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**Single-Arm Study to Assess Comprehensive Infusion Guidance for the
Prevention and Management of the Infusion Associated Reactions (IARs) in
Relapsing-Remitting Multiple Sclerosis (RRMS) Patients Treated With
Alemtuzumab (EMERALD)**

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Abbreviations:

AE	adverse event
AESI	adverse event of special interest
β-HCG	beta human chorionic gonadotropin
BID	twice daily
BVL	brain volume loss
CDI	confirmed disability improvement
CDW	confirmed disability worsening
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
EOS	end of study
FU	follow-up
Gr	grade
H ₁	histamine receptor H1
H ₂	histamine receptor H2
IAR	infusion-associated reaction
IV	intravenous
MRI	magnetic resonance imaging
MS	multiple sclerosis
NSAID	nonsteroidal anti-inflammatory drug.
PO	Per os (orally)
RMP	Risk Management Plan

RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SmPC	Summary of Product Characteristics
SS	safety set
TEAE	treatment-emergent adverse event
Treg	regulatory T cell

ABSTRACT

Background: Alemtuzumab is a humanized IgG monoclonal antibody approved in more than 60 countries for patients with relapsing remitting multiple sclerosis (RRMS). In phase 2 and 3 clinical trials (CAMMS223 [NCT00050778], CARE-MS I [NCT00530348], and CARE-MS II [NCT00548405]), patients receiving alemtuzumab demonstrated significantly greater improvements on clinical and MRI outcomes versus SC IFN β -1a; mild to moderate infusion-associated reactions (IARs) were the most frequently reported adverse events (AEs) associated with alemtuzumab. EMERALD (NCT02205489) was a phase 4, multicenter, multinational, single-arm study designed to assess an algorithm for the prevention and management of IARs in RRMS patients treated with alemtuzumab.

Methods: Patients were treated with a study regimen of enhanced IAR prophylaxis relative to phase 2 and 3 studies. H₁ and/or H₂ antagonists or equivalent gastroprotection (proton pump inhibitors) were given 1 day before alemtuzumab infusion, 1 hour prior to the infusion, and post-infusion. Methylprednisolone was given orally 1 day before infusion, 1 hour prior to the infusion, and as needed post-infusion. Antipyretics were given 1 hour before infusion and as needed post-infusion. Antiemetics and normal saline were given as needed during and post-infusion.

Results: Of the 61 patients screened, 58 (95.1%) were enrolled into the study. Of the 58 patients who received the first infusion of Period 1, 57 (98.3%) completed the 5 days of Course 1. A total of 54 patients received the first infusion of Period 2 and 53 completed

the 3-day course. All patients (n=58) completed the Month 6 visit and 54 the Month 12 visit. 93.1% of patients had at least one IAR (91.4% in Period 1 and 81.5% in Period 2), the majority of which were grade 1 (69.1%) or grade 2 (28.0%). The three most common IARs of headache, pyrexia, and rash occurred in 48.8%, 40.7%, and 24.1% of patients during the first course and 14.8%, 17.2%, and 5.6% of patients during the second course, respectively. The majority of IARs occurred within 6 hours after the start of alemtuzumab infusion, with a peak during the first 2 hours. The types and overall incidence of IARs were consistent with phase 2 and 3 trials. Frequency and distribution of rash were reduced in the EMERALD study compared with previous clinical trials. Serious IARs occurred in 15.5%, a higher rate than reported in clinical trials of alemtuzumab.

Conclusion: Although most alemtuzumab-treated patients experienced IARs as in previous controlled clinical studies, there was an improvement in the frequency and distribution of alemtuzumab-associated rash, which may have been associated with this study's prophylaxis regimen.

Key words:

Alemtuzumab
Multiple sclerosis
Induction therapy
Infusion-associated reaction (IAR)
Rash
Methylprednisolone treatment

1. Introduction

Alemtuzumab is a humanized monoclonal antibody that selectively binds to CD52 to deplete circulating T and B lymphocytes (Hu et al., 2009). After lymphocyte depletion, a distinctive pattern of T- and B-cell repopulation begins within weeks. The immunomodulatory effects of alemtuzumab are potentially achieved through alterations in the number, proportions, and properties of some lymphocyte subsets, with increased representation of regulatory T-cell (Treg) subsets, memory T- and B-lymphocytes, and transient effects on components of innate immunity (ie, neutrophils, macrophages, natural killer cells) (LEMTRADA Summary of Product Characteristics, 2016). This rebalancing of the immune system may contribute to the sustained efficacy of alemtuzumab without re-treatment (Bittner and Wiendl, 2016; Ruck et al., 2015; Turner et al., 2015).

