Results of ASCLEPIOS I and II:
Ofatumumab in relapsing forms of multiple sclerosis

ASCLEPIOS I and II are twin, flexible duration (up to 30 months), double-blind, randomized, multi-center Phase III studies evaluating the safety and efficacy of ofatumumab 20 mg monthly subcutaneous injections versus teriflunomide 14 mg oral tablets taken once daily in adults with a confirmed diagnosis of relapsing forms of multiple sclerosis (RMS).[1,2]

About the studies:

1,882
PATIENTS ENROLLED
18–55 years old

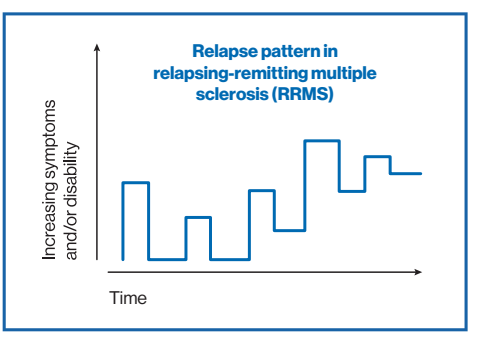
0–5.5[1,2]
EDSS* SCORE
*Expanded Disability Status Scale is used to measure disability

>350
SITES IN 37 COUNTRIES

Key endpoints and findings from the ASCLEPIOS studies†:

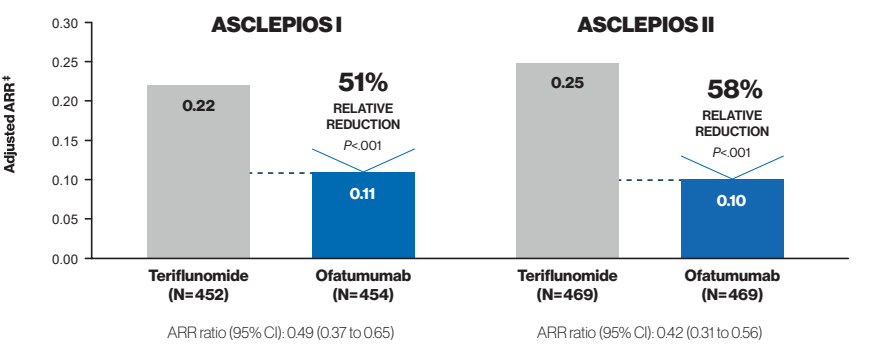
Relapses

- During a relapse, people with MS experience new or worsening symptoms for at least 24 hours.[3]
- The annualized relapse rate (ARR) estimates the average number of relapses a group of patients experienced over a year.[4]
- The ASCLEPIOS I and II studies showed that patients treated with ofatumumab had 51% and 58% reduction in ARR, respectively, compared with teriflunomide.[5]



Relapse frequency varies depending on the type of MS.[6] RMS include clinically isolated syndrome (CIS), RRMS and active secondary progressive MS (aSPMS).[7]

RMS patients on ofatumumab demonstrated a significant reduction in risk of relapses compared with teriflunomide in both studies.[5]



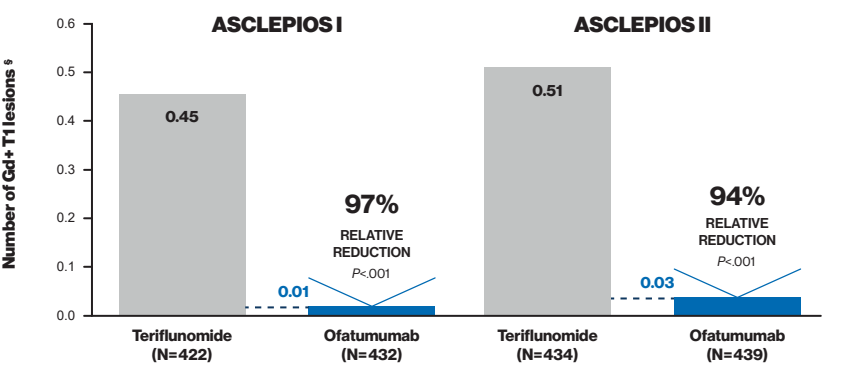
ARR ratio (95% CI): 0.49 (0.37 to 0.65) | ARR ratio (95% CI): 0.42 (0.31 to 0.56)

Full analysis set. Primary endpoint. ‡Negative binomial regression model. N, total number of patients included in the analysis. ARR, annualized relapse rate; CI, confidence interval.

