INTRODUCTION
Pathological models may be relevant and powerful tools for assessing the safety of drug candidates, in parallel of their efficacy, provided they are well-characterized. The complexity and heterogeneity of diabetes is illustrated assessing gold-standard and novel anti-diabetic agents, when administered alone and in combination.

Our aim was to characterize diabetic (db/db) mice, in comparison with non-diabetic lean controls, with respect to their diabetic profile and associated pathological markers relevant to complications related to Type II diabetes. In addition to body weight gain, food and water intake, basal glycemia and plasma insulin and response to glucose challenge, the parameters measured included diuresis, intestinal motility, and also thermal and tactile sensitivity.

MATERIAL & METHODS
Test systems:
- Male Rj: db/db (C57BL/KSjr-db) and lean C57BL/6J mice, weighing 33.35 g and 17.19 g, respectively, on arrival (7 weeks old), were used (n= 9-10 per group). They were supplied by Elevage Janvier, 53940 Le Genest-Saint-Ile, France.

Statistical analysis:
- Unpaired Student’s t tests.
- No indication = not significant
- * = p < 0.05
- ** = p < 0.01
- *** = p < 0.001

Experimental conditions:
- Cumulative food and water intake was measured over 24 hours. The mice were singly housed over the testing period.
- Oral Glucose Tolerance Test (OGTT) was performed after 5-hour fasting. Plasma glucose was measured by colorimetry before and up to 120 minutes after glucose challenge (2 g/kg p.o.).
- Diuresis was evaluated by measuring cumulative urinary volume over 6 hours. The mice were housed in groups of 3 or 4 per metabolism cage with free access to water and deprivation of food over the testing period.
- Small intestine transit was determined after overnight fasting, by measuring the distance covered by charcoal and the total length of the small intestine, 20 minutes after a charcoal meal (0.4 ml/mouse p.o.).
- Colonic transit was determined after overnight fasting, by monitoring the time required for the expulsion of a 3-mm glass bead inserted 2 cm into the distal colon.
- Tactile sensitivity was evaluated by measuring paw-withdrawal latency in response to a pressure using an electronic Von Frey filament or a pinchmeter test (mean of 3 measurements).
- Thermal sensitivity was evaluated by measuring first withdrawal latency in mice placed on a cold plate at 4°C.

RESULTS

Body weight gain
Body weight was significantly higher in db/db mice, as compared with controls, over the testing period between 7 and 15 weeks of age (34.2 ± 0.3 g vs. 18.2 ± 0.2 g, p < 0.001 at 7 weeks of age and 41.0 ± 1.9 vs. 23.1 ± 0.5 g, p < 0.001 at 15 weeks of age).

Food and water intake
Food and water intakes were significantly increased in db/db mice, as compared with controls (+84%, p < 0.001 for food intake and +162%, p < 0.001 for water intake cumulated over 24 hours).

Basal glycemia and plasma insulin
Basal blood glucose was higher in db/db mice between 8 and 15 weeks of age, as compared with controls (28.4 ± 1.6 vs. 11.4 ± 0.6 mmol/l, p < 0.001 at 8 weeks of age and 28.9 ± 1.3 vs. 8.0 ± 0.3 mmol/l, p < 0.001 at 15 weeks of age).
Basal plasma insulin was also higher in db/db mice, as compared with controls (5.74 ± 0.96 vs. 0.94 ± 0.07 ng/ml, p < 0.001 at 11 weeks of age).

OGT
Plasma glucose was higher in db/db mice, as compared with controls (33.4 ± 1.5 vs. 9.5 ± 0.9 mmol/l, p < 0.001) and increased shortly after oral glucose challenge (+27% from baseline at 30 minutes post-challenge) and returned to basal levels within 120 minutes as controls.

Diuresis
Diuresis was significantly higher in db/db mice, as compared with controls (+0.658 g/mouse, p < 0.01 for urinary volume cumulated over 6 hours).

Intestinal and colonic transit
Small intestinal transit was significantly decreased in db/db mice, as compared with controls (distance covered: -13%, p < 0.05 in the charcoal test). A tendency towards a decrease was also observed on colonic transit [expulsion latency: 0h48min vs. 1h05min, ns in the bead test].

Pain sensitivity
db/db mice showed a moderate hyposensitivity, as compared to controls, to tactile stimulation (force-inducing paw withdrawal: +30%, ns in the Von Frey test and +24%, p < 0.05 in the pinchmeter test), but a marked hypersensitivity in response to thermal stimulation [latency to first withdrawal: -54%, p < 0.001 in the cold plate test].

CONCLUSION
These findings indicate differences in db/db mice as compared with non-diabetic lean mice, with respect to their diabetic profile but also comorbidity factors. The db/db model is therefore representative of the polymorphism of diabetes, and can be a useful tool for the efficacy/safety pharmacological evaluation of antidiabetic drugs.

ACKNOWLEDGEMENTS: special thanks to Olivier Poussel, Arnaud Godeau and Erika Léger for their assistance in data management and preparation of this poster.