UniversitätsKlinikum Heidelberg

Neue Medikamente bei der Multiplen Sklerose

... was ist am Horizont?

Alexander Schwarz

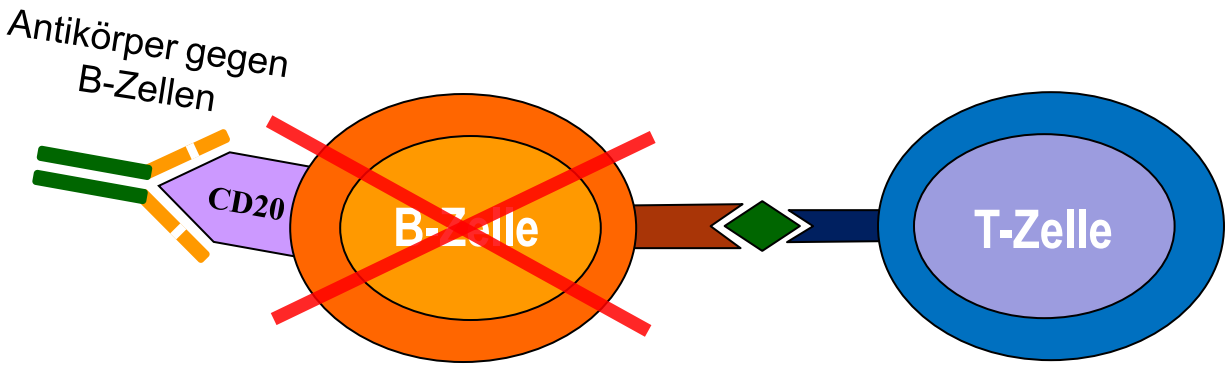
MS-Patiententag 2017

Agenda

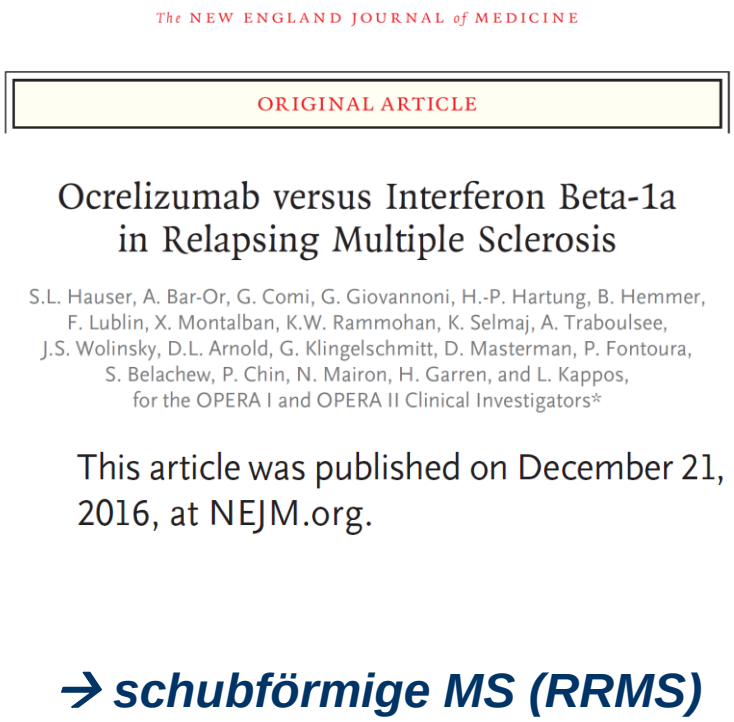
- B-Zelldepletion (Ocrelizumab / Ofatumumab)
- Cladribin
- Siponimod
- Biotin (Vitamin B7)

B-Zelldepletion

B-Zellen und T-Zellen tauschen Signale aus
und aktivieren sich so gegenseitig



Ocrelizumab (OCREVUS™)



