Miglustat therapy normalizes bone mass in mouse model of cystic fibrosis

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BACKGROUND

- Brittle bones have been reported in children, adolescents and adults with cystic fibrosis (CF), independently of sex; this has been termed CF-related bone disease. In CF patients with the F508del mutation in the *Cftr* gene, vertebral fractures and the subsequent dorsal kyphosis decrease pulmonary function, thus accelerating the course of the disease and decreasing the quality of life in CF patients.

- Male and female mice with the homozygous F508del mutation in CFTR develop a severe osteopenic phenotype early on *(Le Henaff C. et al, 2012)*.

- Miglustat (N-butyldeoxynojyrimicin), the active ingredient of Zavesca® was reported to normalize sodium and CFTR-dependent chloride transport in primary human F508del CFTR airway cells and in nasal mucosa in F508del CF mice.

OBJECTIVE

- To evaluate the efficacity of oral miglustat treatment on parameters of the bone microarchitecture, histomorphometry and bone formation rate in F508del mice.

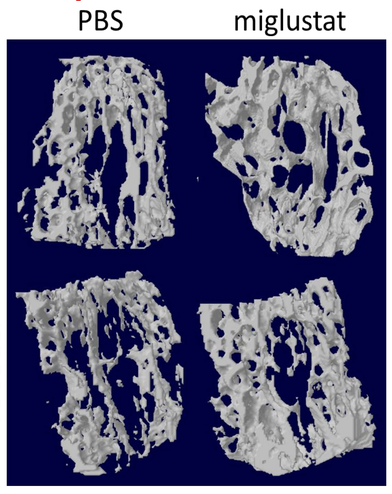
METHODS

- CF mice homozygous for the F508del-CFTR mutation in the 129/FVB outbred background (*cftr*^{tm1Eur}) (F508del) and their wild-type (WT) normal homozygous littermates *(Van Doorninck J H. et al, 1995)* were obtained from the CDTA, Orléans, France.

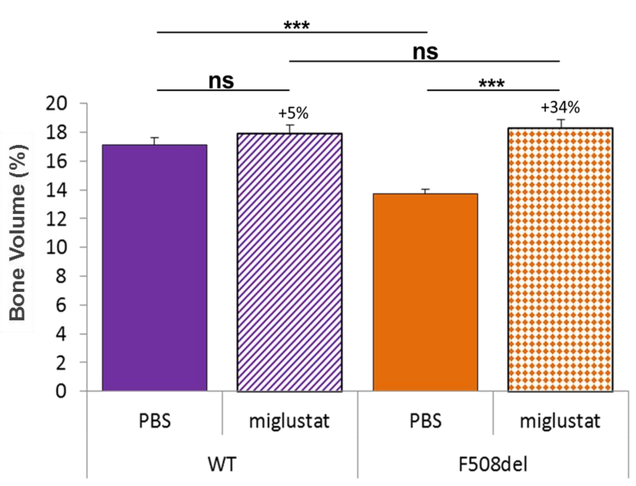
- Administration of 120mg/kg/day miglustat (Zavesca®, Actelion Pharmaceuticals) was realized once a day for 28 days by oral gavage to male mice aged of 6 weeks. Control groups received the same volume of vehicle, i.e. PBS solution. Values represent the mean +/- SEM of n = 5-8 mice per group.
- To evaluate changes in bone phenotype, we have analyzed :
  - ✓ the body weight of mice
  - ✓ the trabecular network of lumbar spine by micro Computer Tomography (µCT, *SkyScan)*
  - ✓ the histomorphometric parameters on sagittal sections (Bonolab, histolab – microvision + method of Parfitt)
  - ✓ the dynamic parameters of bone formation (double labelling : calcein/tetracyclin).

