A Phase II Study of the Efficacy and Safety of High-Dose Cholecalciferol (Vitamin D_3) Oil as Add-on Therapy in Subjects with Relapsing-Remitting Multiple Sclerosis Receiving Subcutaneous Interferon β-1a: SOLAR

J. Smolders[1,2], R. Hupperts[1], R. Vieth[3], T. Holmøy[4], K. Marhardt[5], M. Schluep[6], J. Killestein[7], F. Barkhof[7,8], L.M.E. Grimaldi[9], M. Beelke[10]

[1]Maastricht University Medical Centre, The Netherlands; [2]Canisius Wilhelmina Ziekenhuis, The Netherlands; [3]University of Toronto, Canada; [4]Akershus University Hospital and University of Oslo, Norway; [5]Merck GmbH, Austria; [6]Centre Hospitalier Universitaire Vaudois, Switzerland; [7]VU University Medical Centre, The Netherlands; [8]University College London, UK; [9]Fondazione Istituto San Raffaele G. Giglio di Cefalù, Italy; [10]Worldwide Clinical Trials GmbH, Germany

INTRODUCTION

- Vitamin D is the precursor of a potent immunoregulatory molecule.
- The role of vitamin D in the pathogenesis and progression of multiple sclerosis (MS) has received increasing interest in recent years.[1]
- Low serum levels of vitamin D (25(OH)D_3) have been associated with greater risk of developing MS, and with poorer outcomes in MS patients.[2-4]
- However, whether supplementation of vitamin D improves outcomes is uncertain, since existing clinical evidence is contradictory and involves small patient numbers.[5,6]

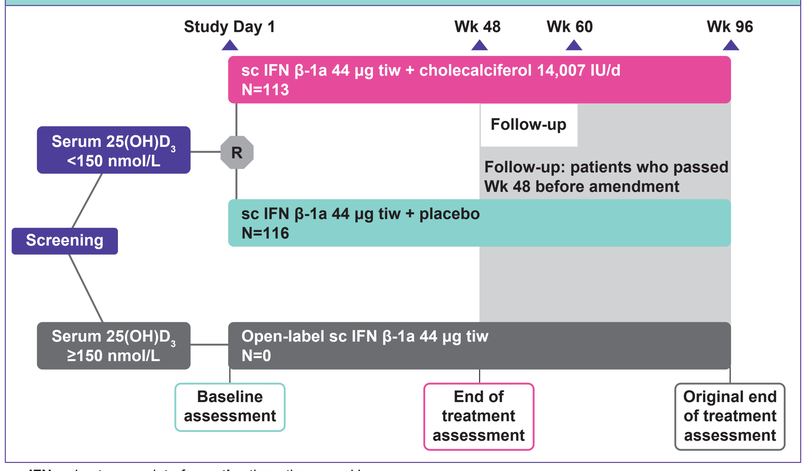
OBJECTIVES

- To investigate the efficacy and safety of cholecalciferol (vitamin D_3) as add-on therapy to subcutaneous interferon (sc IFN) β-1a.

METHODS

- SOLAR was a prospective, randomised, double-blind, multicentre, 48-week study (NCT01285401).
- Patients with relapsing-remitting MS and serum 25(OH)D_3 levels <150 nmol/L were randomised to sc IFN β-1a 44 µg three times weekly plus either oral cholecalciferol (14,007 IU/day [350 µg]) or matching placebo (**Figure 1**).
  - A third arm was planned for patients with serum 25(OH)D_3 levels ≥150 nmol/L but no patients met this criterion (**Figure 1**).

Figure 1. SOLAR Study Design



sc IFN, subcutaneous interferon; **tiw**, three times weekly.

- Primary endpoint: proportion of patients at Week 48 with no evidence of disease activity (NEDA), defined as: no relapses; no Expanded Disability Status Scale (EDSS) score progression; and no new Gd-enhancing T1 lesions, or new or enlarging T2 MRI lesions.
  - Original primary endpoints: mean number of combined unique active (CUA) lesions at Week 48 and proportion of relapse-free patients at Week 96.
  - Due to delays in patient recruitment the primary endpoints were changed to NEDA, allowing a reduction in sample size and study duration.
- Secondary endpoints at Week 48 included: mean annualised relapse rate (ARR); EDSS progression; mean number of CUA lesions/patient/scan; mean number of new T1-hypointense lesions; change from baseline in total volume of T2 lesions.
- Analysis of NEDA status at Week 48 was estimated in the intent-to-treat (ITT) population using a logistic regression model with treatment and stratification variables as covariates.