The NEW ENGLAND JOURNAL of MEDICINE

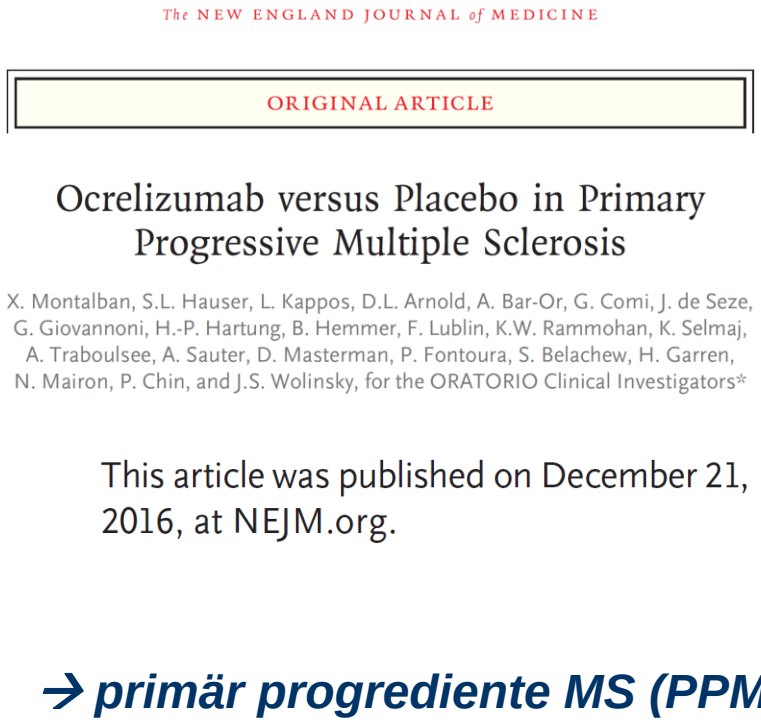
ORIGINAL ARTICLE

Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis

S.L. Hauser, A. Bar-Or, G. Comi, G. Giovannoni, H.-P. Hartung, B. Hemmer, F. Lublin, X. Montalban, K.W. Rammohan, K. Selmaj, A. Traboulsee, J.S. Wolinsky, D.L. Arnold, G. Klingelschmitt, D. Masterman, P. Fontoura, S. Belachew, P. Chin, N. Mairon, H. Garren, and L. Kappos, for the OPERA I and OPERA II Clinical Investigators*

This article was published on December 21, 2016, at NEJM.org.

→ ***schubförmige MS (RRMS)***



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis

X. Montalban, S.L. Hauser, L. Kappos, D.L. Arnold, A. Bar-Or, G. Comi, J. de Seze, G. Giovannoni, H.-P. Hartung, B. Hemmer, F. Lublin, K.W. Rammohan, K. Selmaj, A. Traboulsee, A. Sauter, D. Masterman, P. Fontoura, S. Belachew, H. Garren, N. Mairon, P. Chin, and J.S. Wolinsky, for the ORATORIO Clinical Investigators*

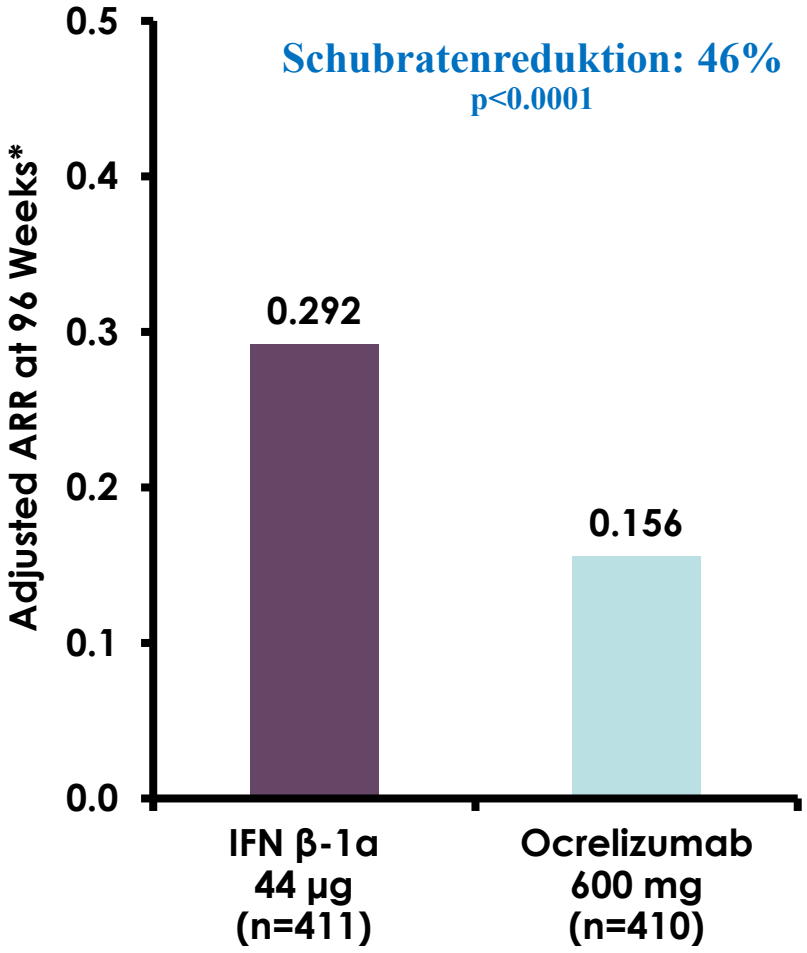
This article was published on December 21, 2016, at NEJM.org.