RESULTS

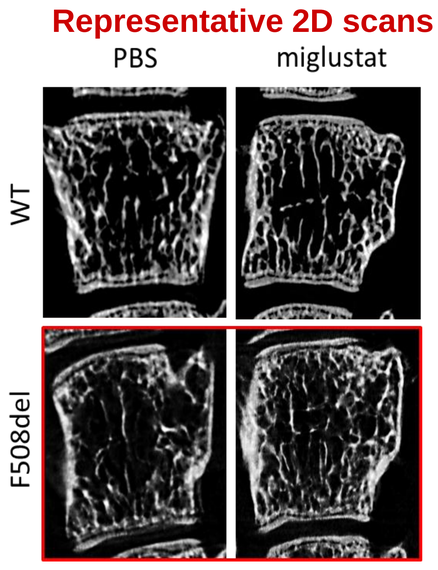
Representative 3D scans



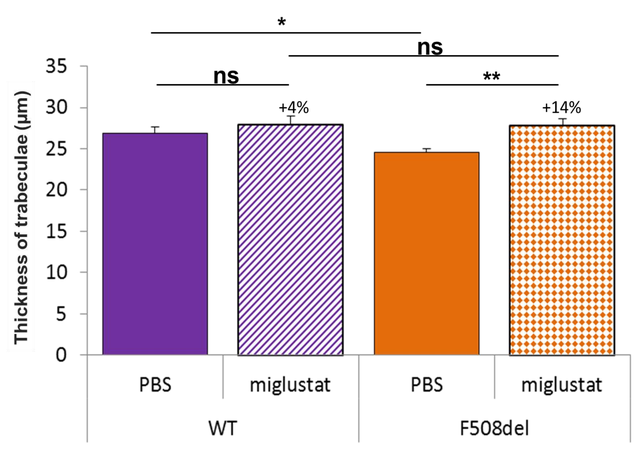
Bone volume



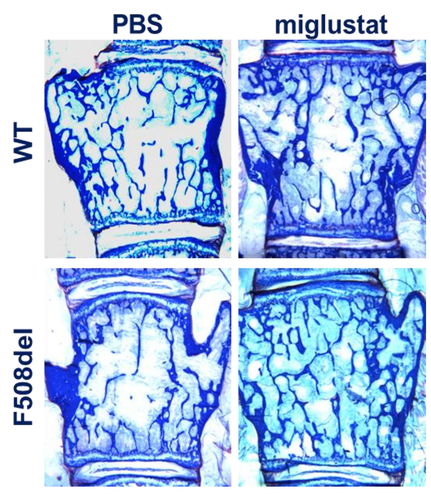
Representative 2D scans



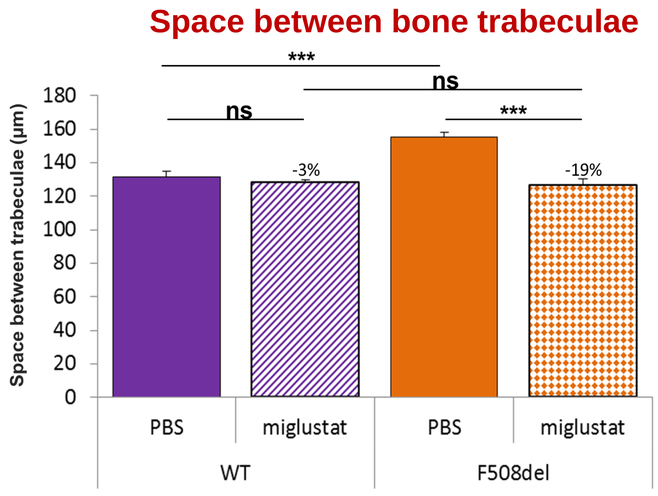
Thickness of bone trabeculae



Histomophometric data



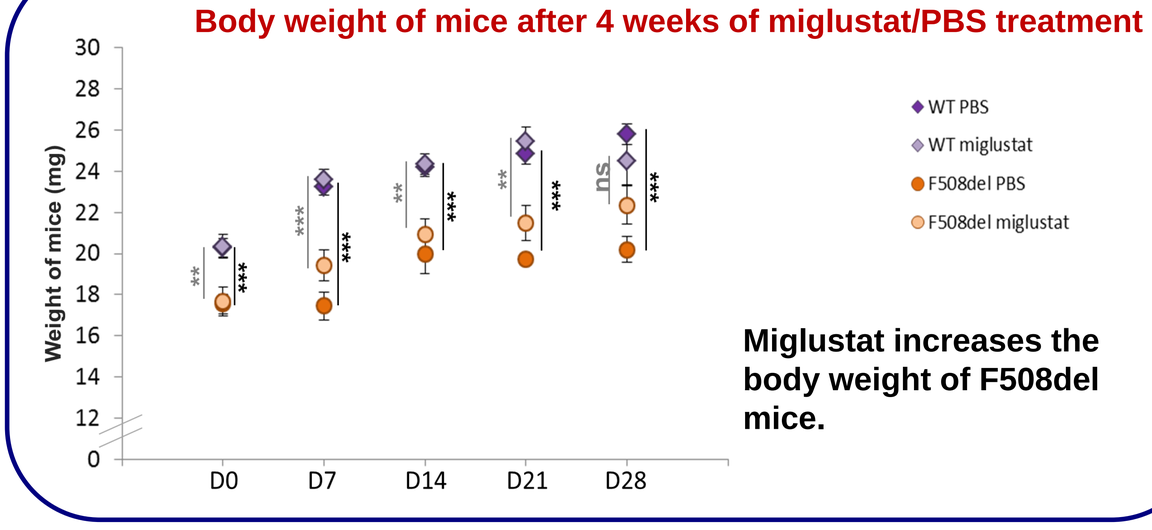
Space between bone trabeculae



*=*P*<0,05 ; **=0,01<*P*<0,05 ; ***=0,001<*P*<0,01

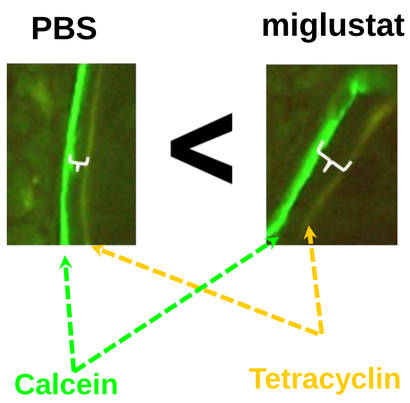
A once-a-day oral treatment with miglustat for 4 weeks normalizes bone volume and improves bone micro-architecture in F508del mice.

Body weight of mice after 4 weeks of miglustat/PBS treatment