Alemtuzumab is a highly effective therapy for relapsing remitting multiple sclerosis (RRMS). Alemtuzumab is indicated for treating adult patients with RRMS with active disease defined by clinical or imaging features based on phase 3 studies, in which treatment-naive patients (CARE-MS I; NCT00530348) or those with inadequate response to prior treatment (CARE-MS II; NCT00548405) showed significantly greater improvements in clinical and magnetic resonance imaging (MRI) outcomes, including brain volume loss (BVL), compared with those receiving subcutaneous interferon β -1a. (Cohen et al., 2012; Coles et al., 2012). Patients who participated in the core CARE-MS I and II trials could enroll in an extension study (NCT00930553), which demonstrated that alemtuzumab-treated patients experienced durable efficacy through 5 years (Coles et al., 2017b; Havrdova et al., 2017). Patients who completed the extension study could

enroll in the 5-year TOPAZ study (NCT02255656) for further long-term evaluation (Coles et al., 2017a; Singer et al., 2017). In TOPAZ, 86% (CARE-MS I) and 81% (CARE-MS II) remained on study through Year 7, with 59% (CARE-MS I) and 47% (CARE-MS II) receiving only the initial two courses of alemtuzumab and no other treatments (Coles et al., 2017a; Singer et al., 2017). By Year 7, 74% and 69% of patients from CARE-MS I and II, respectively, were free of 6-month confirmed disability worsening (CDW), whereas 37% and 44% of patients from CARE-MS I and II, respectively, achieved 6-month confirmed disability improvement (CDI). Additionally, 78% and 73% of patients from CARE-MS I and II, respectively, demonstrated improved or stable disability, as measured by the expanded disability status scale (EDSS). Median yearly BVL remained low at Year 6 (CARE-MS I: -0.17% and CARE-MS II: -0.10%) (Ziemssen and Thomas, 2017). Most patients were free of MRI lesion activity (CARE-MS I: 68% and CARE MS II: 67%) and achieved no evidence of disease activity in Year 7 (CARE-MS I: 61% and CARE-MS II: 60%) (Coles et al., 2017a; Singer et al., 2017).

Infusion-associated reactions (IARs) are the most frequently reported AEs in alemtuzumab-treated patients, affecting ~90% of patients in clinical trials (Cohen et al., 2012; Coles et al., 2017b; Coles et al., 2012; Havrdova et al., 2017). Most IARs were mild-to-moderate in severity and generally decreased in number with each subsequent alemtuzumab treatment course. Incidence of treatment discontinuation due to IARs was low; IARs led to 1 (0.03%) treatment discontinuation in CARE-MS I due to allergic dermatitis and 5 (1.1%) discontinuations in CARE-MS II due to noncardiac chest pain and dyspnea in 1 patient, and pharyngeal edema, rash, purpura, and urticaria each in 1

patient. The most common IARs included headache, rash, nausea, and pyrexia. These reactions may reflect cytokine release associated with alemtuzumab-induced lymphocyte lysis (Cohen et al., 2012; Coles et al., 2017b; Coles et al., 2012; Havrdova et al., 2017).

The primary objective of EMERALD was to assess the impact of a different medication algorithm on development and/or management of IARs in RRMS patients receiving two courses of alemtuzumab.

2. Materials and Methods

2.1 Patients

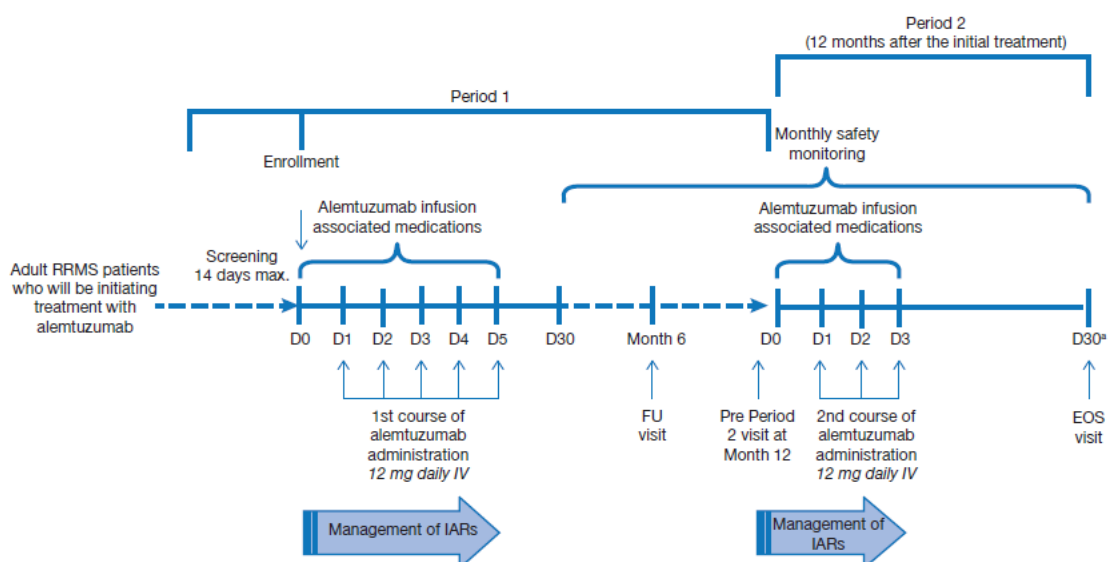
Inclusion criteria were adult RRMS patients who initiated treatment with alemtuzumab according to the approved label in the country of treatment and who signed written informed consent. Patients were excluded if they previously received alemtuzumab, had any known contraindications to alemtuzumab according to labeling in the country of treatment, were participating in another investigational interventional study, had any known contraindications to symptomatic therapy used in infusion-management guidance based on their local approved label, were women of childbearing potential not using birth control and/or were unwilling or unable to be tested for pregnancy, pregnant (as defined as positive β -HCG blood test) or breastfeeding, had known infection with latent or active tuberculosis, or had known infection with hepatitis B or C virus.

