SYNOPSIS

Name of Sponsor:

Fournier Laboratories Ireland Ltd., an Abbott company

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:

ABT-335/SLV348

Name of Active Ingredient:

Fenofibric acid

Study Title:

Effect of Choline Fenofibrate (ABT-335/SLV348) on Macular Edema Measured by Optical Coherence Tomography in Subjects with Diabetic Macular Edema - a One-year, Placebo-controlled, Randomized Study

Coordinating Investigator:

PPD

Study Centers:

Thirty one sites included at least one subject who consented in Austria, Bulgaria, Czech Republic, Denmark, France, Germany, Hungary, Italy, The Netherlands, Poland, Spain, and the UK; No subjects were randomized at sites in Austria and France.

Publication (Reference):

Not applicable

Study Period:

15 SEP 2008 (first subject first visit) to
21 MAR 2011 (last subject last visit)

Phase of Development:

II

Objectives:

Primary Objective:

The primary objective of this study was to evaluate the effects of once daily 135 mg ABT-335/SLV348 versus matching placebo, on changes of macular edema measured by optical coherence tomography (OCT) assessed by total macular volume (TMV) after 12 months (52 weeks) of treatment in subjects with type 2 diabetes mellitus (T2DM) and with diabetic macular edema (DME), in absence or presence of center involvement, when laser treatment could be safely postponed by at least 3 months, and with OCT measures of thickness $\geq$ 300 µm in at least one out of five macular zones including the center zone and the four inner zones (superior, nasal, inferior and temporal) at Baseline.

Secondary Objectives:

The secondary objectives were the following:

- To evaluate other OCT parameters including weighted inner zone (WIZ) thickening, center zone thickness (CZT) and center point thickness (CPT).
- To evaluate changes in Early Treatment Diabetic Retinopathy Study (ETDRS) macular

edema grading and hard exudate grading.

- To evaluate changes of best corrected visual acuity
- To evaluate changes on progression to laser photocoagulation.

Safety Objective:

The safety objective was to evaluate the safety of ABT-335/SLV348 in diabetic patients presenting with DME.

Methodology:

This was a phase II, multinational, multicenter, randomized, prospective, double-blind, placebo-controlled study in subjects with T2DM and DME in the presence or absence of center involvement.

Subjects were to be randomized in a 1:1 ratio to either ABT-335/SLV348 or placebo. The planned duration of the study was approximately 58 weeks (13.5 months), consisting of the following periods:

- 6-week screening period,
- 52-week treatment period (12 months).

Number of Subjects (Planned, Consented, Randomized and Analyzed):
106 subjects were planned, 285 subjects consented, 110 subjects randomized (57 in the SLV348 group and 53 in the placebo group) and 110 subjects analyzed.

Diagnosis and Main Criteria for Inclusion:
A subject was eligible for study participation if he/she met the following criteria: Subject had voluntarily signed and dated an informed consent form; was ≥ 30 years of age; had been diagnosed with T2DM for at least 6 months before Pre-screening; diagnosed with DME in at least one eye with any appropriate investigational method where laser photocoagulation could have been safely postponed by at least 3 months in the investigator's opinion; had at least one eligible eye which was defined as thickness of ≥ 300 µm in at least one of the five following zones: center zone, superior inner zone, nasal inner zone, inferior inner zone and temporal inner zone; subject had a life expectancy greater than one year; subject had documented elevated triglyceride (TG) levels (150 ≤ TG ≤ 500 mg/dL [1.70 - 5.60 mmol/L], changed in amendment 1 to 89 ≤ TG ≤ 500 mg/dL [1.00 - 5.60 mmol/L]) at Screening or in the previous 3 months (in case of concomitant lipid-lowering treatment with a fibrate); if female, subject was either postmenopausal for at least one year or surgically sterile or of childbearing potential with negative results of a serum pregnancy test performed at Screening, and not breastfeeding at Pre-screening; subject also had to be willing to participate in the study and to complete all the scheduled assessments.

Test Product, Dose and Mode of Administration, Batch Number:

Choline fenofibrate as fenofibric acid, 135 mg ABT-335/SLV348, capsule, once daily, orally.

Batch number RD-08-0012 and RD-09-0043 (manufacturing batches).

