NOVARTIS

BONSPRI®

20 mg ofatumumab solution for injection (0,4 mL of 50 mg/mL solution)

Professional Information

Document status: Final

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Professional Information

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

BONSPRI® 20 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 20 mg ofatumumab solution for injection (0,4 mL of 50 mg/mL solution).

Ofatumumab is a recombinant fully human monoclonal immunoglobulin G1 (IgG1) antibody against human CD20 expressed on B cells. Ofatumumab is produced in a murine cell line (NS0) by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

20 mg/0,4 mL Solution for injection in a pre-filled syringe

The single-use solution for injection is sterile, preservative-free, clear to slightly opalescent, and colourless to slightly brownish-yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BONSPRI is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS).

4.2 Posology and method of administration

Posology

The recommended dose is 20 mg BONSPRI administered by subcutaneous injection with:

- initial dosing at weeks 0, 1 and 2, followed by
- subsequent monthly dosing, starting at week 4.

Missed Doses

If an injection of BONSPRI is missed, it should be administered as soon as possible without waiting until the next scheduled dose. Subsequent doses should be administered at the recommended intervals.

Special populations

Adults over 55 years old

No studies have been performed in MS patients over 55 years.

Based on the limited data available, no dose adjustment is considered necessary in patients over 55 years old (see section 5.2). Patients enrolled in the ongoing clinical trials continue to be dosed with 20 mg ofatumumab monthly after they reach the age of 55.

Renal impairment

No specific studies of ofatumumab in patients with renal impairment have been performed.

Patients with mild renal impairment were included in clinical studies. There is no experience in patients with moderate and severe renal impairment. However, as ofatumumab is not excreted via urine it is not expected that patients with renal impairment require dose modification (see section 5.2).

Hepatic impairment

No studies of ofatumumab in patients with hepatic impairment have been performed.

Since hepatic metabolism of monoclonal antibodies such as ofatumumab is negligible, hepatic impairment is not expected to impact its pharmacokinetics. Therefore, it is not expected that patients with hepatic impairment require dose modification (see section 5.2).

Paediatric population

The safety and efficacy in paediatric MS patients below the age of 18 years have not yet been established. No data are available.

<u>Method of administration</u>

BONSPRI is intended for patient self-administration by subcutaneous injection.

The usual sites for subcutaneous injections are the abdomen, the thigh and the upper outer arm.

The first injection of BONSPRI should be performed under the guidance of a healthcare professional (see section 4.4).

Comprehensive instructions for administration are provided in the PATIENT INFORMATION LEAFLET "Instructions for use of BONSPRI pre-filled syringe."

4.3 Contraindications

History of confirmed hypersensitivity to Bonspri (the active substance or to any of the excipients listed in section 6.1).

4.4 Special warnings and precautions for use

Injection-related reactions

Injection site reaction (local) symptoms observed in clinical studies included erythema, swelling, itching and pain.

Systemic injection-related reactions (SIRRs) observed in clinical studies occurred predominantly with the first injection. Symptoms observed include fever, headache, myalgia, chills and fatigue and were predominantly (99,7 %) non-serious and mild to moderate in severity. There were no life-threatening injection reactions in RMS clinical studies. Patients should be informed that injection-related reactions generally occur within 24 hours and predominantly following the first injection. Injection-related reactions can be managed with symptomatic treatment, should they occur.

Additional SIRRs reported in the post-marketing setting include rash, urticaria, dyspnoea, angioedema (e.g., tongue, pharyngeal or laryngeal swelling), and rare cases which were reported as anaphylaxis.

Most of the cases were non-serious and occurred with first injection. While there were some cases which were serious and resulted in discontinuation of Bonspri treatment, there were also serious cases where patients were able to continue Bonspri treatment without further incidents.

Some SIRR symptoms may be clinically indistinguishable from Type 1 acute hypersensitivity reactions (IgE-mediated). Patients should be informed that injection-related reactions generally occur within 24 hours and predominantly following the first injection. Injection-related reactions can be managed with symptomatic treatment, should they occur.

A hypersensitivity reaction may present with any injection, although typically would not present with the first injection. For subsequent injections, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. Patients with known IgE mediated hypersensitivity to Bonspri must not be treated with Bonspri (see section 4.3).

Only limited benefit of premedication with steroids, antihistamines, or paracetamol was seen in RMS clinical studies. Ofatumumab-treated patients who received premedication with methylprednisolone (or an equivalent steroid) experienced fewer symptoms such as fever, myalgia, chills and nausea. However, the use of steroid premedication increased the occurrence of flushing, chest discomfort, hypertension, tachycardia and abdominal pain even in the absence of ofatumumab treatment (i.e. in patients receiving placebo injections). Therefore, use of premedication is not required.

The first injection of BONSPRI should be performed under the guidance of an appropriately trained healthcare professional.

<u>Infections</u>

It is recommended to evaluate the patient’s immune status prior to initiating therapy.

Based on its mode of action, ofatumumab has the potential for an increased risk of infections. Administration should be delayed in patients with an active infection until the infection is resolved.

Ofatumumab should not be given to patients in a severely immunocompromised state until the condition is resolved.

