 mg linagliptin as monotherapy or in combination therapy with other antidiabetic oral agents (pioglitazone, metformin, or metformin plus a sulphonylurea). Treatment with linagliptin was generally well tolerated and the assessment of safety did not reveal major trends of clinical relevance. Long-term treatment with linagliptin was not associated with any relevant body weight change. The incidence of hypoglycaemic events was in line with the results of the preceding trials; hypoglycaemic events were most frequently experienced by patients who received double background therapy of metformin and sulphonylurea. In patients who had been randomised to linagliptin in the preceding trials, the glucose-lowering effect of linagliptin achieved during the 24 weeks of treatment in the previous trials was sustained throughout the present trial up to Week 78; in patients previously treated with placebo, a decrease in HbA_{1c} and fasting plasma glucose was observed. Overall, long-term treatment with linagliptin showed sustained glycaemic control, was weight neutral, safe, and well tolerated.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement results for primary and secondary endpoints of the trial. 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.

Results for	**presented in**
HbA_{1c} (%) over time (Secondary endpoint)	Table 15.2.2.1.1: 1
FPG (mg/dL) over time (Secondary endpoint)	Table 15.2.2.2: 1
Patients with transitions in clinical laboratory tests relative to reference ranges (Primary endpoint)	Table 15.3.3: 2
Vital signs over time (Primary endpoint)	Table 15.3.4: 1

Table 15.2.2.1.1: 1 Descriptive statistics of HbA1c (%) over time by exposure to linagliptin
Treated set (observed cases, values after rescue theraphy were set to missing)

	Old lina (N=1531)						New lina (N=587)					
	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Baseline	1531	7.37	0.90	5.1	7.30	12.3	587	7.87	1.04	5.3	7.80	11.7
Week 6	1401	7.31	0.88	5.1	7.20	12.9	530	7.37	0.87	4.9	7.30	10.6
Week 18	1302	7.25	0.81	5.0	7.20	11.7	510	7.11	0.79	4.8	7.00	9.9
Week 30	1183	7.21	0.81	5.1	7.10	12.7	469	7.10	0.78	4.9	7.00	10.1
Week 42	1091	7.24	0.74	5.3	7.20	10.3	440	7.14	0.76	5.2	7.10	9.5
Week 54	1008	7.26	0.76	5.4	7.20	11.1	417	7.18	0.79	5.3	7.10	10.5
Week 66	949	7.20	0.74	5.4	7.10	10.6	399	7.16	0.80	5.1	7.00	9.9
Week 78	904	7.17	0.77	5.0	7.10	12.2	373	7.11	0.80	5.1	7.00	10.3
Change from baseline to week 6	1401	-0.02	0.47	-3.5	0.00	3.0	530	-0.46	0.51	-2.7	-0.40	1.1
Change from baseline to week 18	1302	0.03	0.63	-2.8	0.00	3.0	510	-0.63	0.72	-4.3	-0.50	2.1
Change from baseline to week 30	1183	0.06	0.71	-3.0	0.00	5.1	469	-0.60	0.78	-4.7	-0.50	2.3
Change from baseline to week 42	1091	0.13	0.65	-2.5	0.10	3.5	440	-0.53	0.78	-4.0	-0.40	1.5
Change from baseline to week 54	1008	0.19	0.70	-2.6	0.20	3.8	417	-0.45	0.81	-3.9	-0.40	2.5
Change from baseline to week 66	949	0.14	0.73	-2.7	0.10	4.9	399	-0.44	0.85	-3.9	-0.40	3.1
Change from baseline to week 78	904	0.12	0.76	-2.9	0.10	6.7	373	-0.49	0.85	-4.0	-0.40	1.9

Table 15.2.2.2: 1 Descriptive statistics of FPG (mg/dL) by exposure to linagliptin over time
Treated set (observed cases, values after rescue theraphy were set to missing)