Duration of Treatment:

Six-week screening period (pre-screening and screening) and 52-week (12 months) treatment period.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Matching placebo capsule, once daily, oral.

Batch number RD-08-0018 and RD-09-0042 (manufacturing batches).

Criteria for Evaluation

Efficacy:

The primary variable was the change from Baseline to Endpoint (Final visit [Visit 7] or last measurement in case of premature withdrawal, laser photocoagulation, ocular surgical intervention or intra-vitreal injection, with availability of at least one OCT evaluation performed under study treatment) in the TMV of the "worst eye" (defined as the eye with the highest TMV at Baseline in the eligible eyes population).

The secondary variables from OCT measurements, analyzed from Baseline to Endpoint for the "worst eyes" were the following:

- Change in WIZ thickening.
- Change in inner zone volume (center zone and four inner zones).
- Change in mean inner zone thickness.
- Change in maximum retinal thickness.
- Change in CZT.
- Change in CPT.
- Percentage of subjects with "worst eye" at least 8% and 10% change in the TMV.
- Percentage of subjects with "worst eye" at least 30%, 40% and 50% change in WIZ thickening.
- Percentage of subjects with CZT $\geq$ 250 µm and $\geq$ 300 µm post-Baseline.
- Percentage of subjects with regressions of CZT dropped to < 250 µm.

The secondary variables from the other ophthalmology assessments for the "worst eyes" from Baseline to Endpoint were the following:

- Change in ETDRS macular grading of the fundus photographs.
- Change in ETDRS hard exudate grading of the fundus photographs.
- Change in ETDRS visual acuity score.
- Distribution of the changes in visual acuity.
- Change in ETDRS grading of the 7-field photographs.
- Proportion of laser photocoagulations and/or ocular surgical intervention and/or intra-vitreal injections for DME.

Other secondary variables, from Baseline to Endpoint, were the following:

- Mean percent change in total cholesterol, low-density lipid cholesterol (calculated), high-density lipid cholesterol and triglycerides.
- Mean changes in systolic blood pressure/diastolic blood pressure.
- Mean change in urinary albumin excretion rate.
- General safety by means of vital signs, laboratory investigations and adverse events

(AEs).

Safety:

Safety was measured by the following:

- AEs/serious AEs.
- Laboratory parameters (including assessment of lipid, transaminases, creatinine and creatine kinase abnormalities).
- Vital signs.
- Physical examination.

Statistical Methods:

There were three hierarchical main subject samples of interest. The Safety sample was used for the analysis of the safety and tolerance data. The efficacy analyses were performed on the Full Analysis (FA) sample and the Per Protocol (PP) sample, with the FA subject sample regarded as primary. The PP sample included subjects without major protocol deviations.

The study was powered to detect a 6% (SD 10%) difference in TMV between groups (laser photocoagulation was shown to result in mean reduction in TMV of 0.5 to 0.8 mm^3, a proportionate reduction of about 6 to 9%).

The primary analysis was an intent to treat per-subject on the worst eye with the larger TMV at Baseline when both eyes were eligible, comparing between the two groups Baseline and last measurement with an analysis of covariance model. As part of sensitivity analyses, presence of clinical significant macular edema at Baseline was included in the model and all eligible eyes were analyzed using an appropriate model (generalized estimating equation [GEE]) to account for repeated measures and correlated data when both eyes were eligible. In case of laser therapy, intravitreal injection or eye surgery the last measurement prior to such intervention was to be used.

Summary – Conclusions

Efficacy Results:

The two treatment groups were comparable at Baseline for the demographic and the ophthalmological characteristics. At Baseline means TMV were similar 8.536 ±1.759 mm^3 and 8.570 ± 1.459 mm^3 in the two treatment groups.

Primary Efficacy Variable

In the worst eye, the mean change from Baseline at Endpoint in TMV was larger in the SLV348 group (-0.349 ± 0.901 mm^3) compared to the placebo group (-0.106 ±1.269 mm^3). Similar results were observed for the all eligible study eyes with a mean change from Baseline at Endpoint of -0.339 mm^3 in the SLV348 group and -0.130 mm^3 in the placebo group.