2.2 Study Design

EMERALD was a multicenter, multinational, single-arm, phase 4, open-label study conducted at 19 sites in Belgium, France, the Netherlands, and Spain. EMERALD was a two-period study with mandatory administration of a comprehensive medication regimen aimed to prevent and/or manage alemtuzumab-associated IARs during the standard two-treatment course (**Figure 1**). Period 1 was defined from the first alemtuzumab dose to Day 0 of Period 2. During Period 1, patients began pre-infusion medications on Day 0 (the day before the first infusion). Period 2 was defined from the first alemtuzumab dose in Period 2 to end of study (Day 30 of Period 2). Infusion period was defined as the start of alemtuzumab dose through 24 hours after each infusion

during Periods 1 and 2. The On-study Period was defined as the first alemtuzumab dose of Period 1 to end of study.

Figure 1.—Study Design. ^a After the end of Period 2, patients were followed by their physician in a regular healthcare setting until the 48-month safety monitoring period is completed. Abbreviations: EOS, end of study; FU, follow-up; IAR, infusion-associated reaction; IV, intravenous; RRMS, relapsing remitting multiple sclerosis.



After a maximum of a 2-week screening, patients were enrolled. Patients began the pre-infusion regimen the day before starting the first alemtuzumab course, infusions of 12 mg/day for 5 consecutive days (total dose of 60 mg), accompanied by the infusion-management medications. The second course was administered 12 months later, wherein patients received alemtuzumab infusions of 12 mg/day for 3 consecutive

days (total dose of 36 mg) with the same pre-infusion regimen and infusion-management medications. Guidance for administering the infusion-management medication algorithm is shown in **Table 1**. Patients underwent monthly safety monitoring throughout the study.

1 **Table 1. Administration Algorithm of Mandatory and “As Needed” Associated Medication During EMERALD**

Medication	Day 0	Days of alemtuzumab infusions		
	1 day before infusion ^a	Pre-infusion ^b	During infusion ^c	Post-infusion ^d
H ₁ antagonist according to the local label (eg, cetirizine 10 mg or equivalent) in the afternoon	Mandatory	–	–	Mandatory
H ₁ antagonist 25 mg IV diphenhydramine or equivalent	–	Mandatory	In case of pruritus/rash	–
H ₂ antagonist in the morning and afternoon or equivalent gastro-protector medications prescribed according to the local label (ie, proton pump inhibitors)	Mandatory	Mandatory	–	Mandatory
Methylprednisolone 1,000 mg orally (Medrol [®]) (10 tablets of 100 mg each in the morning)	Mandatory	–	–	–
Methylprednisolone IV 1,000 mg (50% dose reductions from Day 3 [500 mg] to Day 5 [125 mg] in Period 1 and from Day 1 [750 mg] to Day 3 [250 mg] in Period 2)	–	Mandatory following immediately IV diphenhydramine	–	As needed
NSAID/antipyretic: 500 mg oral paracetamol or equivalent	–	Mandatory	In case of pain/headache ^e	As needed ^e
Antiemetic but no phenothiazine (eg, ondansetron 8 mg or equivalent)	–	–	In case of nausea	As needed
Acyclovir 200 mg orally or equivalent	–	Mandatory ^f	–	Mandatory ^f
0.9% sodium chloride (normal saline) bolus IV ^g	–	–	In case of dehydration	–

^a 1 day before infusion patients took medications at home which were recorded in a patient diary.

^b 1 hour prior to infusion.

^c If IARs occurred during infusion, the patient may receive as needed.

^d The evening of alemtuzumab infusion.

^e Not to exceed maximum daily recommended dose according to the local label.

^f Patients must continue to receive acyclovir 200 mg PO BID or equivalent until Day 30 to minimize herpes virus infection.

^g Fluid intake was encouraged and monitored.

Abbreviations: BID, twice daily; H₁, histamine receptor H₁; H₂, histamine receptor H₂; IAR, infusion-associated reaction; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PO, orally.

2

3

1 The end-of-study visit was performed on Day 30 of Period 2. After study
2 completion, patients were followed by their physician in a regular healthcare setting until
3 the 48-month safety monitoring period was completed according to the Summary of
4 Product Characteristics (SmPC) and Risk Management Plan (RMP).

5 Primary endpoints were proportion of patients with at least one IAR during the
6 study period, overall and by severity grade, and distribution of IARs by severity grade.
7 Serious adverse events (SAEs) were evaluated. Monitoring of potential autoimmune
8 AEs according to the RMP for alemtuzumab included urinalysis with microscopy,
9 complete blood count with differential, and serum creatinine before treatment initiation
10 and monthly during the study; thyroid-stimulating hormone levels were tested before
11 treatment initiation and every 3 months.

