Impact of avigbagene parvec (FLT201) on markers of bone health in adults with Gaucher disease type 1

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Background

Gaucher disease type 1 (GD1) is a rare genetic lysosomal storage disorder caused by mutations in the *GBA1* gene, resulting in deficient glucocerebrosidase (GCase) and impaired breakdown of glycosphingolipids.[1] Bone involvement (intraosseous vascular compromise) is a major contributor of morbidity in GD1 even after years of therapy with enzyme replacement therapy (ERT) or substrate reduction therapy (SRT).[2,3]

- Progressive and severe skeletal disease can occur in patients with minor or even absent visceral and hematologic involvement.[4]

Bone involvement in GD occurs via infiltration of bone marrow with subsequent compression of healthy cells and imbalances in osteoclast/ osteoblast activity.[2,5,6]

- Changes include remodeling abnormalities of bone, resulting in loss of bone mineral content, cortical thinning, lytic lesions, fractures, and joint destruction.
- Lyso-Gb1 a substrate which accumulates in GD1 is particularly toxic to bone and impacts the immune environment, vascularity, hematopoiesis, and cellular function.
- Despite ERT/SRT, patients continue to experience bone marrow infiltration and reduction in bone marrow density, with debilitating pain that impacts quality of life.

Corticosteroids, utilized in many investigational gene therapy trials, are known to cause glucocorticoid-induced osteoporosis if use is over an extended period.[7,8]

- Bone loss may occur with or without other manifestations and its severity is dependent on both the dose and duration of treatment.

Avigbagene parvec (FLT201) an investigational gene therapy for the treatment of GD1, is designed to overcome the limitations of ERT/SRT.

- Novel, proprietary, liver-tropic capsid (AAVS3) with a unique GBA1-85 transgene encoding an engineered variant of β-glucocerebrosidase (GCase85).

GALILEO-1 and GALILEO-2

GALILEO-1 was a first-in-human clinical trial of adult patients with GD1 who had been on stable background therapy of ERT or SRT for at least 2 years. All participants have enrolled in GALILEO-2, the long-term follow up study. Immune management regimen began 3 weeks post-infusion, and consisted of oral glucocorticosteroids (GC).

Results

Six participants have received a single low dose of FLT201: 4.5 x 10^{11} vg/kg. Duration of prednisone exposure was a mean of 18 weeks (range 14 – 25 weeks). Four patients discontinued ERT/SRT and have remained off since Week 11 at the latest.

All patients manifest evidence of bone disease at study entry. Efficacy outcomes (BMB, DXA) of the four patients that are no longer receiving ERT/SRT and bone response to GC (osteocalcin, bsALP) of all 6 patients are presented.

	Age/gender	Duration of SoC	Bone manifestations at study entry	Duration of GC
Patient 1	35 yo M	4 years	• Markedly low BMD (Z-score: ≤ -1.0) • Moderate bone marrow infiltration (BMB score: 7) • Moderate bone pain (via BPI, GD-DS3)	25 weeks
Patient 2	25 yo M	22 years	• Markedly low BMD (Z-score: ≤ -1.0) • Moderate bone marrow infiltration (BMB score: 7)	16 weeks
Patient 3	24 yo M	9 years	• Markedly low BMD (Z-score: ≤ -1.0) • Marked/severe bone marrow infiltration (BMB score: 11)	17 weeks
Patient 4	30 yo F	14 years	• Normal BMD • Marked/severe bone marrow infiltration (BMB score: 11)	19 weeks
Patient 5	24 yo M	4 years*	• Low BMD (Z-score: < 0) • Marked/severe bone marrow infiltration (BMB score: 13)	17 weeks
Patient 6	58 yo F	24 years*	• Markedly low BMD (Z-score: ≤ -1.0) • Moderate bone marrow infiltration (BMB score: 7) • Mild bone pain (via GD-DS3)	14 weeks

GC: prednisone or prednisolone; SoC: ERT and/or SRT; * remains on ERT/SRT; BPI: Brief Pain Inventory; GD-DS3: GD Disease Severity Score System

Bone Marrow Burden (BMB)

The BMB score takes into account the progressive pattern of toxic substrate infiltration into the bone marrow, displacing healthy marrow.