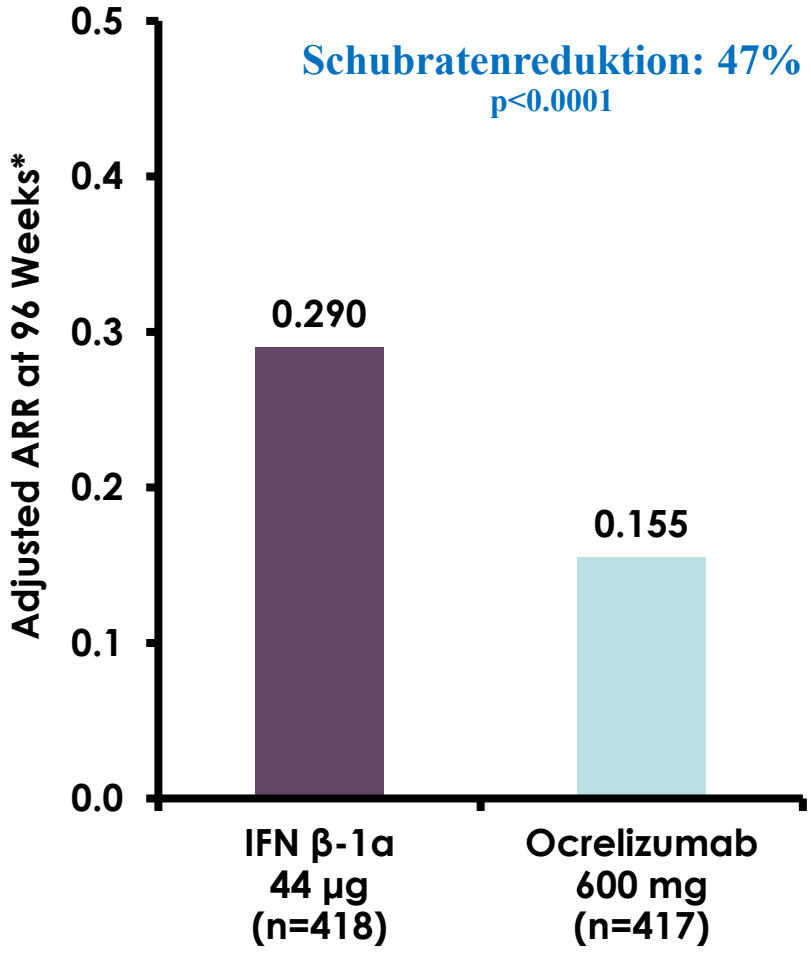
→ ***primär progrediente MS (PPMS)***

Ocrelizumab bei **RRMS** (OPERA I und OPERA II)

Fragestellung:	**Ist eine Entfernung der B-Zellen mit dem Antikörper *Ocrelizumab* zur Schubprophylaxe der MS wirksam?**
Design:	**Insgesamt mehr als 1600 Patienten weltweit Testung gegen Interferon-beta (Rebif®)**
Ziel:	**Bessere Reduktion der jährliche Schubrate als Rebif®**
Dauer:	**2 Jahre**

