1 SECONDARY EFFICACY ENDPOINT – METABOLISM BIOMARKERS AND SCORES

1.1 METABOLISM BIOMARKERS

Glucose metabolism

Most patients (77.3%) had non-clinically significant (NCS) baseline **fasting glucose** levels above ULN; the remaining patients (22.7%) had baseline fasting glucose levels within normal range. From baseline up to Month 6, no significant change was observed in mean fasting glucose levels by dose cohort, by fibrosis stage, by number of cells administered, and by number of injections. However, fasting glucose levels tended to decrease over time, particularly in F3 patients.

Excluding the concentrations from the (four) patients who started receiving insulin (or analogues) prior to or after the start of the study, F3 patients presented lower baseline levels of **fasting insulin** compared to F4 patients (201.1 ± 125.4 pmol/L and 270.2 ± 267.4 pmol/L, respectively). Most patients (56.3%) had NCS baseline fasting insulin levels above ULN and the remaining patients (37.5%) had baseline fasting insulin levels within normal range. From baseline up to Month 6, fasting insulin levels tended to decrease for most patients.

There was no difference in mean baseline **HbA1c** levels between dose cohorts or fibrosis stages. Patients had NCS baseline HbA1c levels above ULN (55.0%) or within normal range (45.0%). From baseline up to Month 6, no change was observed in mean HbA1c levels by dose cohort, by fibrosis stage, by number of cells administered, and by number of injections.

Lipid metabolism

Most patients (87.0%) had baseline **HDL** levels within normal range; 13.0% of patients had NCS baseline HDL levels above ULN. From baseline up to Month 6, HDL levels seemed to gradually increase, but the difference was not statistically significant.

Most patients (69.6%) had baseline **LDL** and **triglyceride** levels within normal range; 30.4% of patients had NCS baseline LDL levels above ULN. From baseline up to Month 6, no significant change was observed in mean LDL levels by dose cohort, by fibrosis stage, by number of cells administered, and by number of injections.

Most patients (69.6%) had baseline **triglyceride** levels within normal range; 30.4% of patients had NCS baseline triglyceride levels above ULN. From baseline up to Month 6, the levels of triglyceride levels tended to decrease. Of note, triglyceride levels were lower at the latest time point available compared to baseline levels for all patients who had baseline triglyceride levels > 2 mmol/L.

F3 patients presented higher baseline levels of **total cholesterol** compared to F4 patients (5.01 ± 1.26 mmol/L and 4.36 ± 1.51 mmol/L, respectively). Most patients (65.2%) had baseline total cholesterol levels within normal range; 34.8% of patients had NCS baseline total cholesterol levels above ULN. From baseline up to Month 6, no change was observed in mean total cholesterol levels by dose cohort, by fibrosis stage, by number of cells administered, and by number of injections.

Uric acid

Most patients (65.2%) had baseline **uric acid** levels within normal range; the remaining patients (34.8%) had NCS baseline uric acid levels above ULN. From baseline up to Month 6,

no significant change was observed in mean uric acid levels by dose cohort, by fibrosis stage, by number of cells administered, and by number of injections.

Conclusions on metabolism biomarkers

As expected, the patients' profile at baseline was indicative of metabolic syndrome with increased levels of glucose, insulin, insulin resistance scores, HbA1C and lipid parameters, despite glucose and lipid lowering therapy in a significant proportion of patients. The lipid parameters were slightly better at baseline in F4 patients compared to F3 patients.

Fasting glucose and insulin levels tended to decrease over time, particularly in F3 patients.

Triglyceride levels tended to decrease and HDL levels tended to increase throughout the study up to Month 6. Of note, on Month 6 (compared to baseline), less patients had metabolic syndrome based on both IDF and NCEP ATP III definitions, mainly due to the decreased levels of triglyceride.

Mean baseline uric acid levels were above ULN in 35% of patients, which is also typical for metabolic syndrome. Overall, no change was observed in uric acid levels from baseline up to Month 6.

1.2 METABOLIC SYNDROME AND INSULIN RESISTANCE SCORES

Insulin resistance scores

From baseline up to Month 6, **HOMA-IR** score tended to decrease in most patients, while **QUICKI** score tended to increase in most patients.

Metabolic syndrome criteria as per the IDF and NCEP ATIII definitions

On Months 6, the proportion of patients with metabolic syndrome decreased based on both classifications. According to the IDF criteria, all patients in Dose Cohorts 1 and 2, 71% of patients in Dose Cohort 3 and 50% of patients in Dose Cohort 4 had metabolic syndrome at baseline. By Months 6, the proportions slightly decreased to 50% in Dose Cohort 2 and to 57% in Dose Cohort 3.

The reduction in the number of patients with metabolic syndrome was due to the decrease in the triglyceride levels in 3 patients and to the improvement of blood glucose levels in 2 patients.