Dose-dependent tolerability of intravenous and subcutaneous ofatumumab in clinical studies

Amit Bar-Or[1], Agnes Annette Schubert-Tennigkeit[2], Nicole Mairon[2], Cecile Kerloeguen[2], Mohammad Gufran[3], Shima Shaikh[3], Ayan Das Gupta[3], Eswara Gunisetti[3], Gisbert Weckbecker[2], Wendy Su[4], Krishnan Ramanathan[2], Ratnakar Pingili[4]

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[1]Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Novartis Pharma AG, Basel, Switzerland; [3]Novartis Healthcare Pvt. Ltd., Hyderabad, India; [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

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Agnes Annette Schubert-Tennigkeit, Nicole Mairon, Cecile Kerloeguen, Mohammad Gufran, Shima Shaikh, Ayan Das Gupta, Eswara Gunisetti, Gisbert Weckbecker, Wendy Su, Krishnan Ramanathan and **Ratnakar Pingili** are employees of Novartis.

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Background and objective

- Ofatumumab is an FDA-approved fully human anti-CD20 monoclonal antibody, with a 20 mg s.c. monthly dosing regimen. It is indicated for the treatment of relapsing forms of multiple sclerosis (MS) in adults, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease[1]
- Prior studies evaluated the effect of ofatumumab doses up to 700 mg i.v. and 60 mg s.c. in MS patients and up to 1000 mg i.v. in rheumatoid arteritis (RA) patients[2-5]
- Injection- or infusion-related reactions were the most frequently reported tolerability-related AEs in both MS and RA studies[2-5]

Objective	**To assess the dose-dependency and route of administration (s.c. and i.v.) on the tolerability of ofatumumab in patients with MS and RA**

AE, adverse event; FDA, Food and Drug Administration; i.v., intravenous; MS, multiple sclerosis; RA, rheumatoid arthritis; RMS, relapsing multiple sclerosis; s.c,, subcutaneous

1. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed Aug 24, 2020); 2. Hauser SL, et al. *N Engl J Med.* 2020; 383:546–557; 3. Østergaard M, et al. *Arthritis Rheum.* 2010;62:2227–2238; 10;62:2227–2238; 4. Sorensen PS, et al. *Neurology*. 2014;82:573–581; 5. Bar-Or A, et al. *Neurology.* 2018;90:e1805–e1814.

Methodology and outcomes

- Data were pooled from various ofatumumab studies[$] in MS (N=2075) and RA (N=416) patients administered with different doses using the i.v. or s.c. routes of administration to analyze:
  - The injection- or infusion-related reactions[#] regardless of route of administration or dose over the 24 hours post administration, characterized by overall incidence and its association with the first injection or infusion
  - Tolerability effects in terms of injection- or infusion-related drug interruption, discontinuation, severity, and seriousness

Dose(s) from MS and RA studies	Route of administration	Administration (Self or at site)	Premedication
MS studies			
20 mg	s.c.	Self, at home (after initial training at site)	Optional
3 mg, 30 mg, 60 mg	s.c.	HCP, at site	Acetaminophen Anti-histamine
100 mg, 300 mg, 700 mg	i.v.	Infusion center	Steroid +/- Acetaminophen Anti-histamine
RA studies			
300 mg, 700 mg, 1000 mg	i.v.	Infusion center	Steroid[†] +/- Acetaminophen Anti-histamine

[$]For MS, data were pooled from the APLIOS, ASCLEPIOS I/II, ALITHIOS (s.c. ofatumumab 20 mg, N=1873[^]) and MIRROR studies (s.c. ofatumumab every 12 weeks [q12w]: 3 mg, N=34; 30 mg, N=32; 60 mg, N=34; 60 mg every 4 weeks [q4w], N=64) and the Phase 2a dose-finding study (i.v. ofatumumab 100 mg, N=12; 300 mg, N=15; 700 mg, N=11). For RA, data were pooled from Phase 1/2/3[*] studies with i.v. ofatumumab (300 mg, N=70; 700 mg, N=282; 1000 mg, N=64).

