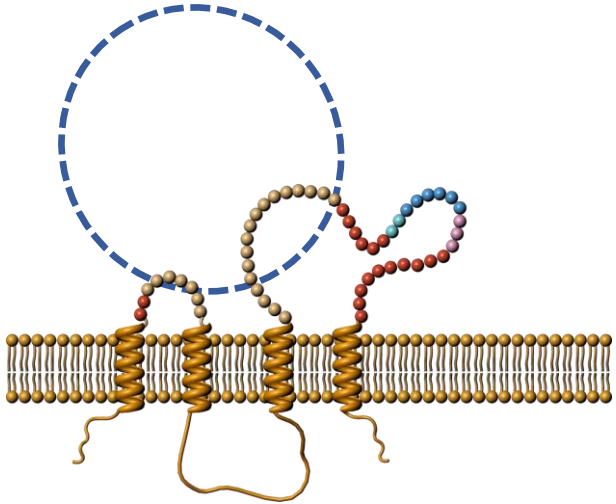
Novartis AG
Investor Relations

ASCLEPIOS



# Ofatumumab (OMB157) / ECTRIMS Data Investor Call

**September 16, 2019**

NOVARTIS

# Disclaimer

This presentation contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995 that can generally be identified by words such as “potential,” “expected,” “will,” “planned,” “pipeline,” “outlook,” or similar expressions, or by express or implied discussions regarding potential new products, potential new indications for existing products, potential product launches, or regarding potential future revenues from any such products; or regarding the development or adoption of potentially transformational technologies and business models; or regarding potential future or pending transactions; or regarding potential future sales or earnings of the Group or any of its divisions or potential shareholder returns; or by discussions of strategy, plans, expectations or intentions. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. You should not place undue reliance on these statements. In particular, our expectations could be affected by, among other things: global trends toward healthcare cost containment, including ongoing government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; regulatory actions or delays or government regulation generally, including potential regulatory actions or delays with respect to any proposed or pending transactions or the development of the products described in this presentation; the potential that the strategic benefits, synergies or opportunities expected from the proposed transactions may not be realized or may be more difficult or take longer to realize than expected; the inherent uncertainties involved in predicting shareholder returns; the uncertainties inherent in the research and development of new healthcare products, including clinical trial results and additional analysis of existing clinical data; our ability to obtain or maintain proprietary intellectual property protection, including the ultimate extent of the impact on Novartis of the loss of patent protection and exclusivity on key products that commenced in prior years and will continue this year; safety, quality or manufacturing issues; uncertainties regarding actual or potential legal proceedings, including, among others, product liability litigation, disputes and litigation with business partners or business collaborators, government investigations generally, litigation and investigations regarding sales and marketing practices, and intellectual property disputes; uncertainties involved in the development or adoption of potentially transformational technologies and business models; our performance on environmental, social and governance measures; general political, economic and trade conditions, including uncertainties regarding the effects of ongoing instability in various parts of the world; uncertainties regarding future global exchange rates; uncertainties regarding future demand for our products; uncertainties regarding potential significant breaches of data security or data privacy, or disruptions of our information technology systems; and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this presentation as of this date and does not undertake any obligation to update any forward-looking statements as a result of new information, future events or otherwise.



NOVARTIS

# Marie-France Tschudin

**President of Novartis Pharmaceuticals**

# Ofatumumab – potentially adding high-efficacy B-cell therapy to the Novartis leading MS portfolio

**Proven innovation track record**

| 2009 | 2010 | 2019 | 2020 |
|---|---|---|---|
| EXTAVIA® interferon beta-1b FOR SC INJECTION | **Gilenya®**<br>First high efficacy oral DMT<br>GILENYA® (fingolimod) capsules 0.5mg | **Mayzent®[2]**<br>First DMT with proven benefit in a typical SPMS population<br>MAYZENT® | **Ofatumumab[1]**<br>First s.c. high-efficacy B-cell therapy<br>Ofatumumab |

