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

M. Coray[1], A. Seitzinger[2], S. Roy[3], M.S. Freedman[4], F. Barkhof[5,6], G. Comi[7], N. De Stefano[8], L. Kappos[9], J. Kuhle[9], M. Mehling[1,9]

[1]Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland; [2]Merck Healthcare KGaA, Darmstadt, Germany; [3]Ares Trading S.A., Eysins, Switzerland (an affiliate of Merck KGaA); [4]University of Ottawa, Department of Medicine and the Ottawa Hospital Research Institute, Ottawa, ON, Canada; [5]Department of Radiology, Amsterdam UMC, Location VUmc, Amsterdam, The Netherlands; [6]UCL Institute of Neurology, London, UK; [7]Università Vita-Salute San Raffaele, Casa di Cura Privata del Policlinico, Milan, Italy; [8]Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy; [9]Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB) and Neurology Departments of Head, Spine and Neuromedicine, Biomedical Engineering and Clinical Research, University Hospital Basel and University of Basel, Basel, Switzerland

CONCLUSIONS

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

Tendency for increased GDF-15 in CDMS non-converters indicates that levels of this anti-inflammatory cytokine may serve as a biomarker of treatment response and stable disease with sc IFN β-1a 44 µg tiw in early MS.

INTRODUCTION

- Subcutaneous interferon beta-1a (sc IFN β-1a) is an established disease-modifying therapy for relapsing multiple sclerosis (MS).[1]
- Estimated cumulative exposure of 1,831,698 patient-years to 30 April 2021.
- Growth differentiation factor 15 (GDF-15) is a cytokine with anti-inflammatory effects.
- Serum levels of GDF-15 are increased in patients with stable MS.[2]
- However, no information is available concerning GDF-15 in patients treated with sc IFN β-1a.

OBJECTIVES

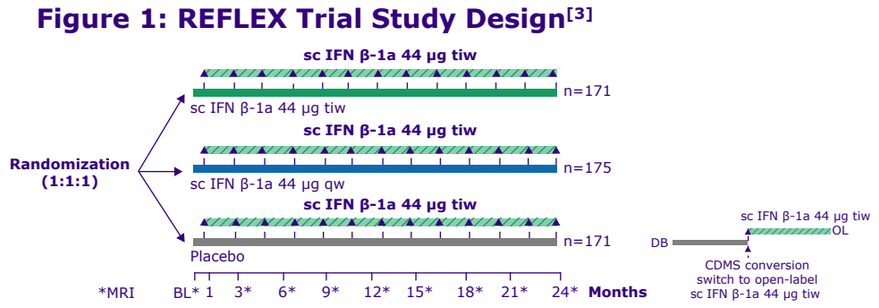
To investigate if serum levels of GDF-15 reflect disease stability in patients with clinically isolated syndrome (CIS) treated with sc IFN β-1a.

METHODS

Post hoc exploratory analysis.

Serum concentrations of GDF-15 were measured by enzyme-linked immunosorbent assay (ELISA) at baseline and for up to 24 months, including the subgroup of clinically definite MS (CDMS) non-converters vs converters.

Figure 1: REFLEX Trial Study Design[3]



CIS patients (first clinical event suggestive of MS within the last 60 days and at least 2 clinically silent lesions on T2-weighted magnetic resonance imaging (MRI) scan, Expanded Disability Status Scale (EDSS) 0–5) and follow up up to 24 months.

CDMS converters defined by either a 2nd attack or a sustained increase (≥1.5 points) in the EDSS score. Patients who converted to CDMS during the study were switched to open-label sc IFN β-1a 44 µg tiw.

DB period corresponds to the period where the patient did not convert, or the period up to the time ofconversion and initiation of sc IFN β-1a.

Whole study period includes all patients, irrespective of conversion to CDMS.

BL, baseline; **CDMS**, clinically definite multiple sclerosis; **DB**, double blind; **EDSS**, Expanded Disability Status Scale; **IFN**, interferon; **MRI**, magnetic resonance imaging; **OL**, open label; **qw**, once weekly; **sc**, subcutaneous; **tiw**, three times weekly