[#]For the ASCLEPIOS and MIRROR studies, only systemic injection- or infusion-related reactions within 24 hours are reported in this presentation; [†]In the first clinical trial with ofatumumab in patients with RA, the patients enrolled in the ori protocol did not receive steroid premedications. However, the occurrence of infusion-related reactions in the first dose group (300 mg i.v.) necessitated protocol amendments that led to the usage of additional pre-medications (i.v. corticoste and p.o. antihistamines); [^]Cut-off date: 30th Nov 2019 and also included patients who switched from teriflunomide to ofatumumab; [*]Phase 3 data up to Week 24 are included in this analysis; HCP, healthcare professional; i.v., intravenous; MS, multiple sclerosis; N, number of patients; RA, rheumatoid arthritis; s.c., subcutaneous; q4w, every 4 weeks; q12w, every 12 weeks

Injection- or infusion-related reactions across different doses and routes of administration (throughout the studies)

Patients with at least one event, n (%)	MS studies								RA studies		
	s.c. doses					i.v. doses			i.v. doses		
	3 mg q12w (n=34)	20 mg q4w (n=1873)	30 mg q12w (n=32)	60 mg q12w (n=34)	60 mg q4w (n=64)	100 mg (n=12)	300 mg (n=15)	700 mg (n=11)	300 mg (n=70)	700 mg (n=282)	1000 mg (n=64)
Overall AEs	26 (76.5)	1337 (71.4)	26 (81.3)	25 (73.5)	56 (87.5)	11 (91.7)	14 (93.3)	11 (100)	59 (84.3)	246 (87.2)	54 (84.4)
Injection- or infusion-related reactions	13 (38.2)	435 (23.2)	11 (34.4)	14 (41.2)	30 (46.9)	8 (66.7)	12 (80.0)	10 (90.9)	41 (58.6)	104 (36.9)	47 (73.4)
Serious reaction	0	2 (0.1)	0	1 (2.9)	2 (3.1)	0	0	0	2 (2.9)	8 (2.8)	3 (4.7)
Treatment discontinuation	1 (2.9)	1 (0.1)	1 (3.1)	0	1 (1.6)	0	1 (6.7)	0	6 (8.6)	18 (6.4)	11 (17.2)
Treatment interrupted	0	0	0	0	0	5 (41.7)[#]	9 (60.0)[#]	8 (72.7)[#]	19 (27.1)[#]	78 (27.7)[#]	32 (50.0)[#]
Severe injection- or infusion-related reactions (Grade ≥3)	1 (2.9)	4 (0.2)	0	1 (2.9)	1 (1.6)	0	0	2 (18.2)	4 (5.7)	10 (3.5)	6 (9.4)
Cytokine release syndrome (CRS)	0	0	0	1 (2.9)	0	0	2 (13.3)	0	0	0	0
Injection- or infusion-related reactions with first injection/infusion	3 (8.8)	322 (17.2)	9 (28.1)	7 (20.6)	15 (23.4)	6 (50.0)	9 (60.0)	6 (54.5)	39 (55.7)	104 (36.9)	46 (71.9)

- **Overall, injection- or infusion-related reactions were the most frequently reported AEs and the incidence was greater with higher doses and the i.v. route of administration when compared to the 20 mg s.c. dose**
- **The majority of injection- or infusion-related reactions were non-serious and Grade 1/Grade 2 in severity, and were predominantly observed with the first injection or infusion**
- **Incidences of discontinuations were higher with the higher doses and with the i.v. route of administration compared to the 20 mg s.c. dose (0.1%)**
- **No drug interruptions were observed across s.c. doses, but the drug was interrupted (paused and restarted) with the i.v. route of administration**
- **All patients with CRS were non-serious except one patient who required hospitalization because the site was unable to remain open sufficiently long enough to observe the subject**
- **The most commonly reported infusion-related symptoms were rash, erythema, urticaria, pruritis, throat irritation, dyspnea and flushing, while injection-related systemic reactions were fever, headache, chills and influenza like illness**