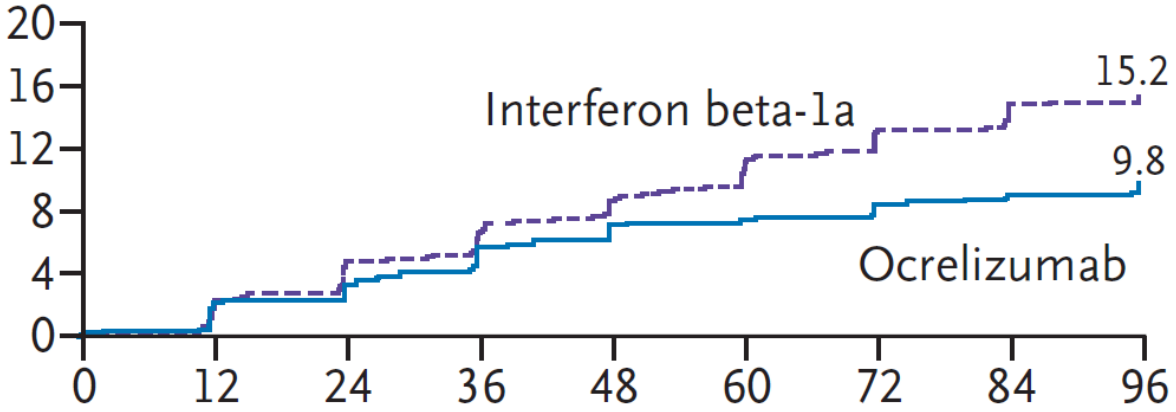
Ocrelizumab bei **RRMS** (OPERA I und OPERA II)





Ocrelizumab bei **RRMS** (OPERA I und OPERA II)

Patienten mit Zunahme der Behinderung [%]

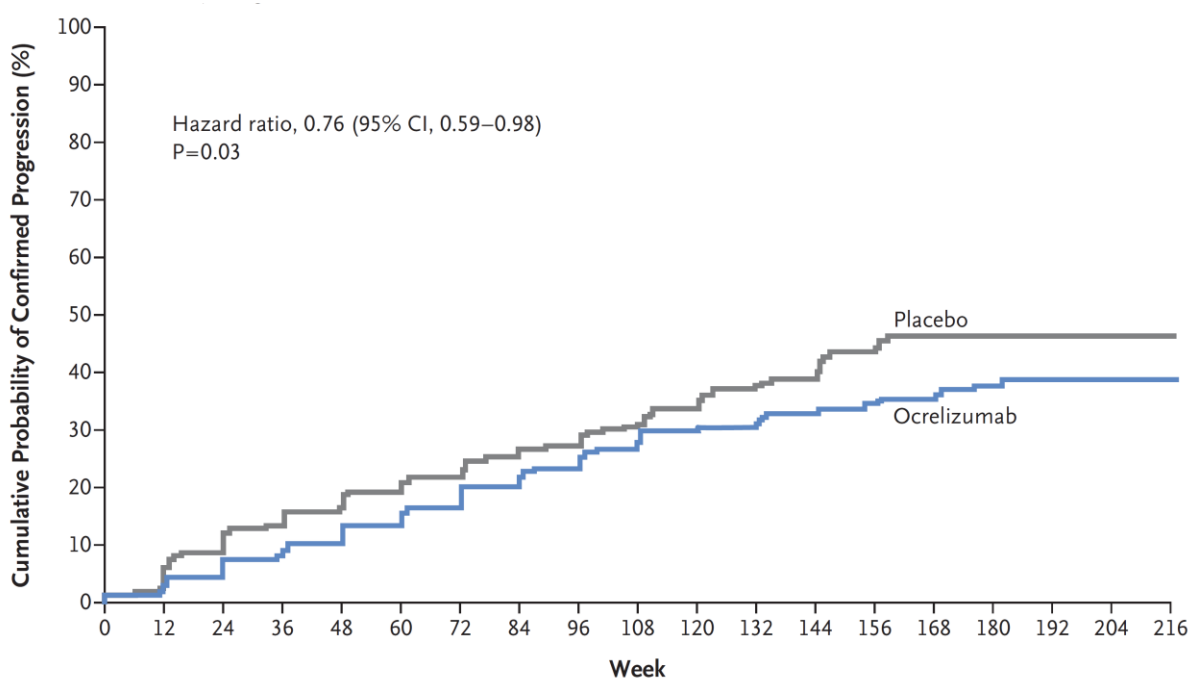


Ocrelizumab bei **PPMS** (ORATORIO)