RESULTS

- 229 patients were randomised to cholecalciferol or placebo as add-on to sc IFN β-1a:
  - The ITT population (81.2%) had a follow-up of 48 weeks.
  - Demographics and disease activity at baseline between groups were similar, except for the time since diagnosis (**Table 1**).

Table 1. Baseline Demographics and Clinical Characteristics

	IFN β-1a + cholecalciferol (N=113)	IFN β-1a + placebo (N=116)	Total (N=229)
Age, years	34.1 (8.0)	33.5 (9.3)	33.8 (8.7)
Female	76 (67.3%)	79 (68.1%)	155 (67.7%)
Time since diagnosis, months	10.4 (8.1)	14.8 (17.0)	N/A
Body weight, kg	75.8 (17.9)	75.1 (17.0)	75.4 (17.4)
Height, cm	171.9 (9.5)	171.3 (9.1)	171.6 (9.3)
BMI, kg/m^2	25.63 (5.67)	25.54 (5.23)	25.58 (5.44)

Data are number (%) or mean (SD).
BMI, body mass index; **IFN**, interferon; **SD**, standard deviation.

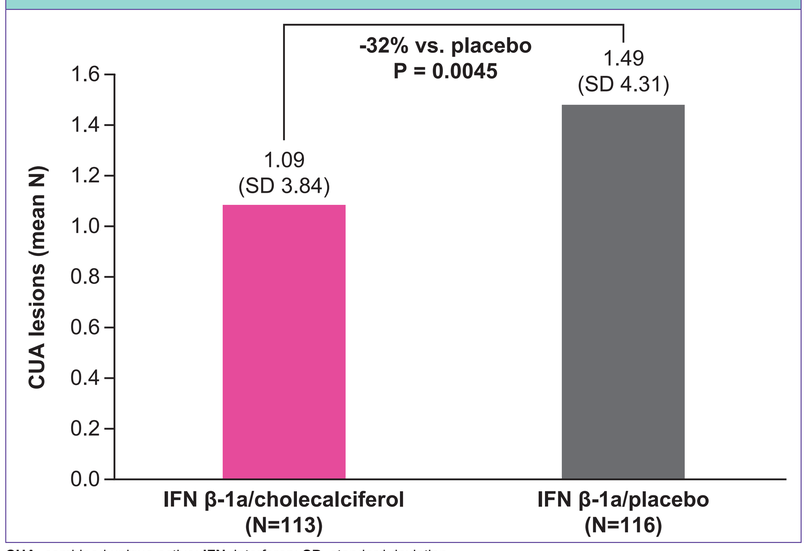
No Difference in % of Patients with NEDA

- Overall, 37% of patients in the sc IFN β-1a + cholecalciferol group had NEDA at Week 48.
- There was no statistically significant difference in NEDA status at Week 48 between treatment groups (cholecalciferol: 37.2% vs. placebo: 35.3%; odds ratio [OR]: 0.97; P = 0.91).

Cholecalciferol was Associated with Significantly Better MRI Outcomes

- Although only one MRI scan was performed after baseline, at Week 48 cholecalciferol was associated with a 32% reduction in the number of CUA lesions versus placebo (1.09 vs. 1.49; incidence rate ratio [IRR]: 0.68; P = 0.0045; **Figure 2**).