12 **2.3 Treatments**

13 Alemtuzumab was administered by intravenous infusion over approximately 4
14 hours. If IARs were evident during the infusion, the individual investigators could
15 prolong the infusion duration based on their clinical judgment. The infusion-
16 management medication regimen was expanded upon recommendations informed by
17 experts from the SmPC for treatment of active RRMS with alemtuzumab (European
18 Medicines Agency) (**Tables 1 and 2**). For example, the SmPC states that patients
19 should be pretreated with corticosteroids immediately before alemtuzumab
20 administration for the first 3 days of each treatment course. During EMERALD, patients
21 received intravenous methylprednisolone on Day 0 and then every day before each
22 infusion for each treatment course of 5 and 3 days, respectively, in Period 1 and Period
23 2, and in the evenings post-infusion as needed. Pretreatment with antihistamines and/or

1 antipyretics, suggested in the SmPC, was mandatory during EMERALD (cetirizine [10
 2 mg orally], diphenhydramine [25 mg intravenously], gastroprotection [proton pump
 3 inhibitors] according to the local label, and paracetamol [500 mg orally]). Oral
 4 prophylaxis for herpes infection is also recommended by the SmPC for all patients
 5 starting the first day of each treatment course and continuing for a minimum of 1 month
 6 following alemtuzumab treatment. Patients in EMERALD received acyclovir (200 mg
 7 orally) twice daily beginning the first day of each alemtuzumab course and continuing
 8 for 30 days following completion of each course. Additional agents not mentioned in the
 9 SmPC, but given as needed during EMERALD, included antiemetics and normal saline
 10 **(Table 1).**

11
 12 **Table 2. Mandatory and “As Needed” Associated Medications for CARE-MS I and II and**
 13 **Guidelines from the SmPC for the Treatment of Active RRMS with Alemtuzumab**

Treatment	CARE-MS I and II	SmPC Guidelines ^a
Antipyretics Antihistamines	Permitted at the Investigator’s discretion to minimize IARs known to be associated with alemtuzumab administration (eg, rash)	Pretreatment with antihistamines and/or antipyretics may be considered
H ₂ receptor blockers Antiemetics	Permitted at the Investigator’s discretion to minimize IARs known to be associated with alemtuzumab administration (eg, rash)	—
Methylprednisolone	As prophylaxis of IARs administered to all patients. All patients in both treatment groups received 1 g/day of IV methylprednisolone for 3 consecutive days at Month 0 and Month 12 The dose of methylprednisolone could be reduced at the investigator’s discretion for patients who did not tolerate the standard regimen ^b	Patients should be pretreated with corticosteroids immediately prior to alemtuzumab administration on each of the first 3 days of any treatment course

Acyclovir	Acyclovir 200 mg twice daily or equivalent, initiated during the trials, was administered to all alemtuzumab patients beginning on the first day of each alemtuzumab course and continuing for 28 days after the last day	Oral prophylaxis for herpes infection should be administered to all patients starting on the first day of each treatment course and continuing for a minimum of 1 month following treatment with alemtuzumab
<p>^a As published by the European Medicines Agency.</p> <p>^b If a patient assigned to the IFN β-1a arm had received corticosteroids for symptomatic treatment of a relapse within 1 month (30 days) of a scheduled steroid infusion, that infusion was omitted.</p> <p>Abbreviations: H₂, histamine receptor H₂; IAR, infusion-associated reaction; RRMS, relapsing-remitting multiple sclerosis; SmPC, Summary of Product Characteristics.</p>		

1

2 Patients in CARE-MS I and II received pretreatment with systemic steroids during

3 each treatment course (1 g/day intravenous methylprednisolone on the first 3 days), and

4 patients with IARs were treated symptomatically with concomitant antipyretics,

5 antihistamines, and antiemetics at treating neurologist's discretion (**Table 2**). In

6 contrast, the EMERALD protocol included a more comprehensive pretreatment regimen

7 with mandatory antipyretics and analgesics, and H₁ and H₂ receptor antagonists. As

8 mentioned previously, the EMERALD protocol required additional oral

9 methylprednisolone administration 1 day before the first infusion, and intravenous

10 methylprednisolone after each treatment course as needed (**Table 1**). Acyclovir was

11 administered both before and after alemtuzumab infusion for prophylaxis against herpes

12 infection as recommended by the SmPC.

13 2.4 Safety Analysis

14 The following safety populations were defined and used for endpoint reporting.

15 The full safety set (SS) was defined as enrolled patients who received at least part of an

16 alemtuzumab dose during Periods 1 or 2. The first SS (Course 1) was defined as

17 patients who received at least part of an alemtuzumab dose during Period 1. The

18 second SS (Course 2) was defined as patients from Course 1 who received at least part

1 of an alemtuzumab dose during Period 2.

2 IAR data are discussed for EMERALD alone, and in comparison with patients
3 who received alemtuzumab 12 mg in the CARE-MS I and II studies.

4 **2.5 AE Definitions**

5 AE and IAR definitions were based on standard designations. An IAR was
6 defined as any AE occurring during or within 24 hours of alemtuzumab infusion. An AE
7 was defined as any untoward medical occurrence in a patient that may or may not have
8 a causal relationship with alemtuzumab. Recording of AEs began from signed informed
9 consent through end of study. An AE was considered serious (SAE) if it either resulted
10 in death, was life-threatening, required hospitalization, resulted in disability/incapacity,
11 was a congenital anomaly/birth defect, or was medically important. Adverse events of
12 special interest (AESIs) were AEs (serious or nonserious) of scientific or medical
13 concern specific to this treatment, which required ongoing monitoring, such as
14 autoimmune cytopenias and other autoimmune disorders, infections, malignancy,
15 hypersensitivity, or anaphylaxis.