Fragestellung:	**Ist eine B-Zelldepletion mit Ocrelizumab zur Therapie der primär progredienten MS wirksam?**
Design:	**Ocrelizumab vs Placebo (Verhältnis 2:1)** **732 Patienten**
Ziel:	**Verminderung der Behinderungsprogression**
Dauer:	**mindestens 120 Wochen**

Ocrelizumab bei **PPMS** (ORATORIO)

Patienten mit Zunahme der Behinderung [%]



Ocrelizumab - Sicherheit und Nebenwirkungen

- Alle Ereignisse:

Ocrelizumab: 83% Rebif®: 83%

- Alle Infekte:

Ocrelizumab: 59% Rebif®: 53%

- Schwere Infekte:

Ocrelizumab : 1,3% Rebif®: 2,9%

- Bösartige Tumore:

Ocrelizumab ges.: 4 Rebif® ges.: 2

Ofatumumab (Phase II)

Per S. Sorensen, MD
Steen Lisby, MD
Richard Grove, MSc
Frederick Derosier, DO
Steve Shackelford, DVM
Eva Havrdova, MD
Jelena Drulovic, MD
Massimo Filippi, MD

Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis

A phase 2 study

Neurology® 2014;82:573-581

Ofatumumab (Phase III)

NOVARTIS

Global Clinical Development - General Medicine

OMB157/Ofatumumab

Clinical Trial Protocol COMB157G2302

A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis

Document type:	Clinical Trial Protocol
EUDRACT number:	2015-005419-33
Version number:	00 (Original Protocol)
Clinical trial phase:	III
Release date:	7-Apr-2016

Ofatumumab (Phase III)

Einschluss:

- schubförmige MS
- Alter: 18-55 Jahre
- Eines der folgenden Kriterien:
  - mind. 1 Schub im letzten Jahr
  - mind. 2 Schübe in den letzten 2 Jahren
  - mind. 1 Kontrastmittelherd im letzten Jahr
- EDSS 0-5.5 Punkte

Ausschluss

- Krankheitsdauer > 10 Jahre *und* EDSS < 2.0
- Chronische Infektionen (Hepatitis, HIV, TBC…)
- jegliche vorausgehende B-Zelldepletion
- Vortherapie mit Alemtuzumab, Mitoxantron, Knochenmarktransplantation, bzw. „starke Immunsuppression“
- **KEIN** Ausschluss für die meisten anderen MS-Therapeutika nach Einhalten einer Auswaschphase (einschl. Natalizumab)

Cladribin bei RRMS (CLARITY-Studie)

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis

Gavin Giovannoni, M.B., B.Ch., Ph.D., Giancarlo Comi, M.D., Stuart Cook, M.D., Kottil Rammohan, M.D., Peter Rieckmann, M.D., Per Soelberg Sørensen, M.D., D.M.Sc., Patrick Vermersch, M.D., Ph.D., Peter Chang, Ph.D., Anthony Hamlett, Ph.D., Bruno Musch, M.D., Ph.D., and Steven J. Greenberg, M.D., for the CLARITY Study Group*

N ENGL J MED 362;5 NEJM.ORG FEBRUARY 4, 2010

- **1326 Patienten weltweit**
- **Testung in 2 Dosierungen gegen Scheintherapie (Placebo)**
- **Ziel: Reduktion der MS-Schübe**
- **Dauer: 2 Jahre**

MOVECTRO®

Cladribine tablets

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about MOVECTRO.

It does not contain all of the available information. It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking MOVECTRO against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your doctor or pharmacist.

Keep this leaflet with the medicine.

You may want to read it again.

MOVECTRO has been studied for safety and effectiveness when given as 4 treatment courses over 2 years. Until more information is available, you should not receive additional treatment courses during or after the 2 years of treatment.

The long term effects beyond 2 years are still being studied. MOVECTRO may have long term effects that are not yet known, e.g. increased risk of cancer. The effect of MOVECTRO on fertility is unknown. Your doctor is the best person to discuss this with you.

Ask your doctor if you have any questions or concerns about taking MOVECTRO.

This medicine is available only with a doctor's prescription.

MOVECTRO is not addictive.