**Leading presence**

Established commercial infrastructure

Deep understanding of customer needs

1. Not yet approved 2. Approved in US

NOVARTIS

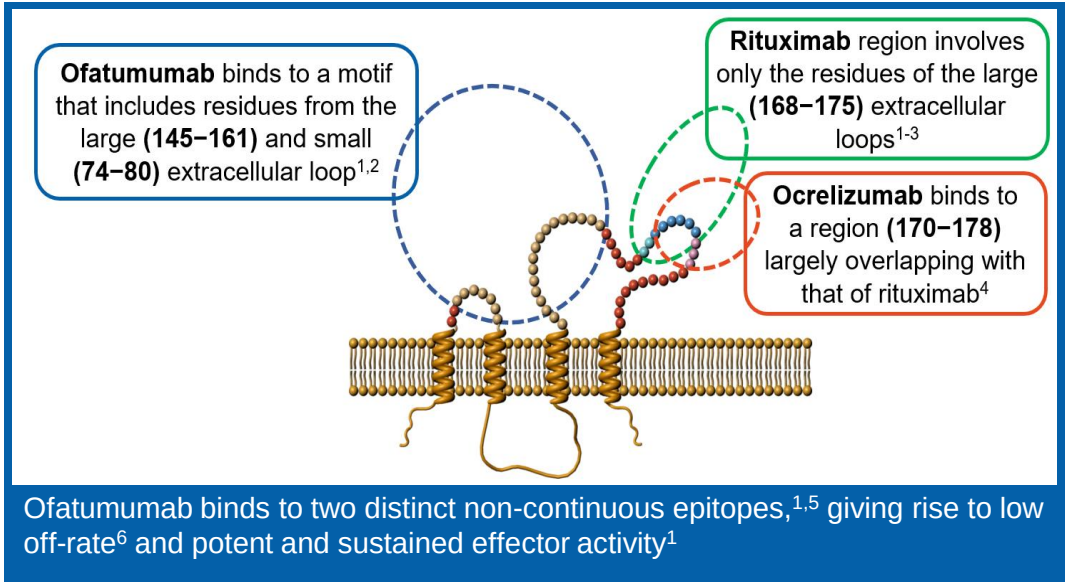
# Danny Bar Zohar

**Head of Clinical Development and Analytics**

# Ofatumumab

## Anti-CD20 therapy in MS

- Ofatumumab the 1st fully human anti-CD20 monoclonal antibody, administered with a monthly 20 mg s.c. dosing regimen[1]
- Phase 2b MIRROR study: ≥90% reduction in Gd+ T1 lesions vs. placebo at week 12 for all cumulative ofatumumab doses ≥30 mg over 12 weeks[7]




Ofatumumab binds to two distinct non-continuous epitopes,[1,5] giving rise to low off-rate[6] and potent and sustained effector activity[1]

Gd+, gadolinium-enhancing; MS, multiple sclerosis; RMS, relapsing MS, s.c., subcutaneous

1. Smith P, et al. Presented at ECTRIMS 2016;P1143. 2. Teeling JL, et al. J Immunol. 2006;177:362–371. 3. Ruuls SR, et al. Biotechnol J. 2008;3:1157–1171. 4. Genovese MC, et al. Arthritis Rheum. 2008;58:2652–2661. 5. Klein C, et al. MAbs. 2013;5:22–33. 6. Pacheco-Fernandez T, et al. AAN 2018;S52.003. 7. Bar-Or A, et al. Neurology. 2018;90:e1805–e1814.

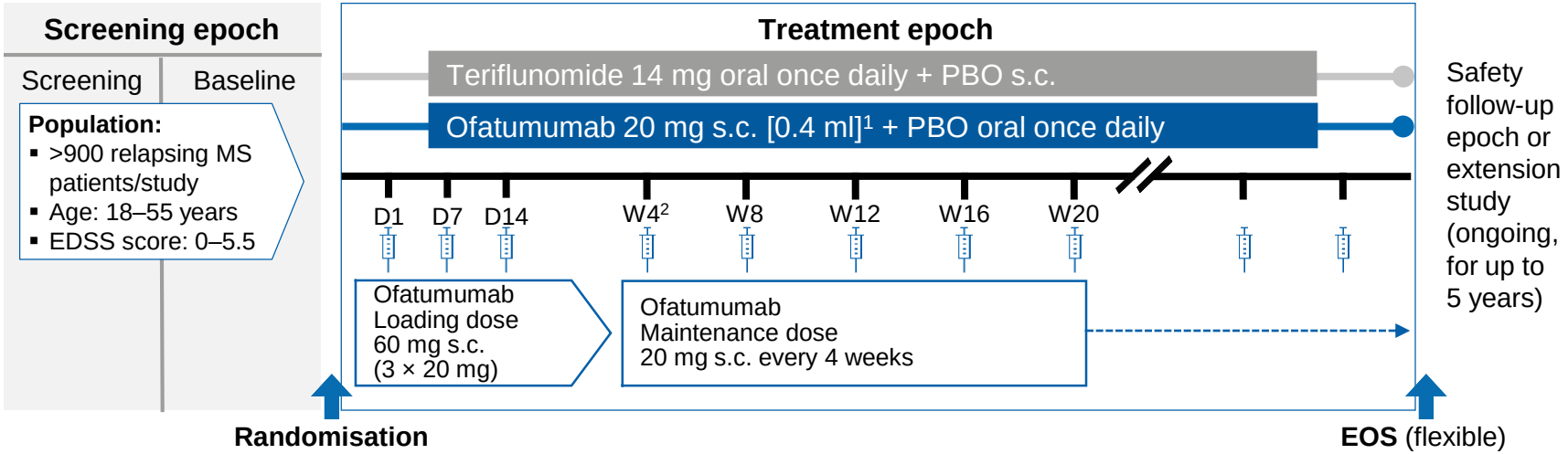


NOVARTIS

# ASCLEPIOS I and II: Study design

Identical study designs, conducted in parallel

Double-blind, double-dummy, active comparator-controlled, parallel-group, multi-centre adaptive and flexible duration design trials (maximum duration for up to 30 months)




1. 20 mg of ofatumumab was administered in an injection volume of 0.4 ml; 2. Week 4 (Month 1) and every 4 weeks thereafter. D, day; EDSS, Expanded Disability Status Scale; EOS, end of study; MS, multiple sclerosis; PBO, placebo; s.c., subcutaneous; W, week



NOVARTIS

# ASCLEPIOS I and II

Study objective and key endpoints

**Objective:** To evaluate the efficacy and safety of ofatumumab compared with teriflunomide in patients with relapsing multiple sclerosis

