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

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Presenter: E. Verdun Di Cantogno

ACKNOWLEDGMENTS

Medical writing assistance was provided by Claire Snaith and Steve Winter of inScience Communications, Springer Healthcare Ltd, UK, and was funded by the healthcare business of Merck KGaA, Darmstadt, Germany.

DISCLOSURES

MC is supported by a research grant from the Swiss National Science Foundation. **AS** is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany. **SR** is an employee of Ares Trading S.A., Eysins, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany). **MSF** has received honoraria or consultation fees from Alexion, Atara Biotherapeutics, Bayer, BeiGene, Celgene (BMS), the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis, Pendopharm, Roche, and Sanofi; was a member of a company advisory board, board of directors, or other similar group for Alexion, Atara Biotherapeutics, Bayer, BeiGene, Celgene (BMS), Clene Nanomedicine, Janssen (J&J), McKesson, the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis, Roche, and Sanofi; has been a participant in a company sponsored speaker's bureau for the healthcare business of Merck KGaA (Darmstadt, Germany) and Sanofi; and has received research or educational grants from Sanofi. **FB** is supported by the NIHR Biomedical Research Centre at UCLH and is a consultant to Biogen, Combinostics, IXICO, the healthcare business of Merck KGaA (Darmstadt, Germany), and Roche. **GC** has received consulting fees from Bayer, Biogen, the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis, Receptos, Roche, Sanofi, and Teva Pharmaceutical Industries Ltd; lecture fees from Bayer, Biogen, the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis, Sanofi, Serono Symposia International Foundation, and Teva Pharmaceutical Industries Ltd; and trial grant support from Bayer, Biogen, the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis, Receptos, Roche, Sanofi, and Teva Pharmaceutical Industries Ltd. **NDS** is a consultant for Biogen, the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis, Roche, Sanofi, and Teva; has grants or grants pending from FISM and Novartis, is on the speakers' bureaus of Biogen, the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis, Roche, Sanofi, and Teva; and has received travel funds from the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis, Roche, Sanofi, and Teva. **LK´s** institution (University Hospital Basel and University of Basel) has received the following exclusively for research support: steering committee, advisory board, and consultancy fees (Actelion [Janssen/J&J], Bayer, Biogen, BMS, Janssen, the healthcare business of Merck KGaA [Darmstadt, Germany], Novartis, Roche, Sanofi, Santhera, and TG Therapeutics); speaker fees (Bayer, Biogen, the healthcare business of Merck KGaA [Darmstadt, Germany], Novartis, Roche, and Sanofi); support of educational activities (Allergan, Bayer, Biogen, CSL Behring, Desitin, the healthcare business of Merck KGaA [Darmstadt, Germany], Novartis, Roche, Pfizer, Sanofi, Shire, and Teva); license fees for Neurostatus products; and grants (Bayer, Biogen, European Union, InnoSwiss, the healthcare business of Merck KGaA [Darmstadt, Germany], Novartis, Roche, Swiss MS Society, and Swiss National Research Foundation). **JK´s** institution (University Hospital Basel and University of Basel) has received the following exclusively for research support: Speaker fees, research support, travel support, and/or served on advisory boards of ECTRIMS, Swiss Multiple Sclerosis Society, Swiss National Research Foundation (320030_160221), University of Basel, Bayer, Biogen, the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis, Roche, Sanofi, and Teva. **MM** has received, during the last 3 years, institutional research support as compensation for serving as a member of advisory boards or steering committees, or as a consultant or speaker, from the following companies: Biogen, the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis, and Roche, and has received research support by the Bangeter-Rhyner Foundation, the healthcare business of Merck KGaA (Darmstadt, Germany), Roche, the SwissLife Foundation, the Swiss Multiple Sclerosis Society, Swiss National Research Foundation, and the University of Basel Research Fund. **EVDC** is an employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA.

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Presenter: E. Verdun Di Cantogno[10]

[1]Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland; [2]the healthcare business of Merck KGaA, Darmstadt, Germany; [3]Ares Trading S.A., Eysins, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany); [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; [10]EMD Serono Research & Development Institute, Inc., Billerica, MA, USA

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 non-converters 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 multiple sclerosis (MS).[1]
- Serum levels of growth differentiation factor 15 (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.