Figure 2. Mean Number of CUA Lesions Per Patient Per Scan at Week 48



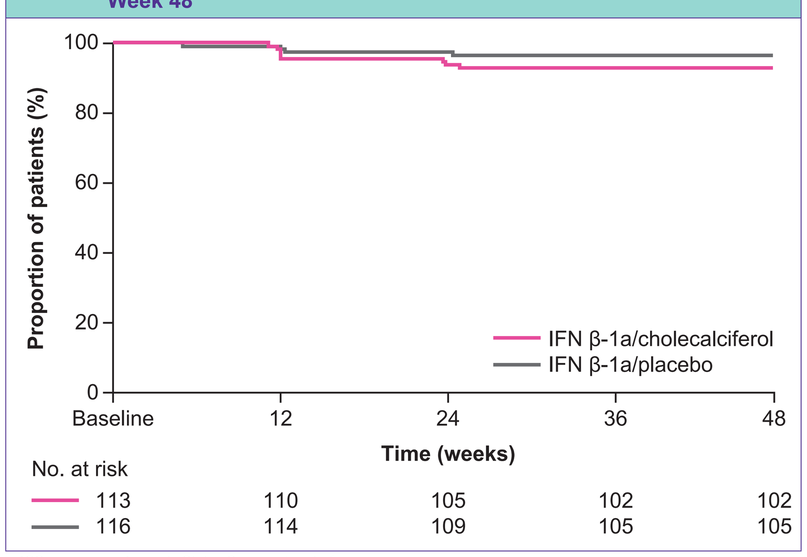
CUA, combined unique active; **IFN**, interferon; **SD**, standard deviation.

- The proportion of subjects free from new T1-hypointense lesions was significantly higher with cholecalciferol versus placebo in patients aged 18–30 years (85.7% vs. 46.8%; OR: 11.03; P = 0.006), but not in the ITT population.
- Compared with placebo, cholecalciferol significantly reduced the mean percentage change from baseline in total volume of T2 lesions at Week 48 (3.57% vs. 6.07%; P = 0.035).

No Difference in EDSS Progression

- The proportion of patients free from any EDSS progression at Week 48 was similar for both treatment groups (cholecalciferol: 71.7% vs. placebo: 75.0%; OR: 0.84; P = 0.57).
- There was no significant difference between treatment groups for time to confirmed EDSS progression up to Week 48 (hazard ratio: 2.02; P = 0.25; **Figure 3**).

Figure 3. Kaplan-Meier Plot of Time to Confirmed EDSS Progression up to Week 48

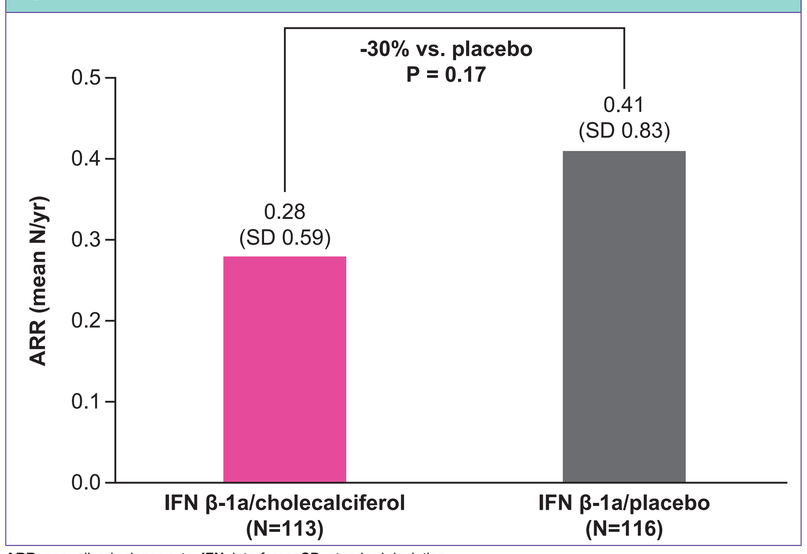


EDSS, Expanded Disability Status Scale; **IFN**, interferon.

ARR was Lower in the Cholecalciferol Group, but did not Reach Significance

- Compared with placebo, patients receiving cholecalciferol had a 30% lower ARR (0.28 vs. 0.41; IRR: 0.69; P = 0.17; **Figure 4**), although statistical significance was not reached.
- The proportion of patients who were relapse-free at Week 48 was similar between the two groups (cholecalciferol: 78.8% vs. placebo: 75.0%; OR: 1.26; P = 0.47).

Figure 4. Mean Annualised Relapse Rates at Week 48



ARR, annualised relapse rate; **IFN**, interferon; **SD**, standard deviation.

Despite the High Treatment Dose, No Additional Safety Issues were Identified with Cholecalciferol Add-On

- The incidence of severe treatment-emergent adverse events (TEAEs) was overall low and similar between treatment groups (**Table 2**).
- There were no new or unexpected TEAEs with cholecalciferol treatment and the observed TEAEs were broadly similar across the two treatment groups.
  - The most common TEAEs in the cholecalciferol group were headache (n=20 [17.7%]) and nasopharyngitis (n=18 [15.9%]).
  - The most common TEAEs in the placebo group were headache (n=22 [19.0%]) and influenza (n=19 [16.4%]).