- Signal intensity represent bone infiltration; extent of involvement in the femur is assessed including possible infiltration of epiphyses and apophyses; in the spine, involvement can be patchy, with localized areas of abnormal marrow, to diffuse, where marrow is more completely replaced.

Clinical impact of bone marrow infiltration.[2]

- Individuals with extensive infiltration are more likely to experience bone compilations.
- Changes may increase the risk of bone marrow-based haematological malignancies.
- The BMB score is highly correlated to pain (r=0.725, p=0.027) and lyso-Gb1 levels (r=0.701; p=0.035).[9]

Results (n=4)

At study entry, 2 patients had moderate bone marrow involvement and two had marked to severe bone marrow involvement. After receiving FLT201, mean BMB reduced from borderline marked to moderate (Figure 1). A clinically relevant improvement in BMB was seen in one patient with a total BMB score reducing from 11 at baseline to 7 at Month 24. This reduction was seen as early as Month 3 (Figure 2). All other patients remained within 1 point of their baseline values at Month 24.[10]

Figure 1: Mean BMB Score (n=4)

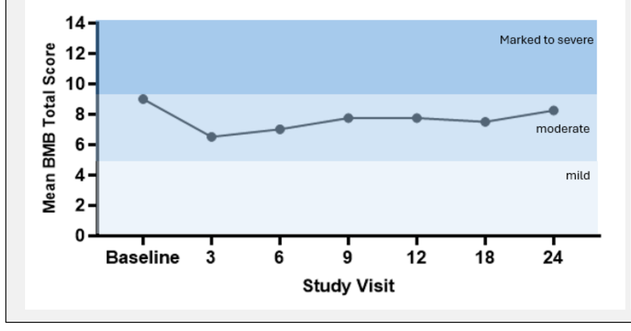
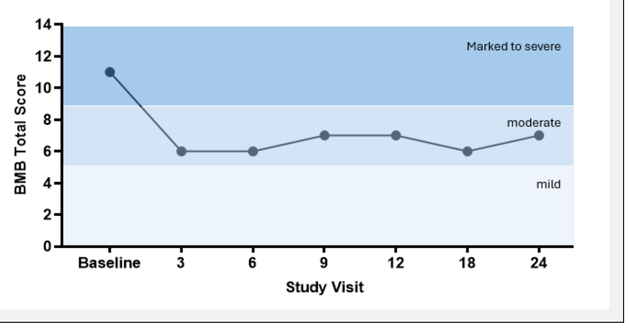


Figure 2. BMB Score Patient 3



Trabecular and Cortical Bone: DXA

In Gaucher disease, osteoblastic and osteoclastic activity is disrupted, leading to low bone mineral density (BMD) and skeletal pathology.

- DXA Z-scores correlate to Lyso-Gb1 levels (spine [r=-0.929, p=0.001] ; femur [r=-0.893, p=0.007]).[9]

Clinical implications of low BMD in GD1[5,11,12]

- Gaucher patients with DXA Z-scores ≤ -1.0 have a more than fivefold increase in risk to experience a fracture at any site compared to patients with Z-scores > -1.0 (OR of 5.55 [p < 0.01]).

Even after years of treatment, patients continue to demonstrate low BMD.[12]

Results (n=4)