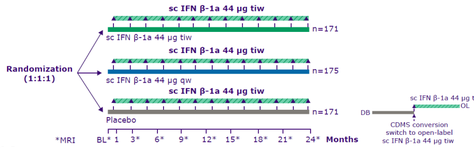
OBJECTIVE

To investigate if serum levels of GDF-15 predict disease stability in patients with clinically isolated syndrome (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 clinically definite MS (CDMS), defined by either a second demyelinating event or a sustained increase (≥1.5 points) in the Expanded Disability Status Scale (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 non-converters 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.

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.
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

RESULTS

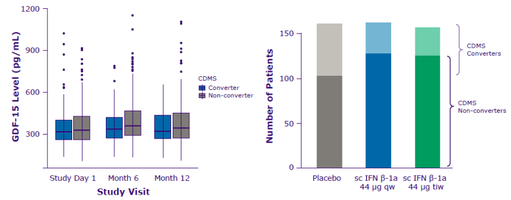
Table 1. GDF-15 levels appeared highest, over time, in those taking sc IFN β-1a 44 µg tiw (double-blind period)

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

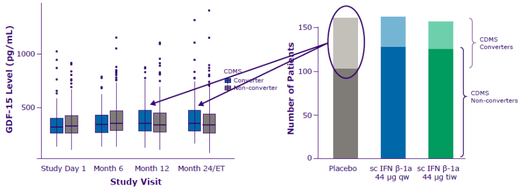
- For placebo, more converters to CDMS were seen at Month 12 and Month 24.
  - Such findings suggest that placebo-treated patients were not stable during this period
- In parallel, GDF-15 levels were not increasing for placebo recipients compared to the tiw group, where the number of converters was minimal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

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



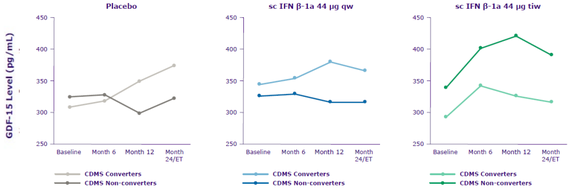
CDMS, clinically definite multiple sclerosis; **GDF-15**, growth differentiation factor 15; **IFN**, interferon; **qw**, once weekly; **sc**, subcutaneous; **tiw**, three times weekly

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 non-converters (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

- 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 (**Figure 4**).

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.

The REFLEX study: NCT00404352.

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Data collection and analysis was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945)

This poster was previously presented at ECTRIMS 2021 Virtual Congress (13–15 October). Medical writing assistance was provided by Claire Snaith and Steve Winter of inScience Communications, Springer Healthcare Ltd, UK, and was funded by the healthcare business of Merck KGaA, Darmstadt, Germany.

INTRODUCTION

- 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 clinically isolated syndrome treated with sc IFN β-1a.**

GDF, growth development factor; **IFN**, interferon; **MS**, multiple sclerosis; **sc**, subcutaneous

REFERENCES
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  - 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 non-converters vs converters. All analyses are descriptive.

*Defined as a first clinical event suggestive of multiple sclerosis within the last 60 days and at least 2 clinically silent lesions on T2-weighted MRI scan, with EDSS score 0–5

CDMS, clinically definite multiple sclerosis; **CIS**, clinically isolated syndrome; **EDSS**, Expanded Disability Status Scale; **GDF**, growth development factor; **IFN**, interferon; **MRI**, magnetic resonance imaging; **qw**, once weekly; **sc**, subcutaneous; **tiw**, three times weekly