No statistically significant difference between SLV348 and placebo was observed for the change in TMV from Baseline to Endpoint in the worst eye (least squares [LS] mean difference from Baseline between placebo and SLV348 [95% confidence interval (CI)]: -0.2 [-0.6; 0.1], p-value: 0.219). Similar findings were seen in the analysis of all eligible eyes and were supported by the GEE analysis (LS means difference from Baseline between placebo and SLV348 [95% CI]: -0.2 [-0.6; 0.1], p-value: 0.138).

Total macular volume values in the worst eye and all eligible study eyes at Baseline, Endpoint and change from Baseline at Endpoint are presented in Table 1 for the SLV348 group, the placebo group and the total population.

Table 1. Summary of Total Macular Volume Values at Baseline, Endpoint and Change from Baseline to Endpoint

FA SAMPLE

	Statistic	S348 (N=52)	Placebo (N=50)	Total (N=102)
Worst Eye				
Total Macular Volume (mm^3)				
Baseline	n	52	50	102
	Mean (SD)	8.536 (1.759)	8.570 (1.459)	8.553 (1.611)
	Median	7.993	8.205	8.141
	Min/Max	6.82/14.78	6.70/14.59	6.70/14.78
Endpoint	n	52	50	102
	Mean (SD)	8.188 (1.596)	8.464 (1.380)	8.323 (1.493)
	Median	7.662	8.190	7.856
	Min/Max	6.54/14.33	6.28/12.49	6.28/14.33
Change from Baseline at Endpoint	n	52	50	102
	Mean (SD)	-0.349 (0.901)	-0.106 (1.269)	-0.229 (1.099)
	Median	-0.343	-0.042	-0.220
	Min/Max	-2.67/2.37	-5.34/2.84	-5.34/2.84
Number of Eligible Eyes	n	77	73	150
Total Macular Volume (mm^3)				
Baseline	n	77	73	150
	Mean (SD)	8.449 (1.605)	8.506 (1.438)	8.477 (1.521)
	Median	7.971	8.216	8.141
	Min/Max	6.57/14.78	5.40/14.59	5.40/14.78
Endpoint	n	77	73	150
	Mean (SD)	8.110 (1.451)	8.376 (1.279)	8.240 (1.372)
	Median	7.653	8.082	7.819
	Min/Max	6.54/14.33	6.28/12.49	6.28/14.33
Change from Baseline at Endpoint	n	77	73	150
	Mean (SD)	-0.339 (0.875)	-0.130 (1.147)	-0.237 (1.019)
	Median	-0.263	-0.062	-0.180
	Min/Max	-2.87/2.37	-5.34/2.84	-5.34/2.84

Note(s): Value at baseline is defined as the last non-missing value before the first study drug administration. Value at endpoint is defined as the last non-missing value under study drug.
Source: Table 10.1.2.3 and Table 10.1.2.4.

Secondary Efficacy Variables

The CZT values at Baseline, Endpoint and change from Baseline at Endpoint in the worst eye and all eligible study eyes are presented in Table 2 for the SLV348 group, the placebo group and the total population.

Table 2. Summary for the CZT Values at Baseline, Endpoint, and Change from Baseline at Endpoint

FA SAMPLE

	Statistic	S348 (N=52)	Placebo (N=50)	Total (N=102)
Worst Eye CZT (µm)				
Baseline	n	52	50	102
	Mean (SD)	357.5 (120.4)	336.8 (111.8)	347.4 (116.2)
	Median	331.0	322.5	327.5
	Min/Max	197/761	198/648	197/761
Endpoint	n	52	50	102
	Mean (SD)	339.8 (118.1)	332.6 (114.9)	336.2 (116.1)
	Median	327.0	322.5	324.5
	Min/Max	176/681	172/692	172/692
Change from Baseline at Endpoint	n	52	50	102
	Mean (SD)	-17.8 (81.4)	-4.2 (105.3)	-11.1 (93.7)
	Median	-11.5	0.0	-7.0
	Min/Max	-199/218	-360/231	-360/231
Number of Eligible Eyes CZT (µm)	n	77	73	150
Baseline	n	77	73	150
	Mean (SD)	345.0 (117.0)	337.6 (109.0)	341.4 (112.9)
	Median	320.0	314.0	318.0
	Min/Max	193/761	198/648	193/761
Endpoint	n	77	73	150
	Mean (SD)	323.7 (111.5)	328.0 (111.9)	325.8 (111.3)
	Median	293.0	317.0	305.0
	Min/Max	176/681	172/692	172/692
Change from Baseline at Endpoint	n	77	73	150
	Mean (SD)	-21.3 (77.1)	-9.6 (94.5)	-15.6 (85.9)
	Median	-14.0	-5.0	-9.5
	Min/Max	-235/218	-360/231	-360/231

