DMT39

Exploratory Analysis of Serum GDF-15 Levels in Patients Receiving Subcutaneous Interferon β-1a in the REFLEX Trial

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CONCLUSIONS

In CIS patients, GDF-15 levels increased during treatment with sc IFN β-1a 44 µg tiw.

The more pronounced increase of GDF-15 levels in CDMS nonconverters treated with sc IFN β-1a 44 µg tiw indicates that levels of this anti-inflammatory cytokine may serve as a biomarker of treatment response and stable disease under such therapy in early MS.

INTRODUCTION

- Subcutaneous interferon beta-1a (sc IFN β-1a) is a well-established disease-modifying therapy for relapsing MS[1]
- Serum levels of GDF-15, a cytokine with anti-inflammatory effects, are increased in patients with stable MS[2]
- However, no information is currently available concerning GDF-15 in patients treated with sc IFN β-1a

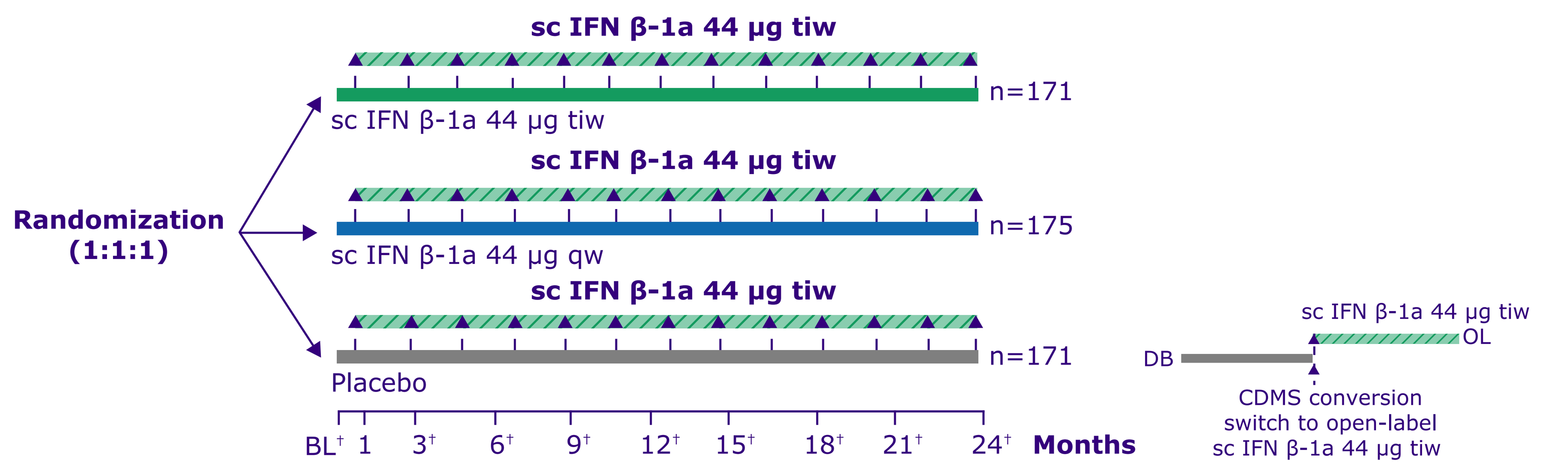
OBJECTIVE

To investigate if serum levels of GDF-15 predict disease stability in patients with CIS treated with sc IFN β-1a.

METHODS

- In the REFLEX study (NCT00404352), 480 patients with CIS* were randomized to treatment with sc IFN β-1a 44 µg qw (n=162), 44 µg tiw (n=157), or placebo (n=161), for up to 24 months
- Time from randomization to CDMS, defined by either a second demyelinating event or a sustained increase (≥1.5 points) in the EDSS score, was the primary endpoint
  - Patients who converted to CDMS during the study were switched to open-label sc IFN β-1a 44 µg tiw
- In this post hoc exploratory analysis, serum concentrations of GDF-15 were measured by enzyme-linked immunosorbent assay at baseline and for up to 24 months, including the subgroup of CDMS nonconverters vs converters. All analyses are descriptive

Figure 1. REFLEX trial study design[3]



*Defined as a first clinical event suggestive of MS within the last 60 days and at least 2 clinically silent lesions on T2-weighted MRI scan, with EDSS score 0–5. †MRI.
DB period corresponds to the period where the patient did not convert, or the period up to the time of conversion and initiation of sc IFN β-1a. **Whole study period** includes all patients, irrespective of conversion to CDMS.