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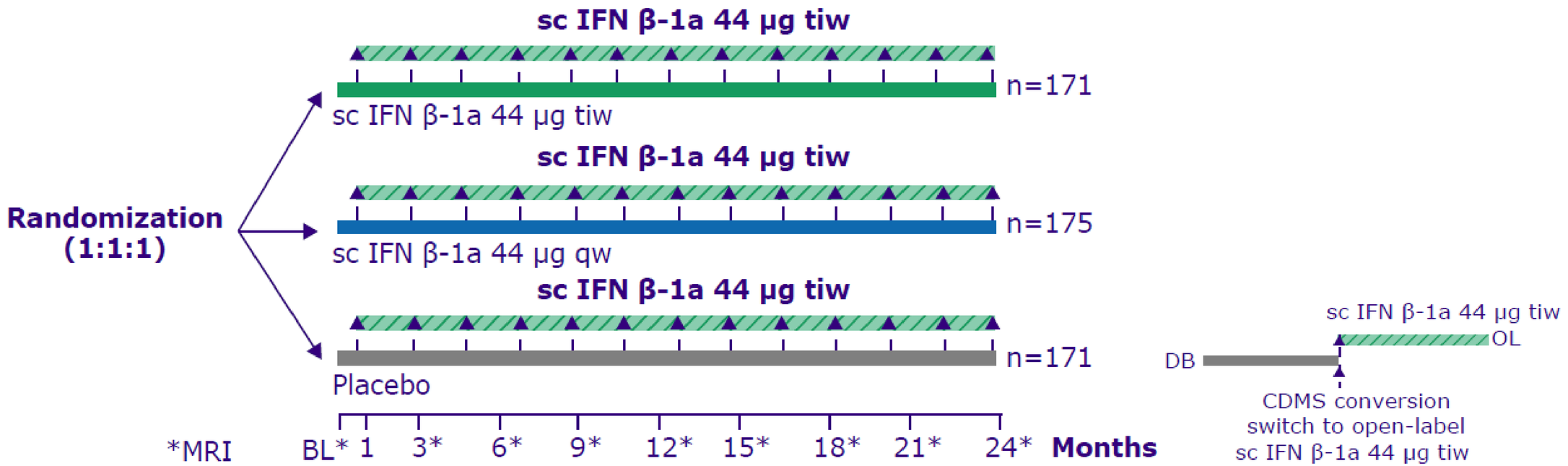
METHODS

Figure 1. REFLEX trial study design[3]



CDMS converters defined by either a 2nd attack or a sustained increase (≥1.5 points) in the Expanded Disability Status Scale 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 of conversion and initiation of sc IFN β-1a.
Whole study period includes all patients, irrespective of conversion to CDMS.
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RESULTS

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Month 6 Mean (SD) Median	n=141 358.63 (133.23) 326.69	n=147 375.31 (145.57) 342.35	n=135 430.89 (166.32) **391.47**	n=423 387.49 (151.44) 353.13
Month 12 Mean (SD) Median	n=112 333.55 (116.14) 298.88	n=131 355.17 (145.97) 327.81	n=126 429.02 (173.75) **409.43**	n=369 373.82 (153.33) 337.30
Month 24/ET Mean (SD) Median	n=89 355.91 (179.02) 322.80	n=109 352.38 (129.59) 320.68	n=114 420.28 (311.05) **390.86**	n=312 378.20 (226.01) 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