	Old lina (N= 1532)						New lina (N= 589)					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Baseline	1528	151.48	35.11	148.00	55.8	353.0	587	164.43	37.29	162.00	79.0	333.0
Week 6	1413	150.87	35.06	148.00	72.0	342.0	532	147.01	32.45	142.00	68.0	306.0
Week 18	1271	148.70	33.04	144.00	76.0	331.0	499	146.20	31.57	142.00	67.0	268.0
Week 30	1166	146.48	30.24	144.00	67.0	326.0	466	142.92	29.91	140.00	61.0	292.0
Week 42	1073	146.40	29.35	142.00	67.0	308.0	437	145.35	28.02	144.00	76.0	249.0
Week 54	1004	145.57	28.96	144.00	49.0	299.0	416	143.33	26.86	140.00	76.0	250.0
Week 66	955	142.50	28.75	139.00	68.0	330.0	398	142.18	29.39	140.00	77.0	281.0
Week 78	904	143.63	30.75	139.00	67.0	348.0	366	141.08	28.10	139.00	81.0	250.0
Change from baseline to week 6	1413	1.21	30.54	2.00	-182.0	150.0	531	-15.17	30.84	-12.87	-184.0	169.0
Change from baseline to week 18	1270	2.13	31.47	2.00	-208.0	152.9	499	-13.92	33.54	-12.00	-196.0	114.0
Change from baseline to week 30	1166	1.52	31.84	2.00	-188.0	220.0	466	-16.17	33.00	-14.00	-198.0	67.0
Change from baseline to week 42	1073	2.97	31.07	3.31	-200.0	189.0	437	-11.87	31.27	-9.08	-178.0	85.0
Change from baseline to week 54	1004	3.44	30.52	3.93	-155.0	164.0	416	-12.62	30.96	-9.08	-157.0	110.0
Change from baseline to week 66	955	0.88	31.96	2.00	-166.0	229.0	398	-12.87	30.16	-11.13	-151.0	90.0
Change from baseline to week 78	904	1.90	34.11	1.52	-180.0	195.0	366	-13.64	31.67	-13.00	-155.0	130.0

TABLE 15.3.3: 2 Frequency of patients [N(%)] with transitions relative to reference range

HAEMATOLOGY

Parameter/ Treatment	Last Value on Treatment: High, Norm to Low	at risk*	Last Value on Treatment: Low,Norm to High	at risk**	Min Post Baseline: High, Norm to Low	at risk*	Max Post Baseline: Low, Norm to High	at risk**
Haematocrit								
Old lina	81 (5.7)	1417	30 (2.0)	1465	197 (13.9)	1417	105 (7.2)	1465
New lina	24 (4.5)	537	17 (3.1)	551	69 (12.8)	537	39 (7.1)	551
Lina total	105 (5.4)	1954	47 (2.3)	2016	266 (13.6)	1954	144 (7.1)	2016
Haemoglobin								
Old lina	99 (7.2)	1372	8 (0.5)	1485	232 (16.9)	1372	42 (2.8)	1485
New lina	38 (7.3)	524	5 (0.9)	567	80 (15.3)	524	22 (3.9)	567
Lina total	137 (7.2)	1896	13 (0.6)	2052	312 (16.5)	1896	64 (3.1)	2052
Red blood cell ct.								
Old lina	140 (10.6)	1318	7 (0.5)	1470	280 (21.2)	1318	27 (1.8)	1470
New lina	50 (9.9)	504	4 (0.7)	552	97 (19.2)	504	12 (2.2)	552
Lina total	190 (10.4)	1822	11 (0.5)	2022	377 (20.7)	1822	39 (1.9)	2022
White blood cell ct.								
Old lina	17 (1.2)	1464	42 (3.0)	1407	117 (8.0)	1464	194 (13.8)	1407
New lina	7 (1.3)	560	21 (3.9)	541	47 (8.4)	560	82 (15.2)	541
Lina total	24 (1.2)	2024	63 (3.2)	1948	164 (8.1)	2024	276 (14.2)	1948
Platelets								
Old lina	35 (2.4)	1461	7 (0.5)	1486	83 (5.7)	1461	25 (1.7)	1486
New lina	15 (2.7)	557	0	571	42 (7.5)	557	12 (2.1)	571
Lina total	50 (2.5)	2018	7 (0.3)	2057	125 (6.2)	2018	37 (1.8)	2057

* High or normal value at baseline
** Low or normal at baseline
Note: Calculations for this table use all on-treatment values, including repeated measurements.