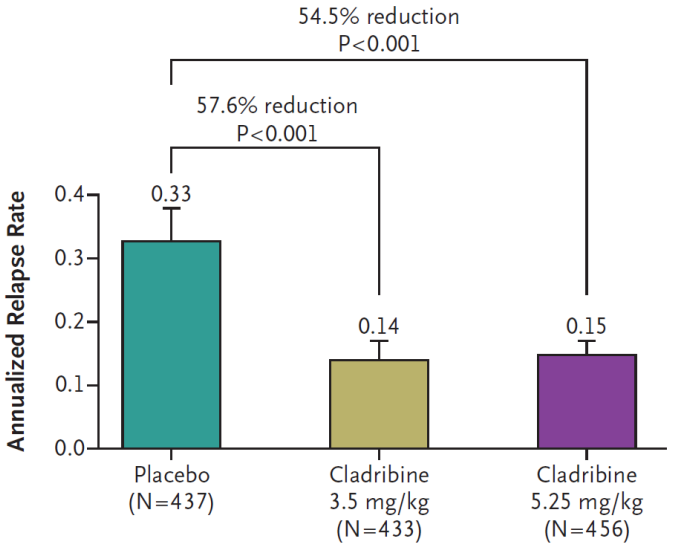
- You are taking other medicines that weaken your immune system or affect your bone marrow (e.g. cyclosporin, methotrexate, mitozantrone, azathioprine, natalizumab, or ongoing use of corticosteroids)
- You have moderate or severe kidney or liver disease

  If necessary, your doctor can do tests to check your liver or kidney function.
- You have been vaccinated within the last three months with a 'live' vaccine, e.g. vaccines for shingles, typhoid, yellow fever, etc

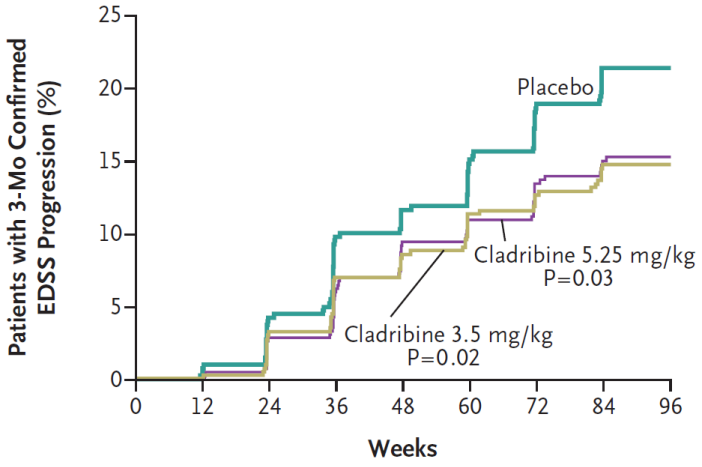
  Ask your doctor if you are not sure if you have had a 'live' vaccine (see also 'Using other medicines' below).

Cladribin bei RRMS (CLARITY-Studie)

jährliche Schubrate



Zunahme der Behinderung



Cladribin / **CLARITY-Studie**

Nebenwirkungen / Sicherheit

- **Alle Infekte:**
  Cladribin: 48% Placebo: 43%

- **Schwere Infekte:**
  Cladribin: 2,6% Placebo: 1,6%

- **Kopfschmerz:**
  Cladribin: 22% Placebo: 17%

- **Neubildungen – bösartig und gutartig:**
  Cladribin: 1% Placebo: 0%

Cladribin / **Alle Studien**

Nebenwirkungen / Sicherheit

- **Alle Infekte:**
  Kein Unterschied zwischen Cladribin und Placebo

- **Schwere Infekte:**
  allenfalls etwas häufiger bei Cladribin

- **Neubildungen – bösartig und gutartig:**
  Kein Unterschied zwischen Cladribin und Placebo

Siponimod (BAF312) bei SPMS

MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG

Novartis announces positive phase III results showing efficacy of BAF312 in patients with secondary progressive MS

- *The Phase III EXPAND study of BAF312 (siponimod) in secondary progressive multiple sclerosis (SPMS) met its primary endpoint of reducing the risk of three-month confirmed disability progression versus placebo*
- *There are currently very limited treatment options for SPMS, a form of MS associated with gradual worsening of symptoms and accumulation of disability, independent of relapses*
- *EXPAND is the largest study ever conducted in SPMS, and is part of Novartis' ongoing leadership and commitment to people with MS*