RESULTS

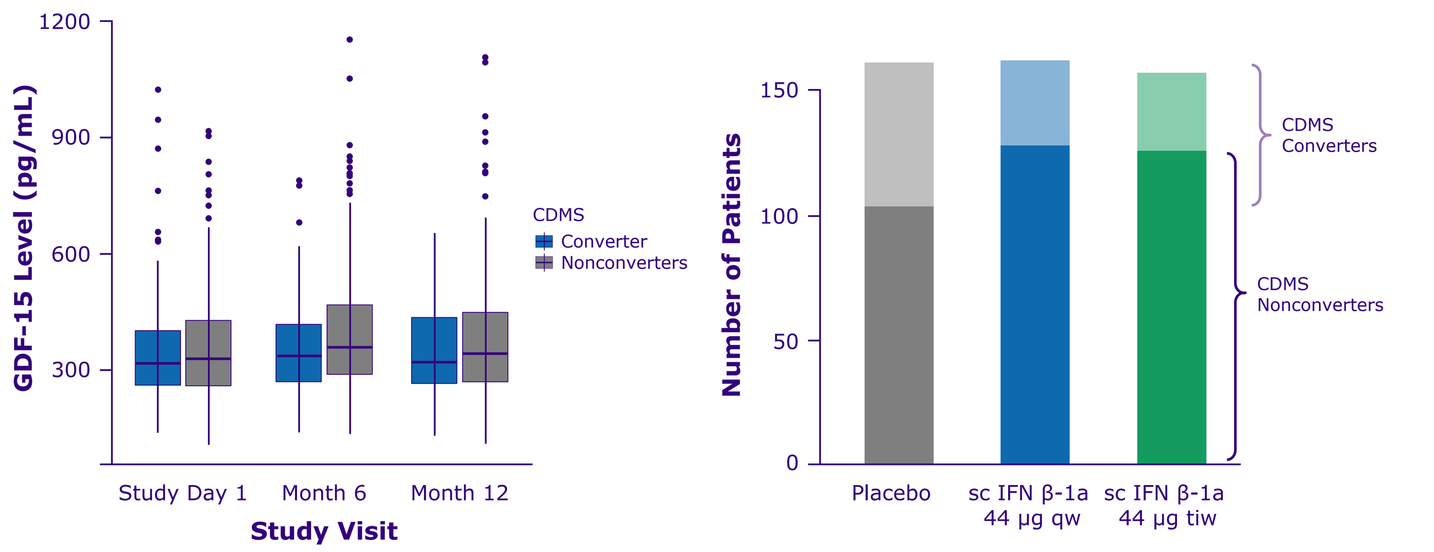
Table 1. GDF-15 levels appeared highest, over time, in those taking sc IFN β-1a44 µg tiw (double-blind period)

GDF-15 Level (pg/mL)	Placebo	sc IFN β-1a 44 µg qw	sc IFN β-1a 44 µg tiw	Total patients
Baseline	n=161	n=162	n=157	n=480
Mean (SD)	358.17 (146.31)	356.67 (137.20)	349.50 (137.96)	354.83 (140.33)
Median	318.71	338.16	**322.99**	325.73
Month 6	n=141	n=147	n=135	n=423
Mean (SD)	358.63 (133.23)	375.31 (145.57)	430.89 (166.32)	387.49 (151.44)
Median	326.69	342.35	**391.47**	353.13
Month 12	n=112	n=131	n=126	n=369
Mean (SD)	333.55 (116.14)	355.17 (145.97)	429.02 (173.75)	373.82 (153.33)
Median	298.88	327.81	**409.43**	337.30
Month 24/ET	n=89	n=109	n=114	n=312
Mean (SD)	355.91 (179.02)	352.38 (129.59)	420.28 (311.05)	378.20 (226.01)
Median	322.80	320.68	**390.86**	335.63

ET, extended time; **GDF-15**, growth differentiation factor 15; **IFN**, interferon; **qw**, once weekly; **sc**, subcutaneous; **SD**, standard deviation; **tiw**, three times weekly

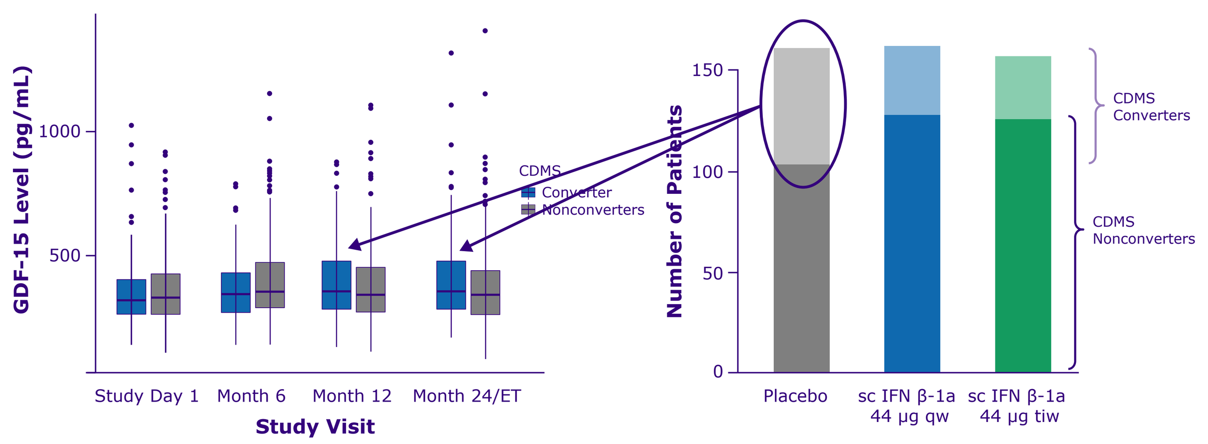
- For placebo, more converters to CDMS were seen at Month 12 and Month 24
  - Such findings suggest that placebo-treated patients were not stable during this period.
- In parallel, GDF-15 levels were not increasing for placebo recipients compared to the tiw group, where the number of converters was minimal (**Figures 2** and **3**)