Source data: Appendix 16.2.8, Listing 2 s15\lab1_fr_15ts.sas 17MAR2011

TABLE 15.3.3: 2 Frequency of patients [N(%)] with transitions relative to reference range

DIFFERENTIAL_AUTOMATIC

Parameter/ Treatment	Last Value on Treatment: High, Norm to Low	at risk*	Low, Norm to High	at risk**	Min Post Baseline: High, Norm to Low	at risk*	Max Post Baseline: Low, Norm to High	at risk**
Neutrophils								
Old lina	9 (0.6)	1455	36 (2.5)	1448	128 (8.8)	1455	150 (10.4)	1448
New lina	5 (0.9)	560	14 (2.5)	560	54 (9.6)	560	60 (10.7)	560
Lina total	14 (0.7)	2015	50 (2.5)	2008	182 (9.0)	2015	210 (10.5)	2008
Eosinophils								
Old lina	0	1506	27 (1.9)	1433	0	1506	125 (8.7)	1433
New lina	0	576	10 (1.8)	546	0	576	46 (8.4)	546
Lina total	0	2082	37 (1.9)	1979	0	2082	171 (8.6)	1979
Basophils								
Old lina	0	1506	2 (0.1)	1503	0	1506	33 (2.2)	1503
New lina	0	576	1 (0.2)	574	0	576	13 (2.3)	574
Lina total	0	2082	3 (0.1)	2077	0	2082	46 (2.2)	2077
Lymphocytes								
Old lina	24 (1.6)	1466	12 (0.8)	1475	97 (6.6)	1466	61 (4.1)	1475
New lina	7 (1.2)	567	6 (1.1)	566	35 (6.2)	567	22 (3.9)	566
Lina total	31 (1.5)	2033	18 (0.9)	2041	132 (6.5)	2033	83 (4.1)	2041
Monocytes								
Old lina	84 (5.8)	1436	7 (0.5)	1491	253 (17.6)	1436	50 (3.4)	1491
New lina	18 (3.3)	551	4 (0.7)	574	93 (16.9)	551	19 (3.3)	574
Lina total	102 (5.1)	1987	11 (0.5)	2065	346 (17.4)	1987	69 (3.3)	2065

* High or normal value at baseline
** Low or normal at baseline
Note: Calculations for this table use all on-treatment values, including repeated measurements.

Source data: Appendix 16.2.8, Listing 2

TABLE 15.3.3: 2 Frequency of patients [N(%)] with transitions relative to reference range

ELECTROLYTES

Parameter/ Treatment	Last Value on Treatment: High, Norm to Low	at risk*	Last Value on Treatment: Low,Norm to High	at risk**	Min Post Baseline: High, Norm to Low	at risk*	Max Post Baseline: Low, Norm to High	at risk**
Sodium								
Old lina	10 (0.7)	1492	35 (2.4)	1489	50 (3.4)	1492	100 (6.7)	1489
New lina	4 (0.7)	571	7 (1.2)	570	17 (3.0)	571	31 (5.4)	570
Lina total	14 (0.7)	2063	42 (2.0)	2059	67 (3.2)	2063	131 (6.4)	2059
Potassium								
Old lina	8 (0.5)	1497	97 (6.9)	1414	24 (1.6)	1497	367 (26.0)	1414
New lina	0	573	36 (6.6)	542	5 (0.9)	573	137 (25.3)	542
Lina total	8 (0.4)	2070	133 (6.8)	1956	29 (1.4)	2070	504 (25.8)	1956
Calcium								
Old lina	21 (1.4)	1493	18 (1.2)	1445	88 (5.9)	1493	108 (7.5)	1445
New lina	5 (0.9)	574	10 (1.8)	553	19 (3.3)	574	47 (8.5)	553
Lina total	26 (1.3)	2067	28 (1.4)	1998	107 (5.2)	2067	155 (7.8)	1998
Phosphate								
Old lina	8 (0.5)	1491	72 (5.1)	1416	56 (3.8)	1491	267 (18.9)	1416
New lina	6 (1.1)	565	31 (5.6)	552	26 (4.6)	565	106 (19.2)	552
Lina total	14 (0.7)	2056	103 (5.2)	1968	82 (4.0)	2056	373 (19.0)	1968

* High or normal value at baseline
** Low or normal at baseline
Note: Calculations for this table use all on-treatment values, including repeated measurements.