Basel, August 25, 2016 – Novartis today announced the Phase III EXPAND study, evaluating

“ multiple sclerosis (SPMS), **met its primary endpoint of a reduction in the risk of disability progression, compared with placebo**. The EXPAND study represents the largest randomized, controlled study in SPMS to date.[i]

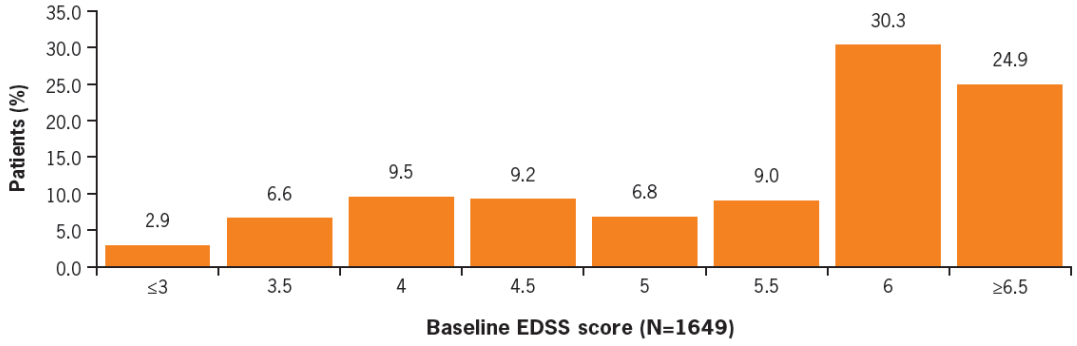
Siponimod bei SPMS (Expand-Studie)

Table 2. Baseline demographics

Characteristic	Total patient population N=1649
Age, years, mean±SD	48.0±7.9
Age group, years, n (%)	
18–30	38 (2.3)
31–40	252 (15.3)
41–55	1043 (63.3)
>55	313 (19.0)
Female, n (%)	989 (60.0)
Race, n (%)	
Caucasian	1559 (94.5)
Asian	48 (2.9)
Black	10 (0.6)
Other	19 (1.2)
Unknown	13 (0.8)

SD, standard deviation

Figure 3. Distribution of baseline EDSS scores



0.9% patients had missing EDSS data at baseline

Ectrims 2015

Siponimod bei SPMS (Expand-Studie)

- **Reduktion einer bestätigten Behinderungsprogression um 21% gegenüber Placebo.**

- **Risikoreduktion auch in vorgegebenen Untergruppen, z.B. Patienten, die keine unterlagerten Schübe haben**

- **MRT-Befunde des Schädels waren ebenfalls besser in der Siponimod-Gruppe**

Ectrims / DGN 2016

Biotin bei PPMS und SPMS

MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study

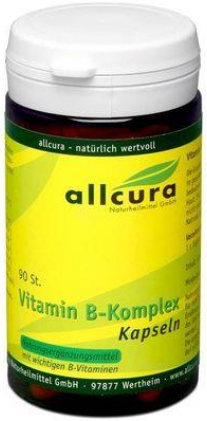
Ayman Tourbah, Christine Lebrun-Frenay, Gilles Edan, Michel Clanet, Caroline Papeix, Sandra Vukusic, Jerome De Sèze, Marc Debouverie, Olivier Gout, Pierre Clavelou, Gilles Defer, David-Axel Laplaud, Thibault Moreau, Pierre Labauge, Bruno Brochet, Frédéric Sedel and Jean Pelletier; on behalf of the MS-SPI study group

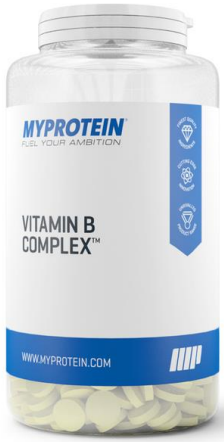
Date received: 17 June 2016; revised: 22 July 2016; accepted: 4 August 2016

MULTIPLE SCLEROSIS JOURNAL

Epub 1. September 2016

Biotin ≙ Vit. B7 ≙ Vit. B8 ≙ Vit. H





→ **Vitamin B Präparate enthalten meist kein Biotin**

Biotin bei PPMS und SPMS

Fragestellung:	**Kann die hochdosierte Gabe von Biotin die Symptome bei MS lindern?**
Patienten:	**Mittleres Alter um 50 Jahre** **Körperlich schwer beeinträchtigt (EDSS um 6.0)**
Design:	**Placebo-kontrollierte Studie** **154 Patienten an 17 Zentren in Frankreich**
Ziel:	**Verbesserung der Behinderung**
Dauer:	**1 Jahr**