## Study endpoints

| | | |
|---|---|---|
| **Primary endpoint**<br>within each study | Annualised relapse rate (ARR)<br>number of confirmed multiple sclerosis relapses in a year | |
| **Key secondary endpoints** | **Pre-specified pooled analysis**<br>▪ 3-month confirmed disability worsening (CDW)*<br>▪ 6-month CDW*<br>▪ 6-month confirmed disability improvement (CDI) | **By individual study**<br>▪ Gadolinium-enhancing T1 lesions<br>▪ New or enlarging T2 lesions<br>▪ Serum neurofilament light chain levels<br>▪ Brain volume loss |

*CDW, confirmed disability worsening and CDP, confirmed disability progression are interchangeable terms, defined by an increase ≥1.5 EDSS points for patients with baseline EDSS of 0, increase of ≥1.0 EDSS points patients with baseline EDSS of 1.0-5.0 and increase of t ≥0.5 EDSS points for patients with baseline EDSS of 5.5



NOVARTIS

# Demographics and baseline characteristics

ASCLEPIOS I and II populations are similar and treatment arms are balanced

| Characteristics | ASCLEPIOS I (N=927) | | ASCLEPIOS II (N=955) | |
|---|---|---|---|---|
| Mean±standard deviation or n (%) | Teriflunomide (N=462) | Ofatumumab (N=465) | Teriflunomide (N=474) | Ofatumumab (N=481) |
| **Age (years)** | 37.8±9.0 | 38.9±8.8 | 38.2±9.5 | 38.0±9.3 |
| **Sex, Female, n (%)** | 317 (68.6) | 318 (68.4) | 319 (67.3) | 319 (66.3) |
| **Weight (kg)** | 75.47±20.0 | 74.8±19.9 | 73.97±17.9 | 73.62±19.0 |
| **Duration of MS since first symptoms (years)** | 8.18±7.2 | 8.36±6.8 | 8.19±7.4 | 8.2±7.4 |
| **Previously treated with DMTs, n (%)** | 280 (60.6) | 274 (58.9) | 293 (61.8) | 286 (59.5) |
| **Number of relapses in last 12 months** | 1.3±0.69 | 1.2±0.63 | 1.3±0.73 | 1.3±0.74 |
| **EDSS score** | 2.94±1.4 | 2.97±1.4 | 2.86±1.4 | 2.90±1.3 |
| **T2 lesion volume ($cm^3$)** | 13.1±14.6 | 13.2±13.3 | 12.0±13.0 | 14.3±14.2 |
| **Patients free of Gd+ T1 lesions, n (%)** | 293 (63.4) | 291 (62.6) | 291 (61.4) | 270 (56.1) |
| **Number of Gd+ T1 lesions** | 1.2±2.6 | 1.7±4.9 | 1.5±4.1 | 1.6±4.1 |

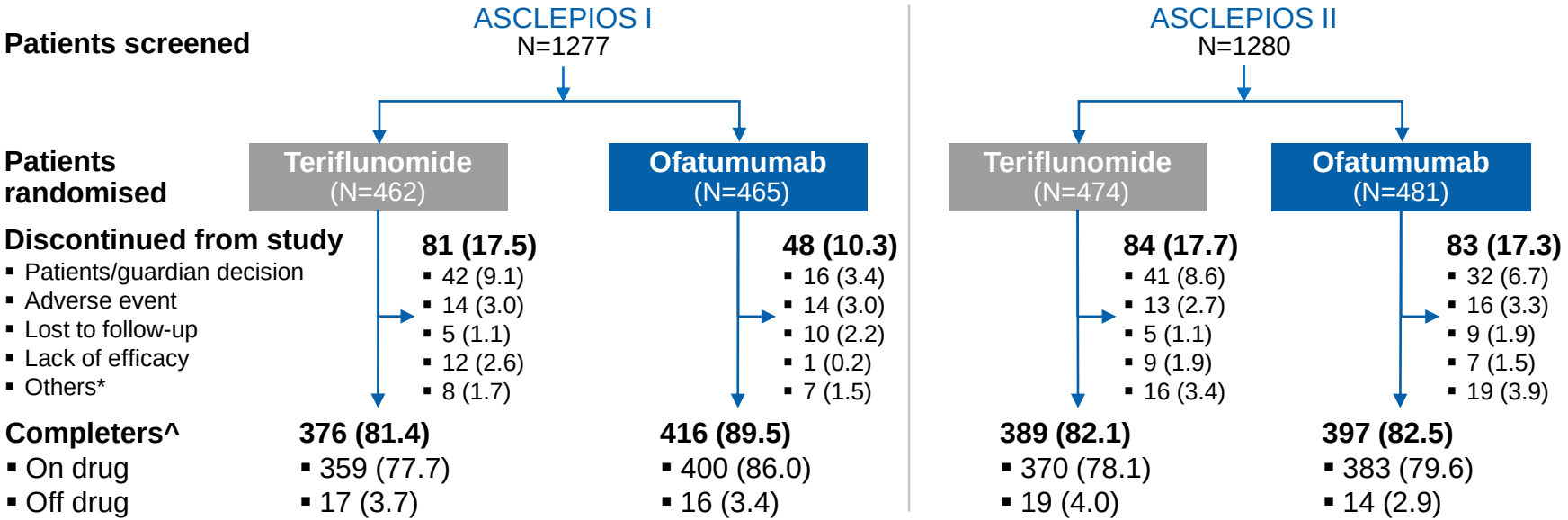
Full analysis set. DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing



NOVARTIS

# ASCLEPIOS I and II

## Patient disposition and analysis population

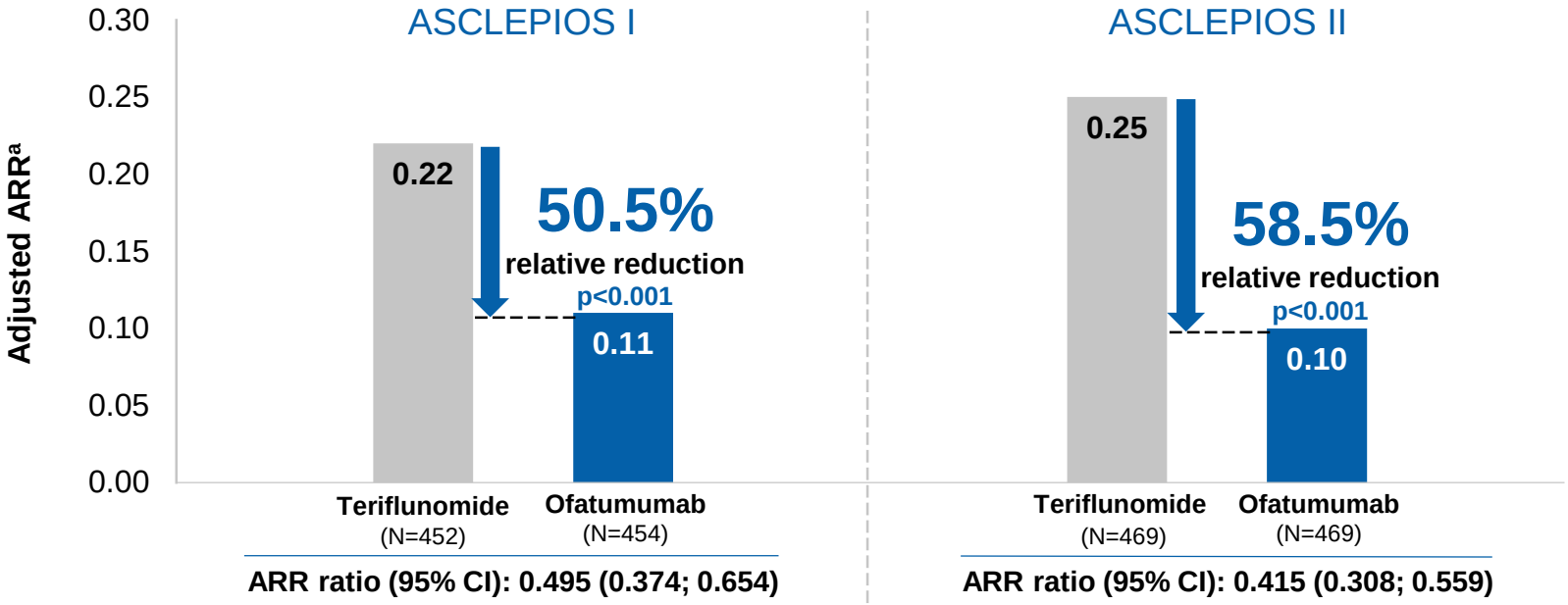



Data are represented as n (%). *Others include: Physician decision, protocol deviation, new therapy for study indication, non-compliance with study treatment, pregnancy and technical problems. On study drug: Patients who took study drug until the treatment epoch completion. Off study drug: Patients who completed the treatment epoch but discontinued study drug prematurely. ^In ASCLEPIOS I , 6 patients and ASCLEPIOS II, 2 patients were considered ongoing' at the time of data cut-off date



NOVARTIS

# Primary endpoint: ofatumumab demonstrated significant reductions in ARR




Full analysis set. Primary endpoint [a] Negative binomial regression model N, Total number of patients included in the analysis. ARR, annualised relapse rate; CI, confidence interval