Source data: Appendix 16.2.8, Listing 2 s15\lab1_fr_15ts.sas 17MAR2011

TABLE 15.3.3: 2 Frequency of patients [N(%)] with transitions relative to reference range

ENZYMES

Parameter/ Treatment	Last Value on Treatment: High, Norm to Low	at risk*	Last Value on Treatment: Low,Norm to High	at risk**	Min Post Baseline: High, Norm to Low	at risk*	Max Post Baseline: Low, Norm to High	at risk**
AST/GOT, SGOT								
Old lina	6 (0.4)	1488	75 (5.3)	1419	30 (2.0)	1488	212 (14.9)	1419
New lina	1 (0.2)	574	24 (4.5)	538	9 (1.6)	574	59 (11.0)	538
Lina total	7 (0.3)	2062	99 (5.1)	1957	39 (1.9)	2062	271 (13.8)	1957
ALT/GPT, SGPT								
Old lina	5 (0.3)	1496	89 (6.5)	1370	35 (2.3)	1496	227 (16.6)	1370
New lina	2 (0.3)	573	24 (4.7)	512	9 (1.6)	573	75 (14.6)	512
Lina total	7 (0.3)	2069	113 (6.0)	1882	44 (2.1)	2069	302 (16.0)	1882
Alkaline phosphatase								
Old lina	14 (0.9)	1487	25 (1.7)	1481	48 (3.2)	1487	63 (4.3)	1481
New lina	9 (1.6)	566	3 (0.5)	562	25 (4.4)	566	10 (1.8)	562
Lina total	23 (1.1)	2053	28 (1.4)	2043	73 (3.6)	2053	73 (3.6)	2043
GGT								
Old lina	10 (0.7)	1486	77 (5.8)	1328	43 (2.9)	1486	195 (14.7)	1328
New lina	8 (1.4)	574	29 (5.7)	509	21 (3.7)	574	71 (13.9)	509
Lina total	18 (0.9)	2060	106 (5.8)	1837	64 (3.1)	2060	266 (14.5)	1837
LDH								
Old lina	78 (6.2)	1259	47 (3.3)	1435	223 (17.7)	1259	158 (11.0)	1435
New lina	30 (6.3)	475	14 (2.6)	543	100 (21.1)	475	55 (10.1)	543
Lina total	108 (6.2)	1734	61 (3.1)	1978	323 (18.6)	1734	213 (10.8)	1978
Creatine kinase								
Old lina	7 (0.5)	1502	91 (6.7)	1364	20 (1.3)	1502	318 (23.3)	1364
New lina	0	574	39 (7.5)	523	6 (1.0)	574	128 (24.5)	523
Lina total	7 (0.3)	2076	130 (6.9)	1887	26 (1.3)	2076	446 (23.6)	1887
Amylase								
Old lina	22 (1.5)	1462	67 (5.1)	1305	56 (3.8)	1462	200 (15.3)	1305
New lina	4 (0.7)	563	35 (6.8)	511	18 (3.2)	563	92 (18.0)	511
Lina total	26 (1.3)	2025	102 (5.6)	1816	74 (3.7)	2025	292 (16.1)	1816

* High or normal value at baseline
** Low or normal at baseline
Note: Calculations for this table use all on-treatment values, including repeated measurements.

Source data: Appendix 16.2.8, Listing 2 s15\lab1_fr_15ts.sas 17MAR2011

TABLE 15.3.3: 2 Frequency of patients [N(%)] with transitions relative to reference range

ENZYMES

Parameter/ Treatment	Last Value on Treatment				Min Post Baseline		Max Post Baseline	
	High, Norm to Low	at risk*	Low,Norm to High	at risk**	High, Norm to Low	at risk*	Low, Norm to High	at risk**
CK-MB enzymatic								
Old lina	0	193	18 (13.2)	136	0	193	35 (25.7)	136
New lina	0	75	7 (13.5)	52	0	75	13 (25.0)	52
Lina total	0	268	25 (13.3)	188	0	268	48 (25.5)	188

* High or normal value at baseline
** Low or normal at baseline
Note: Calculations for this table use all on-treatment values, including repeated measurements.