Imaging of lesions

- Magnetic resonance imaging (MRI) scans are used to directly assess disease activity in the brain by detecting areas of inflammation and scarring or lesions.[8]
- Two common scans are T1 and T2, which measure different types of lesions in the brain. T1 lesions provide information about current disease activity by detecting areas of active inflammation, whereas T2 lesions show the total number of lesions.[8] For better visualization of the lesions the contrast agent called gadolinium (Gd) is used.
- ASCLEPIOS I and II showed that ofatumumab significantly reduced both gadolinium-enhancing (Gd+) T1 lesions and new or enlarging T2 lesions compared with teriflunomide.[5]

Ofatumumab significantly reduced Gd+ T1 lesions when compared with teriflunomide, demonstrating a profound suppression of new inflammatory activity.[5,8]



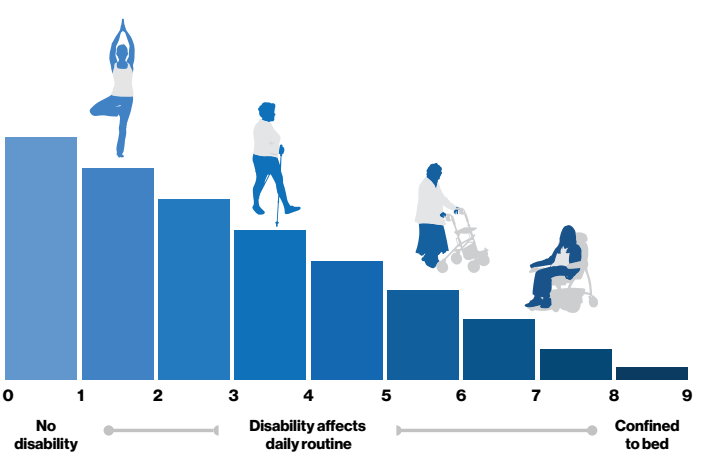
Rate ratio (95% CI): 0.03 (0.01 to 0.05) | Rate ratio (95% CI): 0.06 (0.04 to 0.10)

Full analysis set. Secondary endpoint. End of study. N, total number of patients included in the analysis. §Negative binomial regression model. CI, confidence interval; Gd+, gadolinium-enhancing.

Disability worsening

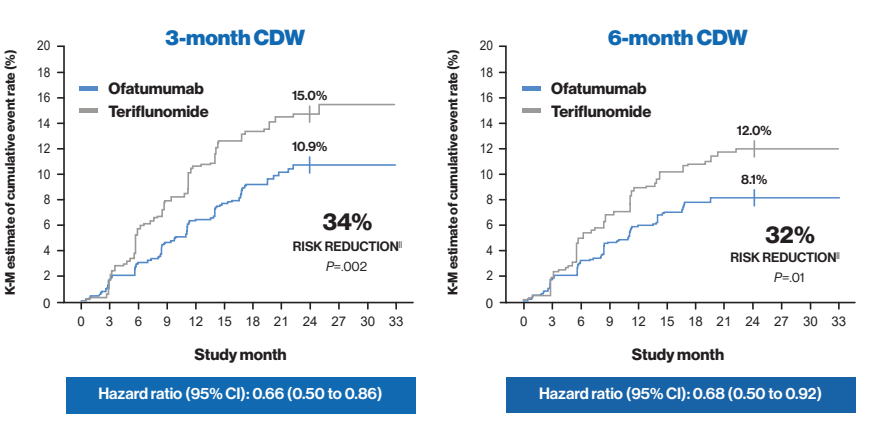
- A sustained change in a person's EDSS score, which quantifies disability, can be considered confirmed disability worsening (CDW), a measure that helps determine disease progression over time.[9]
- CDW can be defined as an increase from the starting EDSS score that lasts for a specific period of time, such as 3 or 6 months in the case of the ASCLEPIOS studies.[1,2]

EDSS



The EDSS is a measure to rate neurologic impairment in MS.[10]

Ofatumumab showed a relative risk reduction of 34% in 3-month CDW and 32% in 6-month CDW versus teriflunomide, in pre-specified pooled analyses.[5]