16 Treatment-emergent adverse events (TEAEs) were any AEs occurring between
17 first dose (Period 1) and end of study. Infusion-associated reactions were any TEAEs
18 occurring during or within 24 hours after each infusion for both infusion periods, and
19 were described for each 2-hour interval. IAR definition and severity grade ratings were
20 consistent with previous clinical trials and described accordingly.

21 **2.6 Ethics**

22 The protocol was approved by the appropriate Independent Ethics
23 Committees/Institutional Review Boards and complied with International Conference on

1 Harmonisation guidelines for Good Clinical Practice (GCP). All patients provided written
2 informed consent prior to screening. The Sponsor conducted training sessions for
3 clinical research associates and held individual site initiation meetings to develop a
4 common understanding of the clinical study protocol, case report form, and study
5 procedures, in compliance with GCP. Monitoring of all investigative sites in Belgium,
6 France, Netherlands, and Spain was performed by the Sponsor's staff according to the
7 Sponsor's procedures. EMERALD is registered at ClinicalTrials.gov (NCT02205489).

8

3. Results

3.1 Patient Characteristics

Demographics, disease characteristics, and disease activity at baseline are shown in **Table 3**. Most patients (91.4%) had received treatment for MS prior to EMERALD, the most common of which were natalizumab (32 patients; 55.2%) and fingolimod (31 patients; 53.4%) (**Table 3**). Among the 31 patients who received fingolimod, 18 (58.1%) discontinued this treatment <4 months prior to alemtuzumab initiation. Median duration between discontinuation of fingolimod and initiation of alemtuzumab was 2.4 months. Of note, total white blood cell and lymphocyte counts were consistent between patients who had received different types of prior disease-modifying therapies (DMTs). During Periods 1 and 2, all patients received medication for concomitant conditions; the most common drug classes were nervous system drugs (98.3% in Period 1 and 98.1% in Period 2, mainly analgesics and psycholeptics) and respiratory system drugs (72.4% in Period 1 and 72.2% in Period 2, mainly antihistamines).

Table 3. Demographics, Disease Characteristics, and Clinical and MRI Data at Baseline

	Total (n = 58)
Female, n (%)	35 (60.3)
Age, y	36.4 ± 8.1
Clinical signs of disease activity at enrollment, n (%)	34/57 (59.6)
MRI signs of disease activity, n (%)	41 (70.7)
Clinical and MRI signs of disease activity, n (%)	29 (50.0)
EDSS score	4.1 ± 1.6
Years since diagnosis ^a	8.0 ± 6.3
Relapses in the past year ^b	1.8 ± 1.1
Median time since last relapse, months	2.1
Any prior MS therapy, n (%)	53 (91.4)

Antineoplastic and immunomodulating agents ^{c,d} , n (%)	51 (87.9)
Natalizumab (Tysabri [®])	32 (55.2)
Fingolimod (Gilenya [®])	31 (53.4)
Glatiramer acetate (Copaxone [®])	23 (39.7)
Interferon beta-1a (Avonex [®])	20 (34.5)
Interferon beta-1a (Rebif [®])	18 (31.0)

^a Years since diagnosis = (date of informed consent - date of diagnosis of multiple sclerosis + 1)/365.25.
^b N = 33 (56.8%) had at least 2 relapse episodes in the past year.
^c Patients without prior antineoplastic and/or immunomodulating therapy received prior nervous system drugs, systemic corticosteroids, or an investigational drug.
^d Not comprehensive; prior antineoplastic and immunomodulating agents ≤ 13.8% not listed.
Data are mean ± SD unless stated otherwise.
Data are comparable between Course 1 and Course 2.
Abbreviations: EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; SD, standard deviation.

1
2 Of the 61 patients screened, 58 (95.1%) were enrolled into the study. Of the 58
3 patients who received the first infusion of Period 1, 57 (98.3%) completed the 5 days of
4 Course 1. Fifty-four patients received the first infusion of Period 2 and 53 completed the
5 3-day course. All patients (n=58) completed the Month 6 visit and 54 the Month 12 visit.

6 **3.2 Infusion-Associated Reactions**

7 A summary of IARs by severity grade for the On-study Period is presented in
8 **Table 4**. IARs occurred in 91.4% (n=53) and 81.5% (n=44) of patients in Course 1 and
9 Course 2, respectively. Types and overall incidence of IARs were similar to those
10 reported previously for alemtuzumab in controlled clinical trials (**Table 5**). The three
11 most common IARs were headache, pyrexia, and rash (**Table 5**). Headache was the
12 most common IAR in EMERALD and occurred in 48.3% and 40.7% of patients in
13 Course 1 and Course 2, respectively. Incidence of rash was reduced in EMERALD
14 compared with CARE-MS I and II. Incidence of pyrexia in EMERALD was higher than in
15 CARE-MS I and II. Insomnia was increased in EMERALD compared with CARE-MS I
16 and II (**Table 5**).