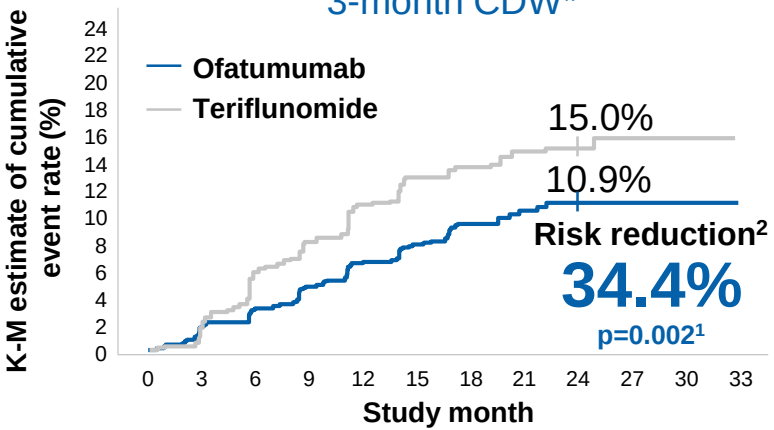


NOVARTIS

# Ofatumumab showed significant reductions in 3- and 6-month CDW*

## Pre-specified pooled analyses

### 3-month CDW*

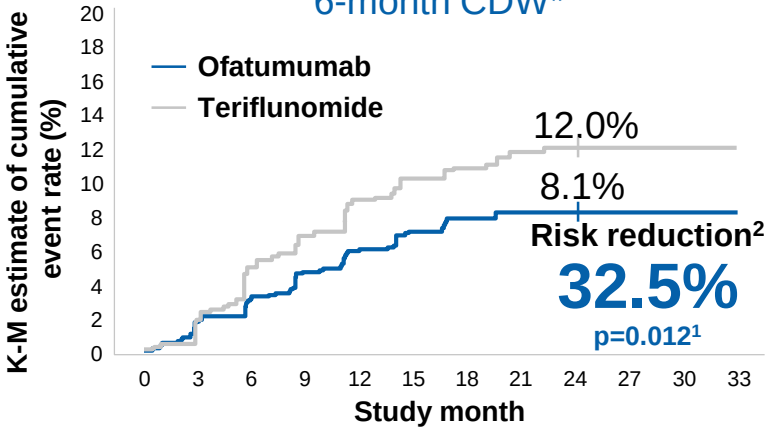



Number of patients at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ofatumumab | 944 | 908 | 878 | 844 | 810 | 784 | 534 | 319 | 176 | 49 | 1 | 0 |
| Teriflunomide | 932 | 901 | 841 | 804 | 756 | 718 | 478 | 298 | 146 | 41 | 1 | 0 |

Hazard ratio (95% CI): 0.656 (0.499; 0.862)

### 6-month CDW*




Number of patients at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 944 | 908 | 878 | 845 | 815 | 791 | 544 | 324 | 180 | 50 | 1 | 0 |
| | 932 | 902 | 849 | 812 | 769 | 734 | 487 | 305 | 151 | 43 | 1 | 0 |

Hazard ratio (95% CI): 0.675 (0.498; 0.916)

Full analysis set. Secondary endpoints *CDW, confirmed disability worsening and CDP, confirmed disability progression are interchangeable terms, defined by an increase ≥1.5 EDSS points for patients with baseline EDSS of 0, increase of ≥1.0 EDSS points patients with baseline EDSS of 1.0-5.0 and increase of t ≥0.5 EDSS points for patients with baseline EDSS of 5.5 1. Indicates statistical significance (2-sided) at the 0.04875 level. 2. Cox regression model. CDP, confirmed disease progression/worsening; CI, confidence interval

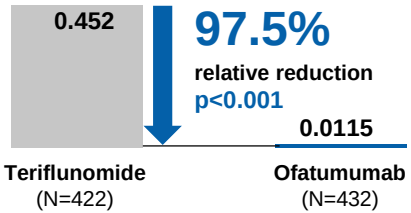


NOVARTIS

# Ofatumumab showed significant reductions in acute focal MRI activity (Gd+ T1 and new/enlarging T2 lesions)

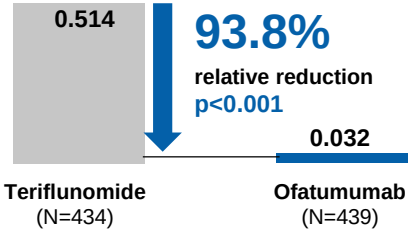
## Number of Gd+ T1 lesions per scan

**ASCLEPIOS I**




Rate ratio (95% CI): 0.025 (0.013; 0.049)

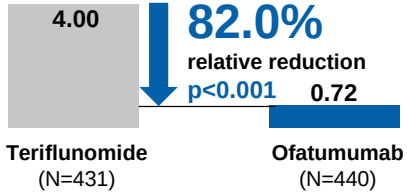
**ASCLEPIOS II**




Rate ratio (95% CI): 0.062 (0.037; 0.101)

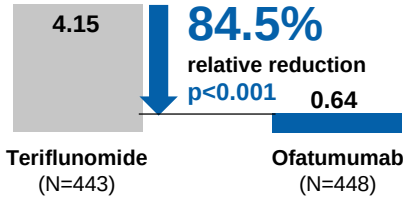
## Number of new / enlarging T2 lesions per scan

**ASCLEPIOS I**




Rate ratio (95% CI): 0.18 (0.15; 0.22)

**ASCLEPIOS II**

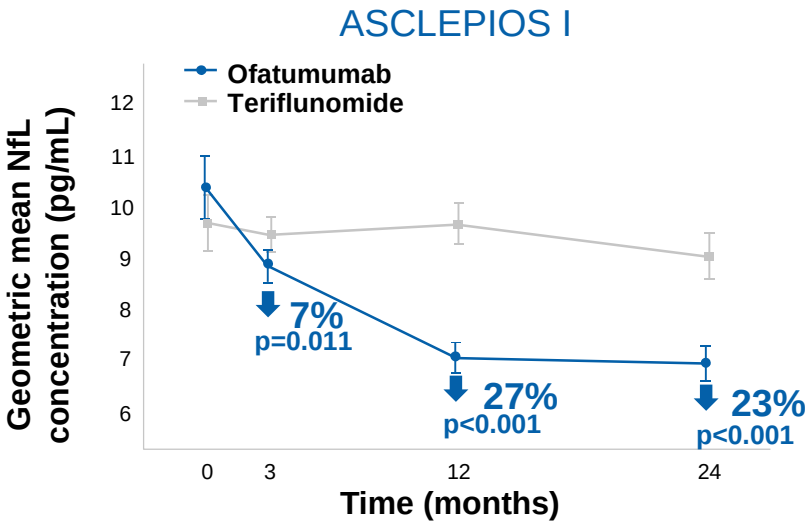



Rate ratio (95% CI): 0.15 (0.13; 0.19)