Note(s): Value at baseline is defined as the last non-missing value before the first study drug administration. Value at endpoint is defined as the last non-missing value under study treatment. CZT = central zone thickness
Source: Table 10.1.2.16 and Table 10.1.2.17.

Changes from Baseline at Endpoint for CZT were observed for the worst eye (SLV348: -17.8 µm, placebo: -4.2 µm) and for all eligible study eyes, but the difference between SLV348 and placebo was not statistically significant (LS mean difference from Baseline between placebo and SLV348 [95% CI]: -5.3 [-40.2; 29.5], p-value: 0.761).

For the worst eye the change from Baseline at Endpoint for WIZ thickening was -18.7 µm in the SLV348 group and -3.0 µm in the placebo group (LS mean difference from Baseline between placebo and SLV348 [95% CI]: -12.5 [-34.7; 9.6], p-value: 0.265), -0.1 mm^3 in the SLV348 group and -0.02 mm^3 in the placebo group (LS mean difference from Baseline between placebo and SLV348 [95% CI]: -0.1 [-0.2 ; 0.1], p-value: 0.264) for inner zone volume, -18.6 µm in the SLV348 group and -3.2 µm in the placebo group (LS mean difference from Baseline between placebo and SLV348 [95% CI]: -11.8 [-35.0; 11.4], p-value: 0.316) for mean inner zone thickness, -15.9 µm in the SLV348 group and -10.7 µm in the placebo group (LS

mean difference from Baseline between placebo and SLV348 [95% CI] : -3.8 [-33.7; 26.0], p-value: 0.799) for maximum retinal thickness, and -16.1 µm in the SLV348 group and -8.3 µm in the placebo group (LS mean difference from Baseline between placebo and SLV348 [95% CI]: 1.1 [-39.3; 41.6] p-value: 0.956) for CPT. Similar results were observed for all eligible study eyes.

For the OCT secondary efficacy variables in the worst eyes the mean change from Baseline at Endpoint was larger in the SLV348 group compared to the placebo group, but no statistically significant difference between SLV348 and placebo was observed.

The proportion of subjects with at least 8% (SLV348: 15 subjects, placebo: 11 subjects) and 10% (SLV348: 12 subjects, placebo: 10 subjects) change from Baseline at Endpoint in TMV in the worst eye did not show a statistically significant difference between SLV348 and placebo (p-values: 0.511 and 0.786, respectively).

In the worst eye, a larger number of subjects in both the SLV348 group (12 subjects [23.1%]) and placebo group (10 subjects [20.0%]) were reported with transient regression of CZT compared to the number of subjects with sustained regression of CZT (SLV348: 3 subjects [5.8%], placebo: 3 subjects [6.0%]). The difference between SLV348 and placebo in the proportion of subjects with sustained or transient regression of CZT was not statistically significant (p-values: 0.869 and 0.886, respectively).

No statistically significant difference between SLV348 and placebo was observed in the proportion of subjects with a change in WIZ thickening from Baseline at Endpoint of 30% (SLV348: 23 subjects, placebo: 16 subjects), 40% (SLV348: 22 subjects, placebo: 15 subjects), and 50% (SLV348: 19 subjects, placebo: 13 subjects) in the worst eye (p-values: 0.201, 0.200, and 0.236, respectively).

A trend to better profile for SLV348 was observed for the ETDRS grading of the 7-field photographs. Overall there were no trends in favor of SLV348 for the ETDRS macular grading and no differences were observed for ETDRS hard exudates grading at Endpoint between SLV348 and placebo.