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RESULTS

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

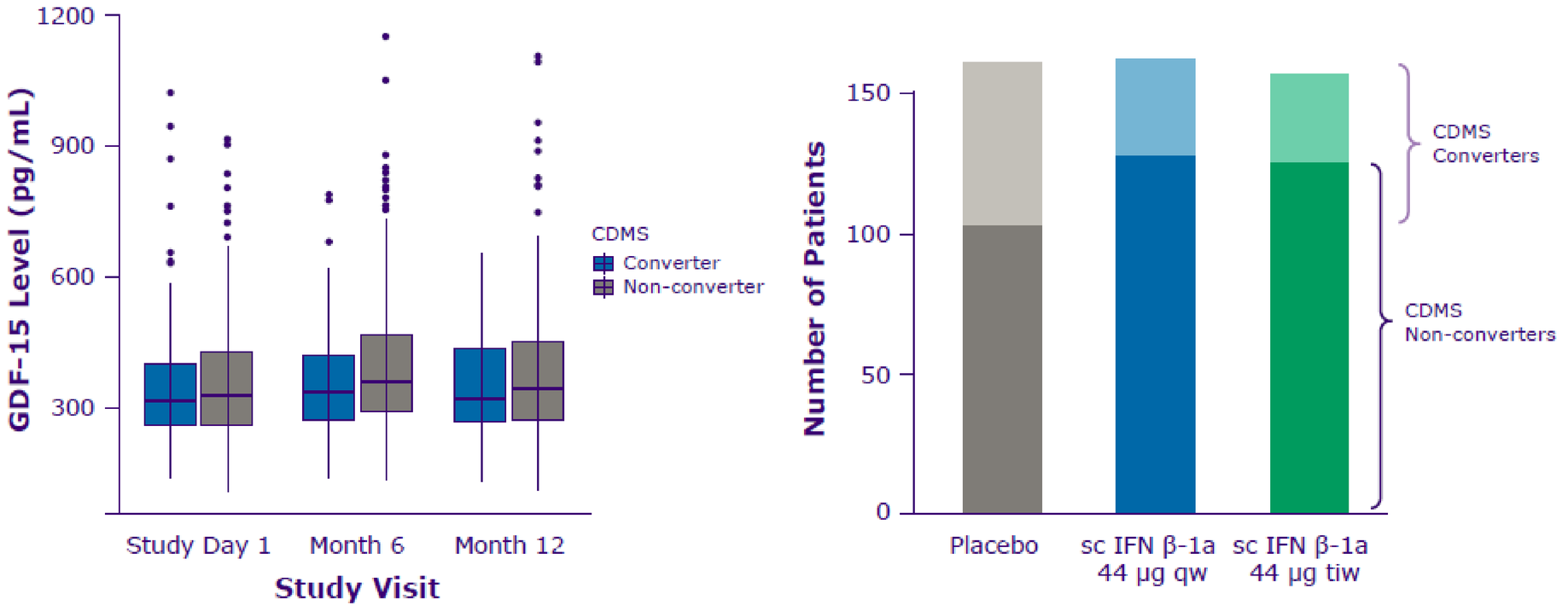

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Figure 3. Most CDMS converters came from the placebo arm (whole study period)