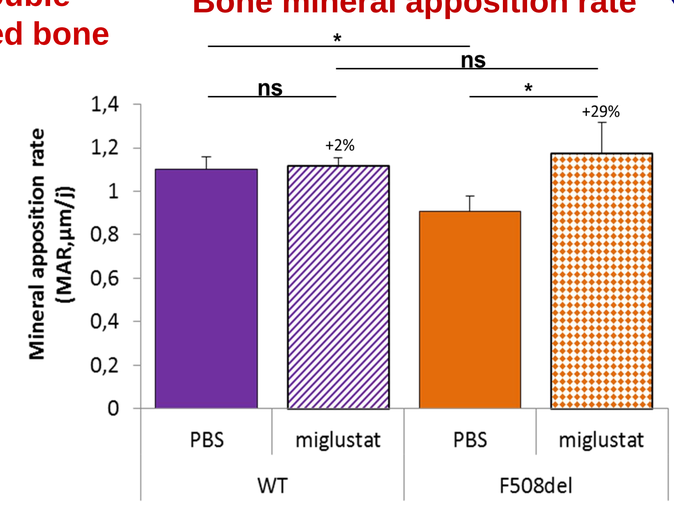


Miglustat increases the body weight of F508del mice.

In vivo tetracycline/calcein double labelling showing an enhanced bone formation in F508del mice.

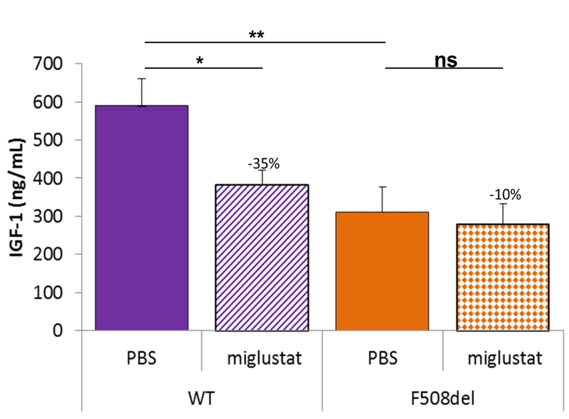


Bone mineral apposition rate

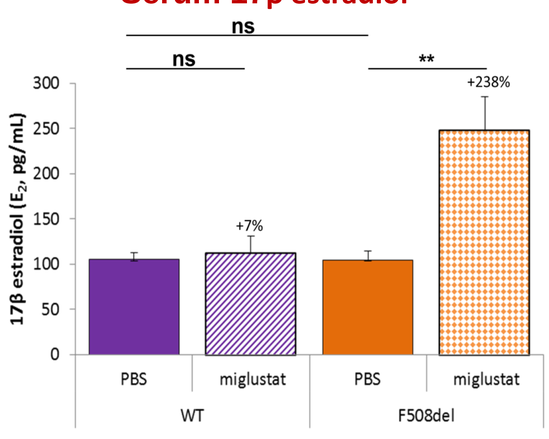


Miglustat induces an increase in mineral apposition rate in F508del mice.

Serum IGF-1



Serum 17β estradiol



Miglustat induces an increase of 17β estradiol level in F508del mice.

CONCLUSION

Oral administration of miglustat normalizes bone mass by increasing bone formation in F508del mice. This study strongly supports miglustat therapy in patients with CF-related bone disease.