The red box highlights the approved dose

[#]Infusion paused and restarted; AEs, adverse events; CRS, cytokine release syndrome; i.v., intravenous; MS, multiple sclerosis; RA, rheumatoid arthritis; s.c. subcutaneous; q4w, every 4 weeks; q12w, every 12 weeks

First injection or infusion related adverse events

In the Phase 3 studies, the frequency of injection-related reactions associated with ofatumumab was predominantly higher with the first injection versus subsequent injections[1]

Patients with at least one event, n (%)	MS studies								RA studies		
	s.c. doses					i.v. doses			i.v. doses		
	3 mg q12w (n=34)	20 mg q4w (n=1873)	30 mg q12w (n=32)	60 mg q12w (n=34)	60 mg q4w (n=64)	100 mg (n=12)	300 mg (n=15)	700 mg (n=11)	300 mg (n=70)	700 mg (n=282)	1000 mg (n=64)
Injection- or infusion-related reactions with first injection/infusion	3 (8.8)	322 (17.2)	9 (28.1)	7 (20.6)	15 (23.4)	6 (50.0)	9 (60.0)	6 (54.5)	39 (55.7)	104 (36.9)	46 (71.9)
Serious reaction	0	2 (0.1)	0	0	0	0	0	0	2 (2.9)	8 (2.8)	3 (4.7)
Treatment discontinuation	1 (2.9)	1 (0.1)	1 (3.1)	0	1 (1.6)	0	0	0	6 (8.6)	18 (6.4)	11 (17.2)
Treatment interrupted#	0	0	0	0	0	4 (33.3)	7 (46.7)	5 (45.5)	18 (25.7)	78 (27.7)	32 (50.0)
Severe injection- or infusion-related reactions (Grade ≥3)	1 (2.9)	4 (0.2)	0	1 (2.9)	1 (1.6)	0	0	1 (9.1)	4 (5.7)	10 (3.5)	6 (9.4)

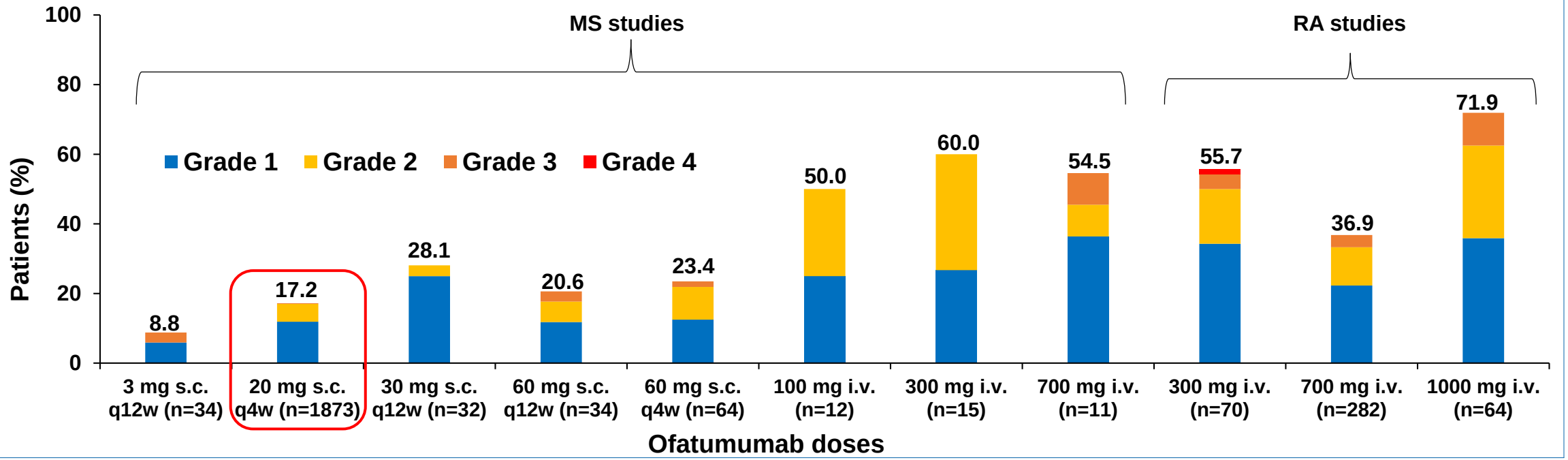
- **The incidence of serious injection-related reactions with the 20 mg s.c. dose was low (0.1%) compared with the higher dose groups**
- **In the 20 mg s.c. group, only 2 of 1873 patients (0.1%) reported serious injection-related reactions with the first injection and these were resolved with no recurrences; no other serious injection-related reactions were reported at any time during the study**
- **The incidence of discontinuations due to injection or infusion reactions was higher with the i.v. route of administration (as observed in RA studies) compared to the s.c. route; among the s.c. subgroup, discontinuations were lower with the 20 mg dose**
- **Symptoms associated with the first injection or infusion were consistent with that observed for all injections**