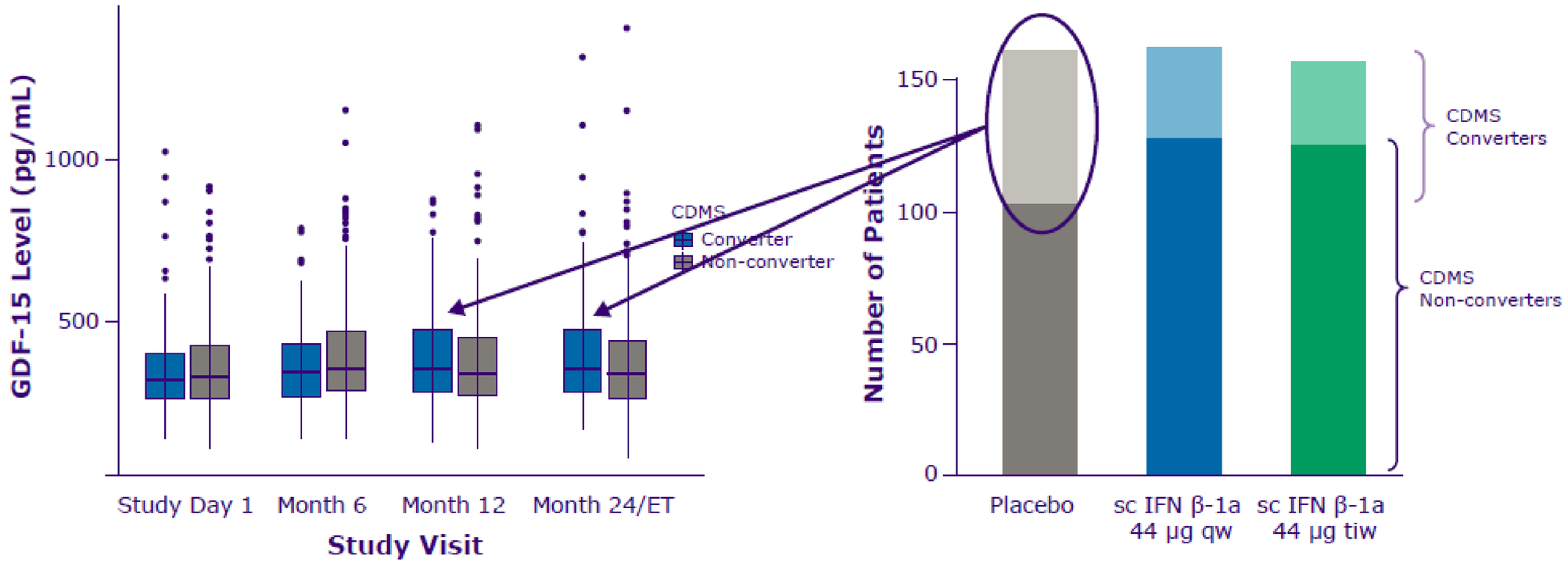

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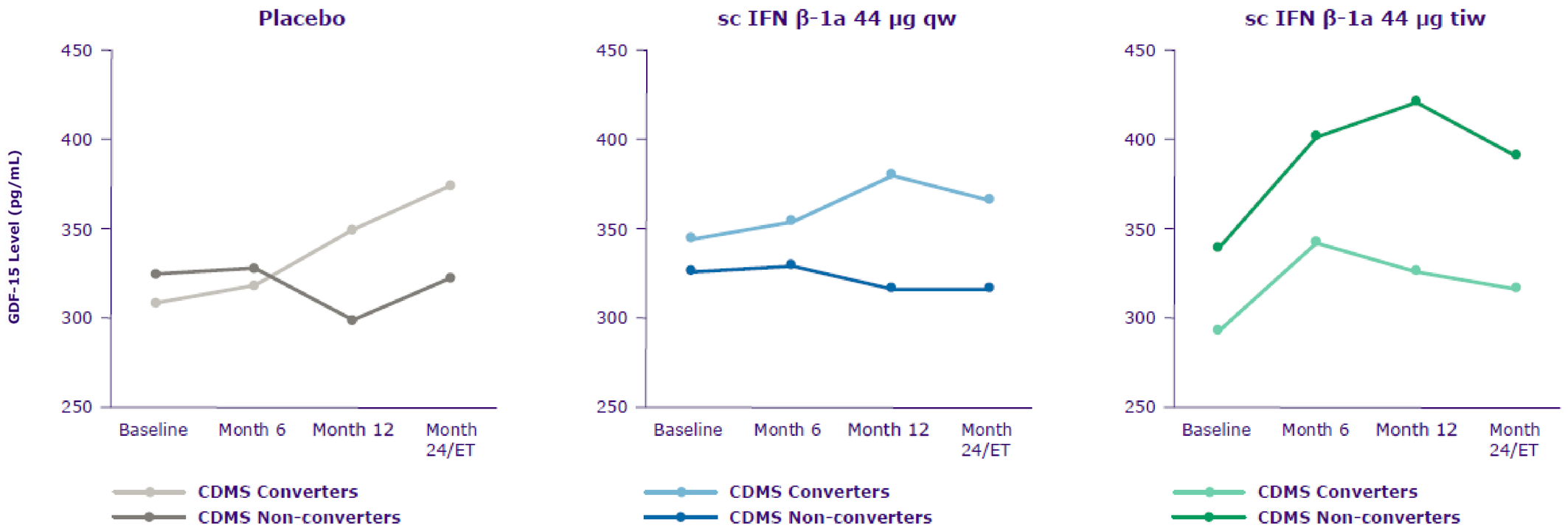
Figure 4. Median GDF-15 levels over time in CDMS converters vs non-converters (whole study period)



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CONCLUSIONS

- **In patients with clinically isolated syndrome, GDF-15 levels increased during treatment with sc IFN β-1a 44 µg tiw.**
- **The more pronounced increase of GDF-15 levels in CDMS non-converters 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.**

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

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