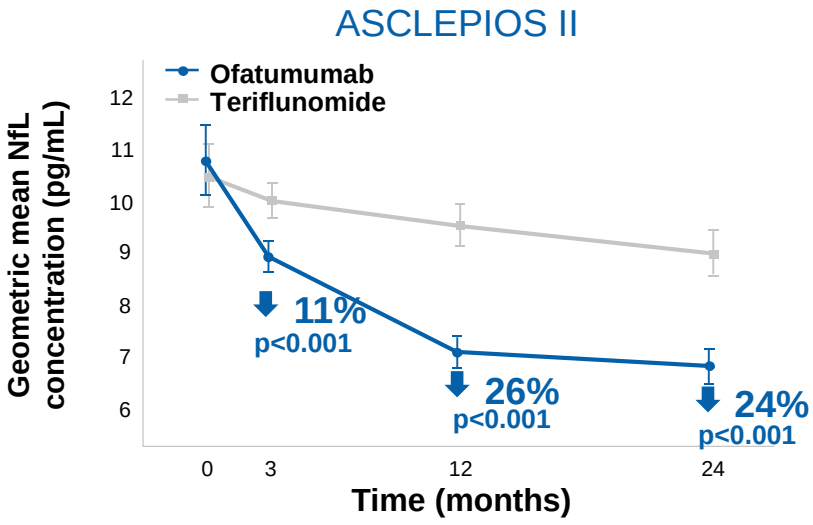


NOVARTIS

# Ofatumumab showed significant & consistent reductions in serum NfL levels from 1st assessment at month 3




**Geometric mean ratio at Month 3 (95% CI):**
0.93 (0.89; 0.98; p=0.011)




**Geometric mean ratio at Month 3 (95% CI):**
0.89 (0.85; 0.93; p<0.001)

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



NOVARTIS

# Summary of efficacy endpoints

| | ASCLEPIOS I | | | | ASCLEPIOS II | | | |
|---|---|---|---|---|---|---|---|---|
| **End point** | **OMB.** | **TER.** | **RRR[c]** | **p value** | **OMB.** | **TER.** | **RRR[c]** | **p value** |
| Annualized relapse rate | 0.11 | 0.22 | 50.5% | <0.001 | 0.1 | 0.25 | 58.5% | <0.001 |
| Gd+ T1 lesions per scan | 0.01 | 0.45 | 97.5% | <0.001 | 0.03 | 0.51 | 93.8% | <0.001 |
| New or enlarging T2 lesions per year | 0.72 | 4.00 | 82.0% | <0.001 | 0.64 | 4.15 | 84.5% | <0.001 |
| Serum NfL levels at month 3[a] | 8.8 | 9.41 | 7%[c] | 0.011 | 8.92 | 10.02 | 11%[c] | <0.001 |
| Brain volume loss[b] | -0.28 | -0.35 | 0.07 | 0.116 | -0.29 | -0.35 | 0.07 | 0.129 |

## PRE-SPECIFICED COMBINED ANALYSIS OF ASCLEPIOS I & II

| **End point** | **OMB.** | **TER.** | **RRR[c]** | **p value** |
|---|---|---|---|---|
| 3-month CDW* | 10.9% | 15.0% | 34.4% | 0.002 |
| 6-month CDW* | 8.1% | 12.0% | 32.5% | 0.012 |
| 6-month CDI | 11.0% | 8.1% | -35.2% | 0.094 |

*CDW, confirmed disability worsening and CDP, confirmed disability progression are interchangeable terms, defined by an increase ≥1.5 EDSS points for patients with baseline EDSS of 0, increase of ≥1.0 EDSS points patients with baseline EDSS of 1.0-5.0 and increase of t ≥0.5 EDSS points for patients with baseline EDSS of 5.5 [a] NfL levels at month three measured as adjusted geometric mean levels and difference is geometric mean ratio (GMR) [b] Brain volume loss is measured as difference in slope between 12 and 24 months, difference measured as adjusted mean difference in slope [c] RRR is relative risk reduction and in cases where it is different- highlighted in footnote



NOVARTIS

# AEs were balanced between groups; no unexpected safety findings

| Safety events, n (%) | Teriflunomide (N=936) | Ofatumumab (N=946) |
|---|---|---|
| **Any adverse events (AEs)** | **788 (84.2)** | **791 (83.6)** |
| **Any serious AEs** | **74 (7.9)** | **86 (9.1)** |
| **Most common AEs (≥5% in any treatment group, preferred term** | | |
| Injection-related reaction | 143 (15.3) | 195 (20.6) |
| Nasopharyngitis | 156 (16.7) | 170 (18.0) |
| Headache | 116 (12.4) | 126 (13.3) |
| Injection-site reaction | 52 (5.6) | 103 (10.9) |
| Upper respiratory tract infection | 120 (12.8) | 97 (10.3) |
| Urinary tract infection | 78 (8.3) | 97 (10.3) |
| Back pain | 58 (6.2) | 72 (7.6) |
| Fatigue | 72 (7.7) | 71 (7.5) |
| Influenza | 59 (6.3) | 62 (6.6) |
| Nausea | 64 (6.8) | 61 (6.4) |
| Blood immunoglobulin M decreased | 21 (2.2) | 56 (5.9) |
| Alopecia | 138 (14.7) | 54 (5.7) |
| Arthralgia | 44 (4.7) | 49 (5.2) |
| Diarrhoea | 111 (11.9) | 49 (5.2) |
| Pain in extremity | 66 (7.1) | 46 (4.9) |
| Depression | 48 (5.1) | 45 (4.8) |
| Hypertension | 55 (5.9) | 35 (3.7) |
| Paraesthesia | 52 (5.6) | 27 (2.9) |