Source data: Appendix 16.2.8, Listing 2 s15\lab1_fr_15ts.sas 17MAR2011

TABLE 15.3.3: 2 Frequency of patients [N(%)] with transitions relative to reference range

SUBSTRATES

Parameter/ Treatment	Last Value on Treatment: High, Norm to Low	at risk*	Last Value on Treatment: Low,Norm to High	at risk**	Min Post Baseline: High, Norm to Low	at risk*	Max Post Baseline: Low, Norm to High	at risk**
Glucose								
Old lina	4 (0.3)	1506	98 (62.8)	156	18 (1.2)	1506	143 (91.7)	156
New lina	0	576	22 (53.7)	41	2 (0.3)	576	33 (80.5)	41
Lina total	4 (0.2)	2082	120 (60.9)	197	20 (1.0)	2082	176 (89.3)	197
Cholesterol, total								
Old lina	0	1507	74 (5.7)	1290	0	1507	223 (17.3)	1290
New lina	0	576	22 (4.6)	478	0	576	90 (18.8)	478
Lina total	0	2083	96 (5.4)	1768	0	2083	313 (17.7)	1768
HDL								
Old lina	116 (11.3)	1023	14 (1.0)	1466	313 (30.6)	1023	31 (2.1)	1466
New lina	48 (12.1)	397	4 (0.7)	565	131 (33.0)	397	19 (3.4)	565
Lina total	164 (11.5)	1420	18 (0.9)	2031	444 (31.3)	1420	50 (2.5)	2031
LDL								
Old lina	0	1506	56 (4.2)	1330	0	1506	202 (15.2)	1330
New lina	0	576	22 (4.3)	510	0	576	87 (17.1)	510
Lina total	0	2082	78 (4.2)	1840	0	2082	289 (15.7)	1840
Urea								
Old lina	7 (0.5)	1503	112 (8.7)	1281	14 (0.9)	1503	334 (26.1)	1281
New lina	1 (0.2)	574	40 (8.0)	499	3 (0.5)	574	127 (25.5)	499
Lina total	8 (0.4)	2077	152 (8.5)	1780	17 (0.8)	2077	461 (25.9)	1780
Creatinine								
Old lina	32 (2.4)	1314	67 (4.6)	1463	141 (10.7)	1314	146 (10.0)	1463
New lina	14 (2.8)	504	18 (3.2)	561	52 (10.3)	504	39 (7.0)	561
Lina total	46 (2.5)	1818	85 (4.2)	2024	193 (10.6)	1818	185 (9.1)	2024
Bilirubin, total								
Old lina	77 (5.2)	1472	11 (0.8)	1460	228 (15.5)	1472	70 (4.8)	1460
New lina	27 (4.8)	567	2 (0.4)	558	80 (14.1)	567	16 (2.9)	558
Lina total	104 (5.1)	2039	13 (0.6)	2018	308 (15.1)	2039	86 (4.3)	2018

* High or normal value at baseline
** Low or normal at baseline
Note: Calculations for this table use all on-treatment values, including repeated measurements.

Source data: Appendix 16.2.8, Listing 2 s15\lab1_fr_15ts.sas 17MAR2011

TABLE 15.3.3: 2 Frequency of patients [N(%)] with transitions relative to reference range

SUBSTRATES

Parameter/ Treatment	Last Value on Treatment: High, Norm to Low	at risk*	Last Value on Treatment: Low,Norm to High	at risk**	Min Post Baseline: High, Norm to Low	at risk*	Max Post Baseline: Low, Norm to High	at risk**
Triglyceride								
Old lina	0	1507	179 (21.2)	843	0	1507	423 (50.2)	843
New lina	0	576	65 (22.0)	295	0	576	152 (51.5)	295
Lina total	0	2083	244 (21.4)	1138	0	2083	575 (50.5)	1138
Uric acid								
Old lina	12 (0.8)	1496	123 (9.2)	1336	35 (2.3)	1496	277 (20.7)	1336
New lina	0	562	50 (9.5)	525	9 (1.6)	562	113 (21.5)	525
Lina total	12 (0.6)	2058	173 (9.3)	1861	44 (2.1)	2058	390 (21.0)	1861
Protein, total								
Old lina	24 (1.6)	1498	16 (1.2)	1320	49 (3.3)	1498	122 (9.2)	1320
New lina	8 (1.4)	576	7 (1.3)	520	14 (2.4)	576	55 (10.6)	520
Lina total	32 (1.5)	2074	23 (1.3)	1840	63 (3.0)	2074	177 (9.6)	1840
Albumin								
Old lina	4 (0.3)	1503	27 (1.9)	1445	12 (0.8)	1503	131 (9.1)	1445
New lina	0	576	10 (1.8)	553	3 (0.5)	576	71 (12.8)	553
Lina total	4 (0.2)	2079	37 (1.9)	1998	15 (0.7)	2079	202 (10.1)	1998