Figure 2. GDF-15 levels increase more over time in CDMS nonconverters than CDMS converters (double-blind period)



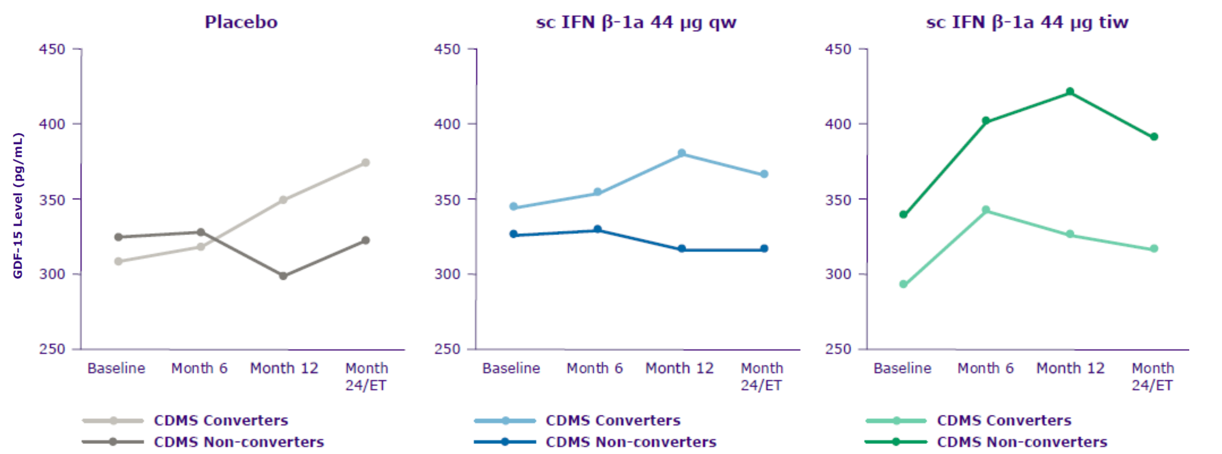
CDMS, clinically definite multiple sclerosis; **GDF-15**, growth differentiation factor 15; **IFN**, interferon; **qw**, once weekly; **sc**, subcutaneous; **tiw**, three times weekly

Figure 3. Most CDMS converters came from the placebo arm (whole study period)



CDMS, clinically definite multiple sclerosis; **ET**, extended time; **GDF-15**, growth differentiation factor 15; **IFN**, interferon; **qw**, once weekly; **sc**, subcutaneous; **tiw**, three times weekly

Figure 4. Median GDF-15 levels over time in CDMS converters vs nonconverters (whole study period)



CDMS, clinically definite multiple sclerosis; **ET**, extended time; **GDF-15**, growth differentiationfactor 15; **IFN**, interferon; **qw**, once weekly; **sc**, subcutaneous; **tiw**, three times weekly

- CDMS nonconverters showed a persistent increasing trend compared to CDMS converters under active treatment; there were no converters between Months 12 and 24
- CDMS converters showed a persistent increasing trend for GDF-15 from Month 6, which coincides to switching treatment to sc IFN β-1a 44 µg tiw and disease stabilization (**Figure 4**)

Abbreviations: BL, baseline; **CDMS,** clinically definite multiple sclerosis; **CIS,** clinically isolated syndrome; **DB,** double blind; **IFN,** interferon; **MRI,** magnetic resonance imaging; **OL,** open label; **qw,** once weekly; **sc,** subcutaneous; **tiw,** three times weekly.

References: 1. Filipi M, et al. *Int J MS Care*. 2020;22:165–172. **2.** Amstad A, et al. *Neurol Neuroimmunol Neuroinflamm*. 2020;7:e675. **3.** Comi G, et al. *Lancet Neurol*. 2012;11:33–41.

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