1

2 **Table 4. Summary of IARs for On-Study Periods 1 and 2**

	SS (n = 58)	Course 1 (n = 58)	Course 2 (n = 54)
IAR within 24 hours of any infusion	54 (93.1%)	53 (91.4%)	44 (81.5%)
Grade 1: Mild	51 (87.9%)	47 (81.0%)	34 (63.0%)
Grade 2: Moderate	36 (62.1%)	32 (55.2%)	19 (35.2%)
Grade 3: Severe	6 (10.3%)	6 (10.3%)	0 (0.0%)
Serious IAR within 24 hours of any infusion	9 (15.5%)	7 (12.1%)	2 (3.7%)
Grade 1: Mild	4 (6.9%)	4 (6.9%)	0 (0.0%)
Grade 2: Moderate	4 (6.9%)	2 (3.4%)	2 (3.7%)
Grade 3: Severe	2 (3.4%)	2 (3.4%)	0 (0.0%)

Patients may have experienced IARs on multiple occasions whereby each IAR was recorded.
Abbreviations: SS, safety set; IAR, infusion-associated reaction.

3

4 **Table 5. Infusion-Associated Reactions (IARs) Occurring in ≥5% of Patients for Periods 1**
5 **and 2 of the EMERALD Study, and for Course 1 and 2 of the CARE-MS I and CARE-MS II**
6 **Studies**

Preferred term n (%)	EMERALD	EMERALD	CARE MS-I	CARE MS-I
	Course 1	Course 2	and II	and II
	12 mg	12 mg	12 mg	12 mg
	(n = 58)	(n = 54)	(n = 811)	(n = 791)
Any class	53 (91.4)	44 (81.5)	687 (84.7)	543 (68.6)
Headache	28 (48.3)	22 (40.7)	289 (35.6)	221 (27.9)
Pyrexia	14 (24.1)	8 (14.8)	124 (15.3)	104 (13.1)
Rash	10 (17.2)	3 (5.6)	294 (36.3)	112 (14.2)
Bradycardia	9 (15.5)	3 (5.6)	24 (3.0)	6 (0.8)
Insomnia	9 (15.5)	-	56 (6.9)	-
Erythema	8 (13.8)	-	28 (3.5)	-

Nausea	8 (13.8)	3 (5.6)	91 (11.2)	57 (7.2)
Pruritus	8 (13.8)	5 (9.3)	72 (8.9)	20 (2.5)
Abdominal pain upper	6 (10.3)	3 (5.6)	11 (1.4)	8 (1.0)
Fatigue	6 (10.3)	-	46 (5.7)	-
Urticaria	6 (10.3)	-	95 (11.7)	-
Abdominal pain	4 (6.9)	-	8 (1.0)	-
Chest discomfort	4 (6.9)	-	40 (4.9)	-
Diarrhea	4 (6.9)	-	15 (1.8)	-
Dyspnea	4 (6.9)	-	43 (5.3)	-
Flushing	4 (6.9)	-	58 (7.2)	-
Constipation	3 (5.2)	-	6 (0.7)	-
Hot flush	3 (5.2)	3 (5.6)	9 (1.1)	2 (0.3)
Musculoskeletal stiffness	3 (5.2)	-	3 (0.4)	-
Presyncope	3 (5.2)	-	1 (0.1)	-
Pruritus generalized	3 (5.2)	-	6 (0.7)	-
Note: Dash represents IARs that appeared in <5% of patients. A patient can be counted in several categories of preferred term by system organ class.				

1
2 Most IARs occurred within 6 hours of initiating alemtuzumab infusion, with a peak
3 during the first 2 hours (**Table 6**). Nearly all IARs decreased in rate from Course 1 to
4 Course 2; incidence was 48.3% and 40.7% for headache, 24.1% and 14.8% for pyrexia,
5 17.2% and 5.6% for rash, and 15.5% and 5.6% for bradycardia, respectively. Hot flush
6 was the only IAR that did not decrease in incidence from Course 1 to Course 2 (5.2%
7 and 5.6%, respectively).

8
9 **Table 6. Number of Patients With Infusion-Associated Reactions (IARs) by 2-Hour Interval**
10 **and by Grade According to Time From Start of Infusion**

Period 1 Total n = 58	Grade 1	Grade 2	Grade 3
0-2 h	30	14	5
2-4 h	9	10	1
4-6 h	18	8	0
6-8 h	7	3	0
8-10 h	7	1	0
10-12 h	9	4	1
12-14 h	7	6	1

Period 1 Total n = 58	Grade 1	Grade 2	Grade 3
14-16 h	7	1	0
16-18 h	2	2	0
18-20 h	5	0	0
20-22 h	5	1	1
22-24 h	4	3	0
24-26 h	3	2	0
Period 2 Total n = 54	Grade 1	Grade 2	Grade 3
0-2 h	15	10	0
2-4 h	8	4	0
4-6 h	11	2	0
6-8 h	4	1	0
8-10 h	2	3	0
10-12 h	1	1	0
12-14 h	6	2	0
14-16 h	4	0	0
16-18 h	1	0	0
18-20 h	2	1	0
20-22 h	2	1	0
22-24 h	2	3	0
24-26 h	1	0	0

1

2 Serious IARs occurred in 15.5% (n=9) of patients who received alemtuzumab

3 (most occurred during the first course) (**Table 7**). This is a higher rate than reported in

4 clinical trials of alemtuzumab. Serious IARs occurred in 3% (n=12) of patients in each

5 CARE-MS I and II. In EMERALD, the most common serious IARs were cardiac

6 disorders, with bradycardia occurring in 3 patients and tachycardia in 1 patient. All other

7 serious IARs occurred in ≤ 1 patient. Bradycardia led to permanent withdrawal of

8 alemtuzumab for 1 patient. Bradycardia and tachycardia were each experienced as

9 serious IARs by 1 patient in CARE-MS I. Bradycardia and tachycardia were not reported

10 as serious IARs in any patient who received alemtuzumab 12 mg in CARE-MS II or in

11 the phase 2 trial (CAMMS223) (Coles et al., 2008; Coles et al., 2012). No IAR led to

12 death in EMERALD, CAMMS223, or CARE-MS I or II.