* High or normal value at baseline
** Low or normal at baseline
Note: Calculations for this table use all on-treatment values, including repeated measurements.

Source data: Appendix 16.2.8, Listing 2 s15\lab1_fr_15ts.sas 17MAR2011

TABLE 15.3.3: 2 Frequency of patients [N(%)] with transitions relative to reference range

URINE_ANALYSIS

Parameter/ Treatment	Last Value on Treatment: High, Norm to Low	at risk*	Low, Norm to High	at risk**	Min Post Baseline: High, Norm to Low	at risk*	Max Post Baseline: Low, Norm to High	at risk**
U.microalbumin creatinine ratio								
Old lina	0	1451	125 (12.0)	1046	0	1451	342 (32.7)	1046
New lina	0	554	38 (9.7)	391	0	554	106 (27.1)	391
Lina total	0	2005	163 (11.3)	1437	0	2005	448 (31.2)	1437

* High or normal value at baseline
** Low or normal at baseline
Note: Calculations for this table use all on-treatment values, including repeated measurements.

Table 15.3.4: 1 Descriptive statistics of vital signs over time
Treated set

	Old lina (N=1532)						New lina (N=589)					
	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Systolic blood pressure [mmHg]												
Baseline	1532	129.80	14.91	91	130.00	197	589	130.15	14.84	90	130.00	180
Week 6	1505	129.11	14.83	88	130.00	200	578	128.55	14.77	90	129.00	189
Week 18	1464	129.27	14.81	88	130.00	190	570	128.94	14.28	90	129.00	196
Week 30	1435	129.54	14.58	89	130.00	193	560	128.97	14.77	90	129.00	181
Week 42	1410	130.30	14.51	90	130.00	207	548	129.39	14.30	90	130.00	188
Week 54	1386	130.43	14.38	90	130.00	200	543	129.63	15.12	90	130.00	186
Week 66	1372	129.59	14.66	89	130.00	198	539	128.77	14.45	90	129.00	194
Week 78/EOT	1477	130.29	14.99	85	130.00	189	567	129.26	14.98	82	128.00	187
Follow up	289	129.90	13.68	86	130.00	166	131	128.36	12.79	100	129.00	162
Change from Baseline to Week 6	1505	-0.72	12.56	-50	0.00	62	578	-1.50	12.59	-45	0.00	40
Change from Baseline to Week 18	1464	-0.54	12.97	-47	0.00	51	570	-1.12	13.06	-40	0.00	47
Change from Baseline to Week 30	1435	-0.30	13.73	-40	0.00	48	560	-1.10	14.01	-54	0.00	46
Change from Baseline to Week 42	1410	0.50	13.96	-52	0.00	77	548	-0.55	13.15	-45	0.00	46
Change from Baseline to Week 54	1386	0.61	14.10	-61	0.00	67	543	-0.30	14.49	-50	0.00	47
Change from Baseline to Week 66	1372	-0.23	14.14	-58	0.00	60	539	-1.14	14.12	-40	0.00	72
Change from Baseline to Week 78/EOT	1477	0.49	14.52	-70	0.00	62	567	-0.61	14.08	-42	0.00	51
Change from Baseline to Follow up	289	0.58	14.39	-42	0.00	38	131	-1.56	14.68	-34	-1.00	32
Diastolic blood pressure [mmHg]												
Baseline	1532	78.13	8.59	51	80.00	107	589	78.31	8.73	50	80.00	109
Week 6	1505	77.95	8.56	33	80.00	110	578	77.96	8.59	52	80.00	109
Week 18	1464	77.89	8.90	49	80.00	118	570	78.58	8.53	58	80.00	109
Week 30	1435	78.14	8.77	34	80.00	117	560	78.26	9.21	51	80.00	130
Week 42	1410	78.18	8.78	52	80.00	110	548	78.36	9.01	52	80.00	120
Week 54	1386	78.10	8.44	51	80.00	109	543	77.95	9.09	53	79.00	116
Week 66	1372	77.60	8.49	50	79.00	113	539	77.28	8.76	52	78.00	111
Week 78/EOT	1477	77.77	8.71	50	80.00	119	567	77.92	8.82	51	80.00	107
Follow up	289	77.75	8.15	55	80.00	105	131	78.76	8.30	56	80.00	103
Change from Baseline to Week 6	1505	-0.22	8.04	-44	0.00	30	578	-0.33	8.00	-32	0.00	30
Change from Baseline to Week 18	1464	-0.25	8.51	-30	0.00	33	570	0.26	8.35	-36	0.00	33
Change from Baseline to Week 30	1435	-0.02	8.54	-39	0.00	33	560	0.02	9.15	-34	0.00	43
Change from Baseline to Week 42	1410	0.02	8.92	-36	0.00	35	548	0.16	9.16	-38	0.00	28
Change from Baseline to Week 54	1386	-0.04	9.07	-41	0.00	31	543	-0.33	8.89	-43	0.00	30
Change from Baseline to Week 66	1372	-0.56	8.89	-36	0.00	30	539	-1.02	9.08	-34	0.00	28
Change from Baseline to Week 78/EOT	1477	-0.35	9.02	-42	0.00	38	567	-0.28	9.18	-31	0.00	30