Biotin bei PPMS und PPMS

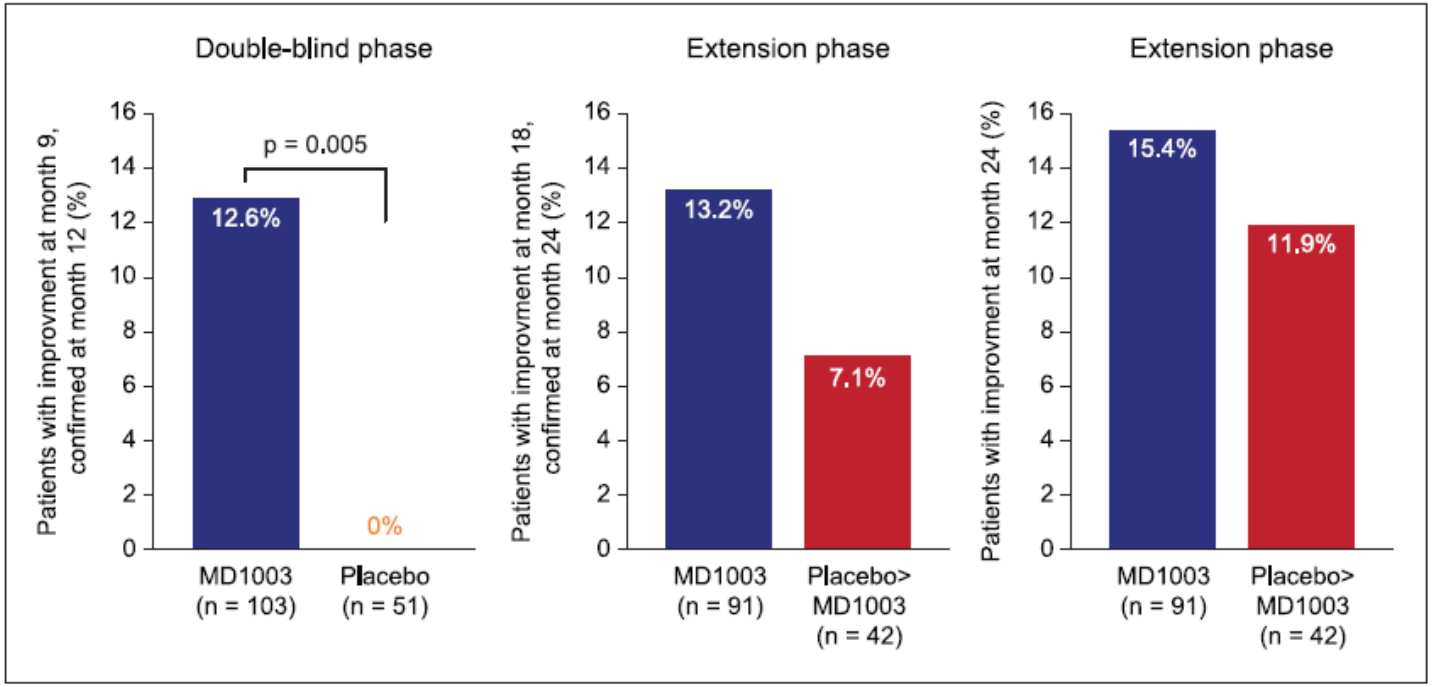


Figure 2. Proportion of patients with reversal of MS-related disability. Reversal of disability was defined as improvement of EDSS or TW25 values confirmed at the next visit (except for month 24 where no subsequent visit was available) compared with best respective values recorded at either the screening or the randomisation visits.
EDSS: Expanded Disability Status Scale; TW25: timed 25-foot walk.

Diskussion

B-Zelldepletion (Ocrelizumab / Ofatumumab)

→ *schubförmige MS und primär progrediente MS*

Cladribin

→ *schubförmige MS*

Siponimod

→ *sekundär progrediente MS*

Biotin

→ *primär progrediente MS und sekundär progrediente MS*