Table 2. Summary of Adverse Events

	IFN β-1a + cholecalciferol (N=113)		IFN β-1a + placebo (N=116)	
	n (%)	m	n (%)	m
Any TEAE	99 (87.6)	601	93 (80.2)	507
Any TESAE	18 (18.2)	23	8 (8.6)	9
Any TEAE leading to discontinuation	4 (4.0)	4	7 (7.5)	12
TEAE by severity:				
Mild	90 (90.9)	414	87 (93.5)	398
Moderate	63 (63.6)	179	52 (55.9)	105
Severe	7 (7.1)	8	4 (4.3)	4
TEAE relationship to treatment:				
Unrelated	92 (92.9)	472	91 (97.8)	448
Unlikely	35 (35.4)	103	18 (19.4)	34
Possible	12 (12.1)	17	14 (15.1)	19
Probable	9 (9.1)	9	6 (6.5)	6

IFN, interferon; **m**, number of events; **n**, number of patients; **TEAE**, treatment-emergent adverse event; **TESAE**, treatment emergent serious adverse event.

CONCLUSIONS

- **SOLAR is the largest (to date), placebo-controlled, randomised, double-blind study of vitamin D_3 as an add-on therapy for MS patients.**
- **Compared with placebo, high-dose vitamin D did not demonstrate an effect on the NEDA primary endpoint at Week 48.**
- **High-dose vitamin D significantly improved MRI outcomes compared with placebo.**
- **Relapse rates were reduced with high-dose vitamin D, although statistical significance was not reached.**
- **There were no additional safety issues with high-dose vitamin D treatment.**
- **SOLAR did not show a significant effect on the primary endpoint, although the MRI findings (CUA lesions, change from baseline in total volume of T2 lesions) and the ARR suggest a benefit of high-dose vitamin D.**

REFERENCES

1. Smolders J, et al. *J Neuroimmunol* 2008;194:7–17.
2. Munger K, et al. *JAMA Neurol* 2006;296:2832–8.
3. Ascherio A, et al. *JAMA Neurol* 2014;71:306–14.
4. Simpson S, et al. *Ann Neurol* 2010;68:193–203.
5. Soilu-Hanninen M, et al. *J Neurol Neurosurg Psychiatry* 2012;83:565–71.
6. Kampman M, et al. *Mult Scler* 2012;18:1144–51.

ACKNOWLEDGMENTS

This study was funded by Merck KGaA, Darmstadt, Germany. Medical writing assistance was provided by Ewan Smith and Shaun Foley of inScience Communications, Springer Healthcare, Chester, UK, and was funded by Merck KGaA, Darmstadt, Germany.

DISCLOSURES

JS: no conflicts of interest. **RH:** institutional research grants and fees for lectures and advisory boards from Biogen, Merck and Genzyme-Sanofi. **RV:** patent royalties for an infant vitamin D supplement. **TH:** speaker honoraria from Merck, Biogen Idec, Sanofi and Novartis; institutional research funding from The Research Council of Norway and The Norwegian South-Eastern Health Authorities. **KM:** employee of Merck Gesellschaft mbH, Austria. **MS:** travel funding, speaker honoraria and/or consulting fees from Biogen, Genzyme, Merck, Novartis, Roche and Sanofi-Aventis; research support from Merck, Novartis and Biogen. **JK:** speaker and consultation fees from Merck, Biogen, Teva, Genzyme, Roche and Novartis; institutional research support from Bayer, Biogen Idec, GSK, Merck, Novartis, Genzyme and Teva. **FB:** Director of the IAC, contracted to perform blinded MRI analysis; consultancy fees from Merck, Novartis, Biogen, Roche, TEVA, Synthon and Genzyme. **LMEG:** speaker honoraria or travel funding from Merck, Biogen Idec, Sanofi-Aventis, Teva and Bayer; institutional support from Biogen Idec and Merck. **MB:** former employee of Merck KGaA.

GET POSTER PDF

Presented at European Charcot Foundation (ECF) 2016; November 24–28, 2016; Baveno, Italy