Table 15.3.4: 1 Descriptive statistics of vital signs over time
Treated set

	Old lina (N=1532)						New lina (N=589)					
	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Change from Baseline to Follow up	289	0.08	9.30	-22	0.00	27	131	0.44	8.52	-20	0.00	22
Pulse rate [bpm]												
Baseline	1532	74.86	9.81	47	74.00	120	589	74.98	10.07	43	75.00	112
Week 6	1505	74.82	9.38	46	75.00	109	578	74.84	9.34	45	75.00	111
Week 18	1464	74.27	9.11	45	74.00	108	570	74.96	9.48	44	75.00	109
Week 30	1435	74.37	9.62	49	74.00	116	560	74.21	9.28	50	74.00	105
Week 42	1411	74.02	9.34	48	74.00	116	548	74.76	9.55	40	74.00	106
Week 54	1386	74.05	9.76	46	73.00	124	543	75.01	10.22	43	74.00	114
Week 66	1372	74.12	9.48	45	74.00	116	539	74.35	9.16	46	74.00	105
Week 78/EOT	1477	74.03	9.76	48	74.00	116	567	74.38	9.84	44	74.00	106
Follow up	289	75.60	9.90	49	75.00	107	131	76.12	8.55	55	76.00	95
Change from Baseline to Week 6	1505	-0.06	8.21	-36	0.00	38	578	-0.07	8.39	-35	0.00	34
Change from Baseline to Week 18	1464	-0.58	8.46	-43	0.00	28	570	0.04	9.06	-38	0.00	34
Change from Baseline to Week 30	1435	-0.42	8.94	-36	0.00	39	560	-0.65	9.08	-35	0.00	28
Change from Baseline to Week 42	1411	-0.71	9.13	-37	0.00	40	548	-0.11	9.36	-33	0.00	37
Change from Baseline to Week 54	1386	-0.64	9.00	-46	0.00	45	543	0.03	9.28	-26	0.00	52
Change from Baseline to Week 66	1372	-0.55	9.17	-38	0.00	40	539	-0.60	8.76	-39	0.00	28
Change from Baseline to Week 78/EOT	1477	-0.74	9.10	-37	0.00	56	567	-0.61	9.34	-33	0.00	35
Change from Baseline to Follow up	289	-0.54	9.83	-28	0.00	40	131	0.58	9.82	-28	0.00	36