The red box highlights the approved dose; #Infusion paused and restarted; i.v., intravenous; MS, multiple sclerosis; RA, rheumatoid arthritis; s.c., subcutaneous; q4w, every 4 weeks; q12w, every 12 weeks

1. Hauser SL, et al. *N Engl J Med.* 2020; 383:546–557.

Incidence of injection- or infusion-related reactions at the first injection/infusion with different doses of ofatumumab

Proportion of patients with injection- or infusion-related reactions at the first injection/infusion



- The Incidence of infusion-related reactions was much higher with a clear dose-dependent pattern compared to the s.c. group
- Although there was no clear dose-dependent pattern in the s.c. group, the 60 mg dose was associated with more severe and/or serious injection systemic reactions
- In the 20 mg s.c group, 99.8% of injection-related reactions were of Grade1/2 in severity
- A Grade 4 infusion-related reaction was reported in one patient[#] with the 300 mg i.v. dose who had an anaphylactoid reaction (symptoms include urticaria, hypotension, loss of consciousness and vomiting) and this was resolved with treatment

The red box highlights the approved dose; [#]The patient with the anaphylactoid reaction was one of the patients who did not receive steroid premedication as per the original protocol.
i.v., intravenous; MS, multiple sclerosis; n, number of patients; q4w, every 4 weeks; q12w, every 12 weeks; RA, rheumatoid arthritis; s.c., subcutaneous

Conclusions

- The incidences of administration-related reactions (i.e. via infusion or injection) were lower with the s.c. route of administration when compared to the i.v. route
- Ofatumumab 20 mg s.c. was well-tolerated when compared with the higher s.c. doses and i.v. doses
  - Unlike the i.v. route of administration where steroid premedication was required, premedication was optional with the 20 mg s.c. dose
  - Injection-related reactions were predominantly reported with the first dose of ofatumumab and the incidence decreased with subsequent doses
  - Most (≥99.8%) of the injection-related reactions were non-serious and mild to moderate in severity
  - Reactions were manageable with low withdrawal rate and recovered with symptomatic treatment, even in the absence of premedication
  - The incidence of discontinuations due to injection-related reactions was low (0.1%)
  - In the ASCLEPIOS studies, the majority of the patients were able to self-administer the 20 mg s.c. dose at home after initial training, with no tolerability concerns[1]
- These results suggest that for chronic diseases such as MS, low dose s.c. injections have a better tolerability profile with higher compliance when compared to the higher doses and i.v. route of administration

i.v., intravenous; MS, multiple sclerosis; s.c., subcutaneous

1. Hauser SL, et al. *N Engl J Med.* 2020; 383:546–557.

Thank you