13

1 **Table 7. Summary of Serious Infusion-Associated Reactions (IARs) by Frequency for On-**
 2 **Study Period**

MedDRA System Organ Class Name and Preferred Term Name	Total n = 58 n (%)
At least one serious IAR	9 (15.5)
Cardiac	4 (6.9)
Bradycardia	3 (5.2)
Tachycardia	1 (1.7)
General and administration site reactions	2 (3.4)
Hyperthermia	1 (1.7)
Pyrexia	1 (1.7)
Investigations	2 (3.4)
Fibrin D dimer increased	1 (1.7)
Gamma-glutamyl transferase increased	1 (1.7)
Skin and subcutaneous tissue	2 (3.4)
Erythema	1 (1.7)
Urticaria	1 (1.7)
Hepatobiliary	1 (1.7)
Hepatocellular injury	1 (1.7)
Immune system	1 (1.7)
Hypersensitivity	1 (1.7)
Note: A patient can be counted in several categories of preferred term by system organ class.	

3
 4 Incidence of infections in EMERALD was similar to that reported previously in
 5 controlled clinical trials with alemtuzumab. The majority of infections reported during the

1 On-study Period were upper respiratory tract infections (n=28; 48.3%), lower respiratory
 2 tract and lung infections (n=9; 15.5%), urinary tract infections (n=13; 22.4%), and
 3 herpes infections (n=9; 15.5%). Of the 9 patients who experienced herpes infections (3
 4 cases of herpes zoster and 6 cases of oral herpes), 7 were considered to be treatment-
 5 related, with 4 cases (57.1%) occurring more than 1 month after Period 1 and acyclovir
 6 treatment, 1 case occurring before study treatment, 1 case occurring during treatment
 7 with acyclovir, and 1 case occurring in the time between Period 1 and 2. Incidences of
 8 infection in CARE-MS I and II were the following: upper respiratory tract infections (15%
 9 and 16%); lower respiratory tract infections (8.2% and 9.7%); urinary tract infections
 10 (17% and 21%); and herpes infections (16% and 16%), respectively (Cohen et al.,
 11 2012; Coles et al., 2012). No infections led to death in EMERALD, CAMMS223, or
 12 CARE-MS I and II.

13 Adverse events of special interest are shown in **Table 8**. The majority of AESIs
 14 occurred during Course 1 (8 of 9; 1 viral hepatitis occurred during Course 2). One case
 15 of immune thrombocytopenic purpura and 3 cases of hyperthyroidism disorder (2
 16 Basedow's disease, 1 hyperthyroidism) were reported during the study period, all of
 17 which were resolved by study end. Two patients (3.4%) had 1 TEAE leading to
 18 permanent treatment discontinuation (bradycardia for 1 patient and viral hepatitis for 1
 19 patient). Herpes zoster, an AESI, occurred in 1 (1.7%) patient.

20

21 **Table 8. Adverse Events (AEs) of Special Interest for On-Study Period**

MedDRA System Organ Class Name and Preferred Term Name	Total n = 58 n (%)
Any class	9 (15.5)

MedDRA System Organ Class Name and Preferred Term Name	Total n = 58 n (%)
Endocrine	3 (5.2)
Basedow's disease	2 (3.4)
Hyperthyroidism	1 (1.7)
Infections and infestations ^a	3 (5.2)
Herpes zoster	1 (1.7)
Hepatitis viral	1 (1.7)
Vulvovaginal candidiasis	1 (1.7)
Blood and lymphatic system	1 (1.7)
Immune thrombocytopenic purpura	1 (1.7)
Hepatobiliary	1 (1.7)
Hepatocellular injury	1 (1.7)
Investigations	1 (1.7)
Human papilloma virus test positive	1 (1.7)
^a Other infections not reported as AEs of special interest are considered TEAEs. Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. Note: A patient can be counted in several categories of preferred term by system organ class.	

1

2

1 **4. Discussion**

2 As with most monoclonal antibodies, IARs are frequently reported AEs
3 associated with alemtuzumab treatment (Caon et al., 2015). The observation that most
4 IARs in EMERALD were mild or moderate and decreased in rate during subsequent
5 infusions is consistent with previous studies and with patient response to other
6 monoclonal antibodies (Lenz, 2007). Consistent with previous controlled clinical trials,
7 no deaths occurred in this study.