The overall best corrected ETDRS visual eye score was good for the worst eye at Baseline (0.26±0.27 logMAR value) and no statistically significant difference between SLV348 and placebo was observed in the change in best corrected ETDRS visual acuity eye score as well as in the change in best corrected ETDRS visual acuity eye score in subjects with an alterated visual acuity at Baseline (< 20/40 or 0.3 logMAR value, N = 38/102) (p-values: 0.623 and 0.114, respectively).

The most frequently reported pre-specified eye procedures after starting treatment were laser photocoagulations, which were reported in a small percentage of subjects in the two treatment groups.

Safety Results:

One subject PPD in the placebo group was withdrawn from the study due to treatment-emergent serious AEs (TESAEs: cardiovascular insufficiency, pulmonary embolism, respiratory failure, and cardiac arrest) with a fatal outcome. This was the only subject who was withdrawn from the study due to AEs. There were no deaths in the SLV348 group.

Five subjects permanently discontinued the treatment due to AEs (two subjects in the SLV348 group and three subjects in the placebo group) but they completed the study.

Treatment-emergent serious AEs were reported by 10 subjects in both the SLV348 and placebo groups.

The majority of subjects reported treatment-emergent AEs (TEAEs) judged by the investigator to be unrelated to the study drug and mild or moderate in severity.

All TEAEs by Preferred Term were reported in ≤ 7% of subjects in any treatment group.

A statistically significant difference between SLV348 and placebo was observed in the percent change from Baseline in high-density lipoprotein cholesterol and triglycerides (LS mean difference from Baseline between placebo and SLV348 [95% CI]: 8.2 [1.7; 14.6], p-value: 0.014 and LS mean difference from Baseline between placebo and SLV348 [95% CI]: -27.1 [-42.0; -12.2], p-value: 0.001, respectively).

In the SLV348 group seven subjects reported marked abnormalities for creatinine (≥177 µmol/L) compared to no subjects in the placebo group. For fasting glucose 10 subjects in the SLV348 group and 13 subjects in the placebo group reported markedly abnormal values (elevated fasting glucose ≥ 13.9 mmol/L).

No statistically significant difference was observed between SLV348 and placebo for the change from Baseline at Endpoint in systolic blood pressure (SBP) (LS means difference from Baseline between placebo and SLV348 [95% CI]: -1.8 [-7.3; 3.7], p-value: 0.518) or diastolic blood pressure (DBP) (LS means difference from Baseline between placebo and SLV348 [95% CI]: -0.4 [-3.6; 2.9], p-value: 0.826).

The vital signs parameter for which the most subjects exhibited abnormal values was increase in weight of more than 7% (10.9% of subjects in the SLV348 group and 11.5% of subjects in the placebo group).

Among the four subjects presenting a partial vision loss reported as AE, one subject in the placebo group had a severe ETDRS visual acuity score decrease during the study. For the three other subjects (SLV348 group), the changes were transient and/or moderate.

No new safety signals or changes in seriousness or severity of known risks were identified.

Conclusion:

- For the change in TMV, in the absence or presence of center involvement, after 12 months of treatment there was a trend to reduction but no statistically significant difference between SLV348 and placebo.
- For the other OCT parameters including WIZ thickening, CZT, and CPT there was consistent trend to reduction with SLV348 but no statistically significant difference between SLV348 and placebo.
- A trend to better profile for SLV348 was observed for the ETDRS grading of the 7-field photographs. Overall there were no trends in favor of SLV348 for the ETDRS macular

grading and no differences were observed for ETDRS hard exudates grading at Endpoint between SLV348 and placebo.

- The overall best corrected ETDRS visual eye score was good for the worst eye at Baseline (0.26±0.27 logMAR value) and no statistically significant difference between SLV348 and placebo was observed in the change in best corrected ETDRS visual acuity eye score as well as in the change in best corrected ETDRS visual acuity eye score in subjects with an altered visual acuity at Baseline (< 20/40 or 0.3 logMAR value, N= 38/102) (p-values: 0.623 and 0.114, respectively).
- Laser photocoagulations were reported in a small percentage of subjects in the two treatment groups.
- ABT-335/SLV348 was well tolerated when administered as 135 mg for 12 months to subjects with DME.