NOVARTIS

# Serious adverse events: overall, low rates, no new signals

| Safety events, n (%) | Teriflunomide (N=936) | Ofatumumab (N=946) |
|---|---|---|
| **Any serious AEs** | **74 (7.9)** | **86 (9.1)** |
| **Most common SAEs (≥1% in any treatment group, by Primary system organ class)** | | |
| Infections and infestations | 17 (1.8) | 24 (2.5) |
| Injury, poisoning and procedural complications | 9 (1.0) | 13 (1.4) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 4 (0.4) | 9 (1.0) |
| Malignancies | 3 (0.3) | 5 (0.5) |
| Nervous system disorders | 15 (1.6) | 7 (0.7) |
| Psychiatric disorders | 2 (0.2) | 10 (1.1) |

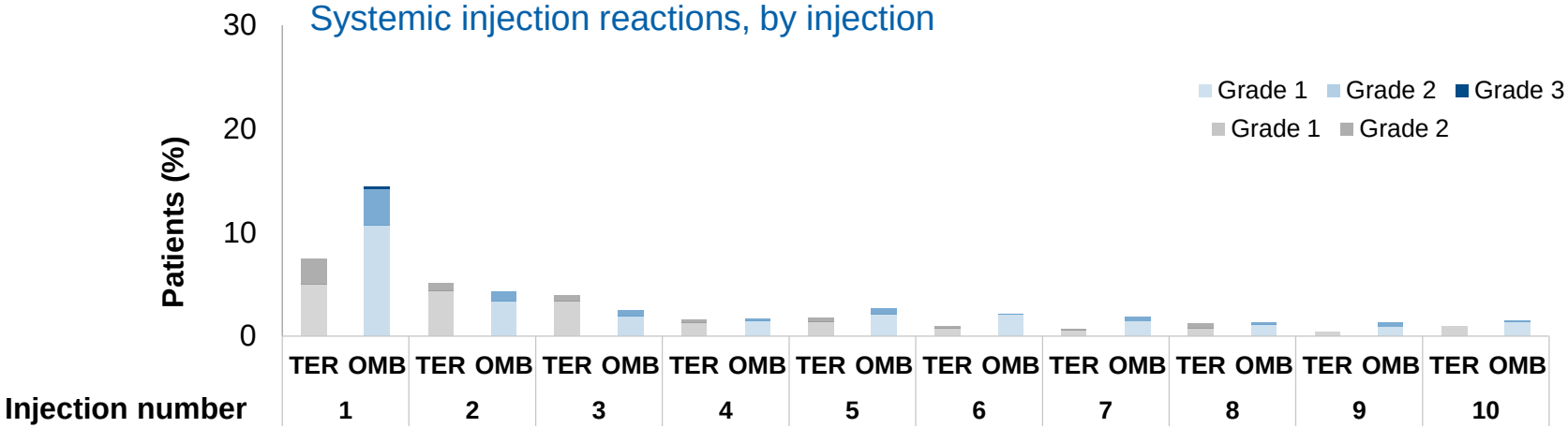
During ASCLEPIOS I and II studies, one death occurred in the teriflunomide arm (fatal aortic hemorrhage)

AEs, adverse events; SAEs, serious adverse events



NOVARTIS

# In patients who reported systemic injection reactions, 99% were mild to moderate




- Imbalance in systemic injection reactions with ofatumumab compared to sham appears to be limited to the 1st injection
- No Grade 4 injections reactions on ofatumumab. A single grade 3 reported at 1st dose
- Ofatumumab group: only 1 patient (0.1%) with non-serious injection reaction discontinued the study due to an injection reaction

OMB, ofatumumab; TER, teriflunomide



NOVARTIS

# Summary and conclusion

ASCLEPIOS I and II studies in a broad RMS population successfully demonstrated that ofatumumab (vs. teriflunomide) showed

- ✓ Superior efficacy in lowering relapse rates and MRI activity
- ✓ Substantial and significant reductions in 3- and 6-month confirmed disability progression
- ✓ Lower levels of NfL (marker of neuronal damage) already at month 3 and at all subsequent visits
- ✓ Favorable safety profile with no unexpected safety signals; no imbalance in rates of infections or malignancies (low on both arms)

**Ofatumumab with monthly 20 mg s.c.* dosing regimen, demonstrated high efficacy and a favorable safety profile**

*20 mg of ofatumumab was administered in an injection volume of 0.4 ml; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; NfL, neurofilament light chain; RMS, relapsing multiple sclerosis