8 EMERALD evaluated use of a comprehensive medication regimen that was
9 developed to prevent and manage IARs during alemtuzumab infusion in a real-world
10 population. However, small sample size, lack of a comparator arm, and differences in
11 population between EMERALD and CARE-MS I and II limit data interpretation. For
12 example, more than half of patients in EMERALD were treated previously with
13 natalizumab, as is common in the real-world population (Berger et al., 2017). In
14 comparison with patients in CARE-MS I and II, patients in EMERALD presented with
15 more comorbidities, were older, had longer disease duration, and had been treated with
16 a greater number of prior MS treatments including immunomodulating therapy. These
17 differences in patient populations may have altered risk of IARs and reduced the
18 feasibility of cross-trial comparison. Furthermore, potential differences in alemtuzumab
19 infusion rates further confounded study assessment, as clinicians may slow infusions to
20 manage IARs (Caon et al., 2015).

21 Despite EMERALD's limitations, IAR types and overall incidence were
22 comparable with those reported in CARE-MS I and II. The only IARs with a substantial
23 difference (two-fold) between Course 1 of EMERALD and CARE-MS I and II were rash

1 (17.2% [EMERALD] vs. 36.3% [CARE-MS I and II]) and insomnia (15.5% [EMERALD]
2 vs. 6.9% [CARE-MS I and II] and 7.6% [CARE-MS II]). It is possible that differences in
3 treatment with methylprednisolone in this study compared with CARE-MS I and II may
4 have contributed to the decreased rash and the increased insomnia. Compared with
5 CARE-MS I and II, patients in EMERALD received additional pretreatment with
6 methylprednisolone 1 day before infusion, as well as post-infusion as needed. Nausea,
7 infections, and other IARs associated with intravenous methylprednisolone (Le Page et
8 al., 2015) did not increase during EMERALD, suggesting that methylprednisolone's
9 effect was most apparent in the reduced incidence of rash. It is possible that insomnia
10 associated with prophylaxis may be more easily tolerated by patients than rash.
11 Prophylaxis shown to reduce rash in alemtuzumab-treated patients may be beneficial in
12 these cases.

13 A higher rate of bradycardia and serious IARs was observed in EMERALD
14 compared with previous trials. Differences in baseline characteristics, such as increased
15 comorbidities, may have contributed to increases in cardiac events among EMERALD
16 patients. An additional comparison of IAR frequency between EMERALD patients with
17 prior DMT use and CARE-MS II patients, all of whom also had prior DMT use, showed
18 increased rates of bradycardia and palpitations for patients in EMERALD. This suggests
19 that factors other than prior DMT use (eg, comorbidities) may increase the risk of
20 cardiac-related IARs after alemtuzumab. In EMERALD, 3 of the 9 patients with
21 brachycardia had history of endocrine, cardiac, and metabolic disorders. Furthermore, 2
22 of these 3 patients had history of bradycardia prior to the study.

1 Additionally, most patients in EMERALD were hospitalized during the entire
2 duration of infusion so they could be closely monitored, which was not required by
3 EMERALD's protocol and may have increased the rate of reported AEs. Twenty-four-
4 hour hospitalization during infusion periods was not part of the protocol in CARE-MS I
5 and II. The in-hospital monitoring of patients in EMERALD, including heart rate, may
6 have facilitated identification of transient heart rate alterations contributing to the higher
7 AE rates observed for these events. The increase in reported incidence of pyrexia,
8 although not a two-fold increase, in EMERALD versus CARE-MS I and II may be
9 associated with the increased frequency of patient temperature measurements during
10 hospitalization in EMERALD, wherein temperature measurements were recorded
11 approximately at 1 hour pre-infusion, hourly during infusion, and 1 hour and 2 hour post-
12 infusion.

13 Pharmacologic intervention for IAR management in previous clinical trials
14 included a variety of doses and schedules, which were largely dictated by individual
15 patient need and physician choice (Caon et al., 2015). Thus, the effectiveness of IAR
16 prophylaxis had been unclear. The EMERALD treatment regimen is generally aligned
17 with recommendations from clinical trial experience and labeling; the key difference is
18 the consistent application of a specific medication algorithm developed from consensus
19 group recommendations that included increased corticosteroid dosing, and mandatory
20 administration of antihistamines, antipyretics, and H₁/H₂ receptor antagonists. (Berger et
21 al., 2017; Caon et al., 2015; McEwan et al., 2016) However, based on the overall
22 findings in this study, there is no compelling advantage to adopt the IAR management
23 approach used in EMERALD. Using medication to manage IARs in the real-world

1 setting should follow the recommendations in labeling and, as is the case in clinical
2 practice, should be left to physician discretion on an individual patient basis.

3

1 **5. Conclusion**

2 In this phase 4 study, we assessed distribution of IARs by severity grade when
3 alemtuzumab is administered to RRMS patients in the real world with a specified
4 medication algorithm aimed at preventing and managing IARs. Inclusion of real-world
5 patients in EMERALD provides an understanding of the AEs physicians will likely
6 encounter with alemtuzumab treatment. It is reassuring that no previously unknown or
7 unexpected SAEs or TEAEs of special interest were reported during this study. We
8 found that types and overall incidence of IARs were generally consistent with previous
9 controlled clinical trials. However, incidence of rash was reduced in this study compared
10 with the previous trials, which may have been associated with this study's prophylaxis
11 treatment regimen. The increased incidence of serious IARs (eg, cardiac events)
12 potentially reflected differences in baseline characteristics in this population.

13

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