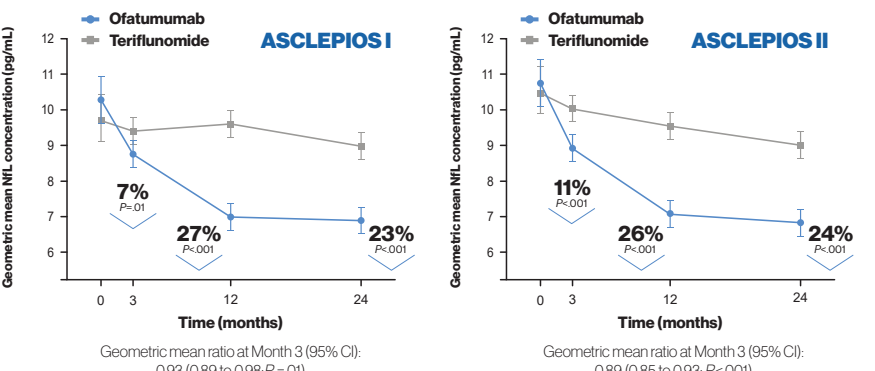


Full analysis set. Secondary endpoints. ‖Cox regression model. CDW, confirmed disability worsening; CI, confidence interval.

Nerve cell damage

- Nerve cells in the central nervous system can become damaged in MS.[11]
- Neurofilament light chain (NfL) is a protein that is released into circulation when axons, a part of nerve cells, are damaged.[11]
- NfL appears to be a promising biomarker to measure nervous system damage and monitor MS disease activity.[11]

Ofatumumab significantly lowered NfL serum levels at Month 3 and in all subsequent assessments during the studies as compared with teriflunomide.[5]



Geometric mean ratio at Month 3 (95% CI): 0.93 (0.89 to 0.98; $P = .01$) | Geometric mean ratio at Month 3 (95% CI): 0.89 (0.85 to 0.93; $P < .001$)

Full analysis set. Secondary endpoint. Repeated measures model. CI, confidence interval; NfL, neurofilament light chain.

- **Ofatumumab had a similar safety profile to teriflunomide, with the frequency of serious infections and neoplasms also being similar across both treatment groups.[5]**
- **Injection-related reactions, nasopharyngitis, headache, injection-site reaction, upper respiratory tract infection and urinary tract infection were the most commonly observed adverse events with ofatumumab, occurring in ≥10% of patients.[5]**

†Secondary endpoints that did not show significance between ofatumumab and teriflunomide include confirmed disability improvement and brain volume loss.[5]

References:
1. ClinicalTrials.gov. *Efficacy and Safety of Ofatumumab Compared to Teriflunomide in Patients With Relapsing Multiple Sclerosis (ASCLEPIOS I).* Available from: https://clinicaltrials.gov/ct2/show/NCT02792218 [Last accessed: August 2020].
2. ClinicalTrials.gov. *Efficacy and Safety of Ofatumumab Compared to Teriflunomide in Patients With Relapsing Multiple Sclerosis. (ASCLEPIOS II).* Available from: https://clinicaltrials.gov/ct2/show/NCT02792231 [Last accessed: August 2020].
3. McDonald W, Compston F, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: Guidelines from the international panel on the diagnosis of multiple sclerosis. *Ann Neurol.* 2001;50(1):121–127.
4. Nicholas R, Friede T. Considerations in the design of clinical trials for relapsing multiple sclerosis. *J Clin Invest.* 2012;2(11):1073–1083.
5. Hauser S, Bar-Or A, Cohen JA, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. *N Engl J Med.* 2020;383:546–557.
6. National MS Society. *Types of MS.* Available from: https://www.nationalmssociety.org/What-is-MS/Types-of-MS [Last accessed: August 2020].
7. Multiple Sclerosis Foundation. *What are the different types of MS.* Available from: https://msfocus.org/Get-Educated/Common-Questions/What-are-the-different-types-of-MS.aspx [Last accessed: August 2020].
8. Trip SA, Miller DH. Imaging in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2005;76(3 Suppl):iii11–iii18.
9. Kappos L, Butzkueven H, Wiendl H, et al. Greater sensitivity to multiple sclerosis disability worsening and progression events using a roving versus a fixed reference value in a prospective cohort study. *Mult Scler.* 2018;24(7):963–973.
10. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology.* 1983;33(11):1444–1452.
11. Nielson Varhaug K, Torkildsen Ø, Myhr K-M, Vedeler CA. Neurofilament light chain as a biomarker in multiple sclerosis. *Front Neurol.* 2019;10:338.

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