NOVARTIS

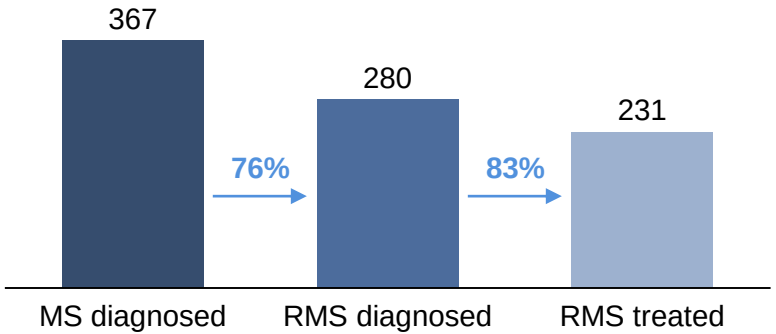
# Paul Spittle

**Head of Global Product & Portfolio Strategy Pharma**

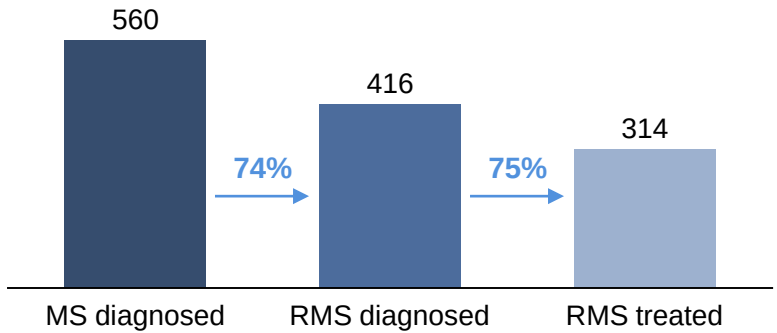
# Significant potential for up to 700k patients living with relapsing MS in US and EU5 alone

## MS patient population

### US




### EU5




**Frequent switching among classes and brands**

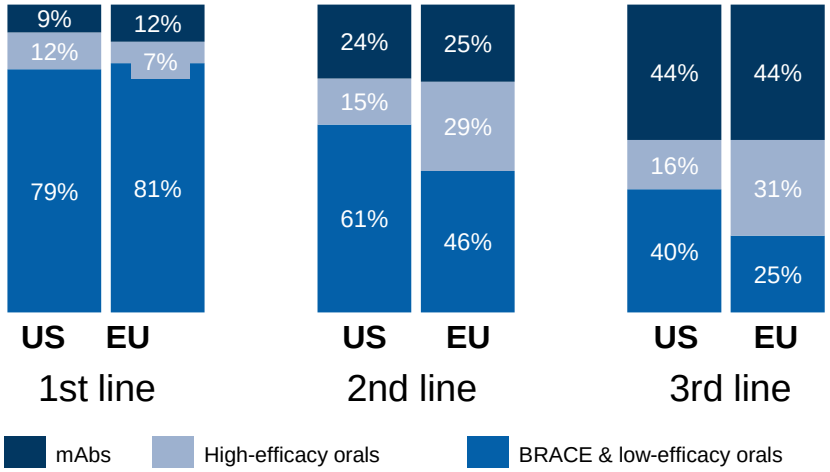
Sources: Calculated based on actual IQVIA SU data validated through DRG Epi database and secondary research



NOVARTIS

# Despite many available treatments, unmet need for better efficacy and safety remains

## Use of disease-modifying treatments in RMS[2]




Even with all DMTs available to patients today, 44% of people with MS aren't satisfied with today's treatments[1]

**44%**

**not satisfied**

Due to

- Lack of efficacy
- Safety concerns
- Side-effects/ tolerability issues

1. EU5 IPSOS Monitos Q2 2019 (Patients dissatisfied with current Oral, Injectables, and IV medications). 2. US Physician ATU, June2019, EU5 IPSOS monitor Q2 2019.



NOVARTIS

# If approved, ofatumumab could address need for higher efficacy therapy for a broad population

| Unmet need | Ofatumumab advantages |
| --- | --- |
| Higher efficacy | Highly efficacious on key measures of disease activity |
| No safety compromises | Depletes B-cells in a targeted way; can be stopped any time |
| Convenient option | Can be used at-home; no need for infusion center |

NOVARTIS

# Conclusion

- ✓ Strong and robust efficacy
- ✓ Favorable safety profile
- ✓ High expectations in large and dynamic patient pool
- ✓ Expected to have convenient dosing and home use
- ✓ Global regulatory submission to start end 2019



NOVARTIS

# BACKUP

NOVARTIS

# ASCLEPIOS I and II

Study population

## Key inclusion criteria

- Male or female patients aged 18 to 55 years
- Diagnosis of MS according to the 2010 Revised McDonald criteria[1]
- Relapsing form of MS: RRMS or SPMS with disease activity as defined by Lublin et al. 2014[2]
- EDSS score of 0 to 5.5
- Documented one of the following
  - ≥2 relapses in the 2 years before screening
  - ≥1 relapse in the year before screening
  - A positive T1 Gd+ scan during the year before randomisation
- Neurologically stable within 1 month prior to randomisation

## Key exclusion criteria

- Patients with primary progressive MS or SPMS without disease activity
- Patients meeting criteria for neuromyelitis optica
- Disease duration of >10 years with an EDSS score of ≤2.0
- Patients with active chronic disease of immune system other than MS or immunodeficiency syndrome
- Patients with neurological findings consistent or confirmed with PML
- Patients at risk of developing or history of syphilis, tuberculosis or hepatitis
- Have received any live/live-attenuated vaccines in 2 months prior to randomisation

EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS

1. Kappos L et al, Presented at *ECTRIMS* 2018. P965. 2. Lublin FD, et al. *Neurology*. 2014;83:278–286.



NOVARTIS