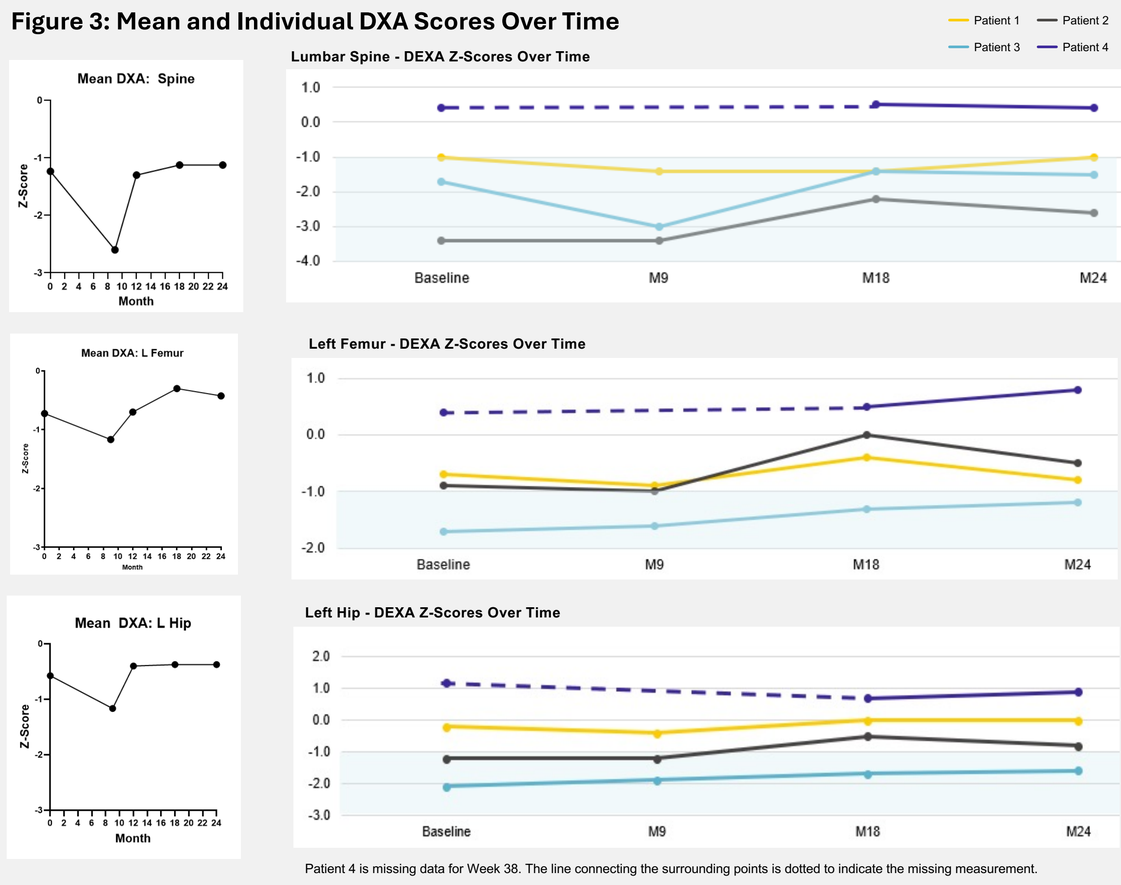
At study entry, 3 patients had Z-scores ≤ -1.0 in at least one anatomic measurement.

- Lumbar regions had the greatest deficits at study entry.

After FLT201, improvements in mean DXA scores were seen (Figure 3).

- Initial worsening of spinal scores is consistent with GC effects and is driven primarily by a single patient. These initial changes were fully reversed after cessation of GC.
- Over the course of 2 years, improvements were seen in the two patients with the lowest BMD. Interestingly, patient 2 entered the trial with well controlled hematological/visceral parameters and a low lyso-Gb1 (data not shown), reinforcing the findings that bone pathology can occur in the absence of other disease manifestations.

Figure 3: Mean and Individual DXA Scores Over Time



Patient 4 is missing data for Week 38. The line connecting the surrounding points is dotted to indicate the missing measurement.

Markers of Bone Turnover: Osteocalcin, bsALP

Reductions in bone biomarkers can be observed early and persist during continued GC exposure; reversal of these manifestations occurs after discontinuation.

- Even in healthy volunteers, reductions occur rapidly and in a dose-dependent fashion.

Results (n=6)

All patients entered the trial with osteocalcin and bsALP levels within the normal range for age and gender. At baseline, mean osteocalcin was 24.0 ng/mL (range: 13.3-34.4) and mean bsALP was 24.4 (range: 13.3-39.1). During the period of GC use, a clear decrease is seen. Following cessation of steroids, all levels returned to baseline (Figure 4, 5).

Figure 4: Mean osteocalcin levels over time

Figure 5: Mean bsALP levels over time

Conclusions

- **Skeletal disease in GD may develop silently and may not correspond with systemic disease; there is a need to better address bone health.**
- **In patients who had been on SoC for years and presenting with continued bone disease, FLT201 demonstrated improvements in both bone infiltration and bone density after discontinuing prior SoC therapies; individual patient factors likely account for variation in response between patients.**
- **Continuous exposure to GCase (via the extended half-life of GCase85 with FLT201) may allow for deeper penetration into hard-to-reach tissues such as bone.**
- **Patients had reversible changes in bone markers during the course of GC, highlighting the bone safety of the short course of GC to manage the immune response.**

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Data cut off as of November 20, 2025

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