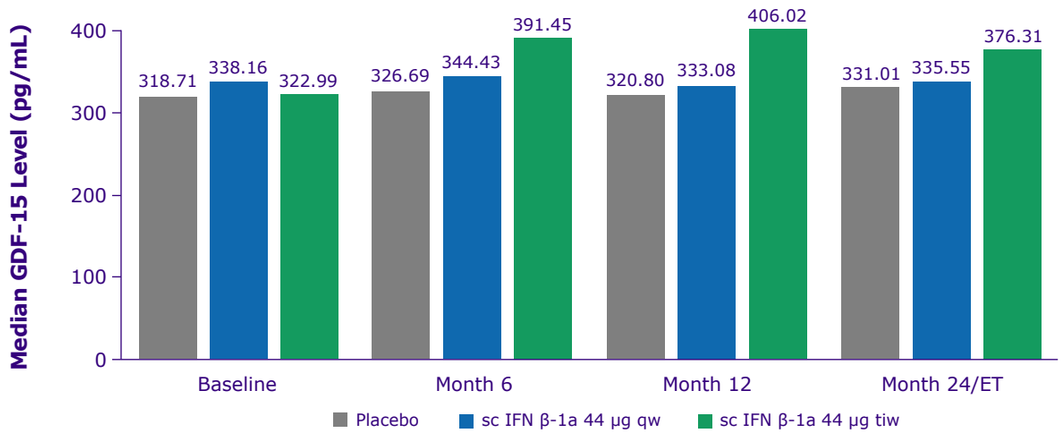
RESULTS

Table 1: GDF-15 Levels Appear Highest, Over Time, in Those Taking sc IFN β-1a 44 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

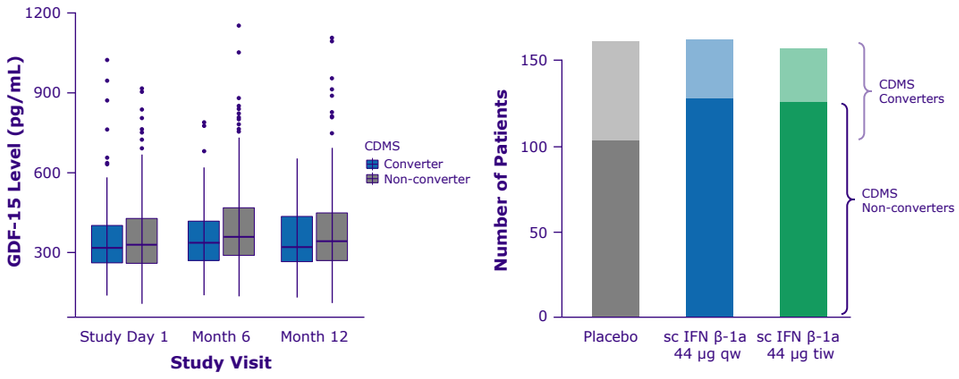
Figure 2: Highest GDF-15 Levels Observed in sc IFN β-1a 44 µg tiw Arm (Whole Study Period)



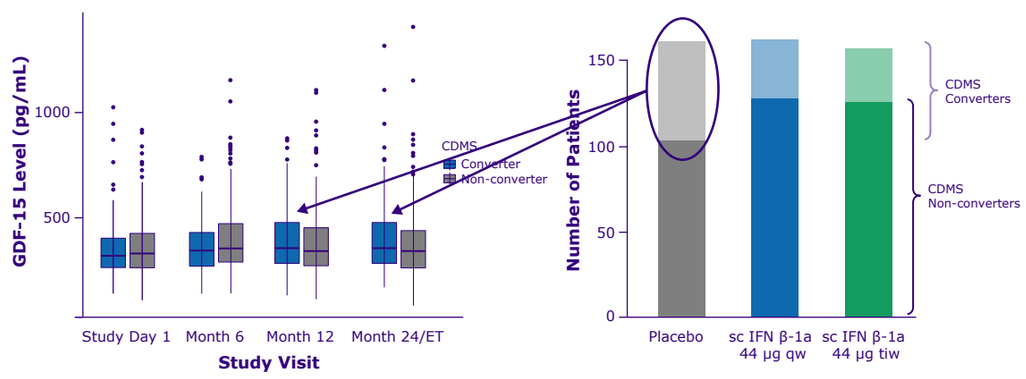
ET, extended time; **GDF-15**, growth differentiation factor 15; **IFN**, interferon; **qw**, once weekly; **sc**, subcutaneous; **tiw**, three times weekly

For placebo, more converters to CDMS were seen at month 12 and month 24 – which suggests that 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 3 & 4: GDF-15 Levels (pg/mL) Increase More Over Time in CDMS Non-converters than CDMS Converters (Double-blind Period)



Figures 5 & 6: Most CDMS Converters Came from the Placebo Arm (Whole Study Period)



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

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

CDMS non-converters 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.

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