In RMS clinical studies, the proportion of patients with infections was similar in the ofatumumab and the teriflunomide treatment groups. In the phase III pivotal clinical studies, 51,6 % of ofatumumab treated patients experienced at least one infection, compared to 52,7 % of teriflunomide treated patients.

Treatment of severely immunocompromised patients

It is not recommended to use other immunosuppressants concomitantly with ofatumumab except corticosteroids for symptomatic treatment of relapses.

Progressive multifocal leukoencephalopathy

No cases of progressive multifocal leukoencephalopathy (PML) have been reported for ofatumumab in the RMS clinical studies. However, since John Cunningham (JC) virus infection resulting in PML has been observed in patients treated with anti CD20 antibodies and other MS therapies, physicians should be vigilant for any clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, treatment with BONSPRI should be suspended until PML has been excluded.

Hepatitis B virus reactivation

No cases of hepatitis B virus (HBV) reactivation were identified in BONSPRI RMS clinical studies. However, hepatitis B reactivation has occurred in patients treated with anti-CD20 antibodies, which in some cases resulted in fulminant hepatitis, hepatic failure and death.

Patients with active hepatitis B disease should not be treated with BONSPRI. HBV screening should be performed in all patients before initiation of treatment with BONSPRI. As a minimum, screening should include hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) testing. These can be complemented with other appropriate markers as per local guidelines. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult a liver disease expert before the start of treatment

and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Vaccinations

All immunisations should be administered according to immunisation guidelines at least 4 weeks prior to initiation of BONSPRI for live or live attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of BONSPRI for inactivated vaccines.

BONSPRI may interfere with the effectiveness of inactivated vaccines.

The safety of immunisation with live or live attenuated vaccines following BONSPRI therapy has not been studied. Vaccination with live or live attenuated vaccines is not recommended during treatment and after discontinuation until B cell repletion (see section 5.1).

Vaccination of infants born to mothers treated with BONSPRI during pregnancy

In infants of mothers treated with BONSPRI during pregnancy live or live attenuated vaccines should not be administered before the recovery of B cell counts has been confirmed. Depletion of B cells in these infants may increase the risks from live or live attenuated vaccines.

Inactivated vaccines may be administered as indicated prior to recovery from B cell depletion, however assessment of vaccine immune responses, including consultation with a qualified specialist, should be considered to determine whether a protective immune response was mounted (see section 4.6).

4.5 Interaction with other medicines and other forms of interaction

Ofatumumab does not share a common clearance pathway with medicines that are metabolised by the cytochrome P450 system or other medicine metabolising enzymes.

Additionally, there is no evidence that CD20 monoclonal antibodies (mAbs) are involved in the regulation of the expression of drug metabolising enzymes. Interactions between BONSPRI and other medicinal products have not been investigated in formal studies.

Vaccinations

The safety of and the ability to generate a primary or anamnestic (recall) response to immunisation with live, live-attenuated or inactivated vaccines during ofatumumab treatment has not been investigated. The response to vaccination could be impaired when B cells are depleted. It is recommended that patients complete immunisations prior to the start of BONSPRI therapy (see section 4.4).

Other immunosuppressive or immune-modulating therapies

The risk of additive immune system effects should be considered when co-administering immunosuppressive therapies with BONSPRI.

When switching from medicinal products with prolonged immune effects, such as ocrelizumab, cladribine, fingolimod, natalizumab, teriflunomide, mitoxantrone or dimethyl fumarate, the duration and mode of action of these medicinal products should be taken into account because of potential additive immunosuppressive effects when initiating BONSPRI.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

Women of childbearing potential should use effective contraception (methods that result in less than 1 % pregnancy rates) while receiving BONSPRI and for 6 months after the last administration of BONSPRI.

Pregnancy

There is a limited amount of data from the use of ofatumumab in pregnant women. Ofatumumab may cross the placenta and cause foetal B-cell depletion based on findings from animal studies (see section 5.3). No teratogenicity was observed after intravenous administration of ofatumumab to pregnant monkeys during organogenesis.

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. The potential duration of B-cell depletion in infants exposed to ofatumumab *in utero*, and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown (see sections 4.4 and 5.1).

To help determine the effects of ofatumumab in pregnant women, healthcare professionals are encouraged to report all pregnancy cases and complications that happen during treatment or within 6 months after the last dose of BONSPRI to the marketing authorisation holder, in order to allow monitoring of these patients through the Pregnancy outcomes Intensive Monitoring program (PRIM).

Breastfeeding

The use of ofatumumab in women during lactation has not been studied. It is unknown whether ofatumumab is transferred into human milk; however, human IgG is present in human milk. There are no data on the effects of BONSPRI on the breast-fed newborn/infant or on milk production. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for BONSPRI and any potential adverse effects on the breast-fed newborn/infant from BONSPRI.

Fertility

There are no data on the effect of ofatumumab on human fertility.

Non-clinical data did not indicate potential hazards for humans based on male and female fertility parameters assessed in monkeys.

4.7 Effects on ability to drive and use machines

BONSPRI is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Approximately 1 500 patients with RMS received ofatumumab in clinical studies. In the two phase III pivotal studies, 1 882 patients with RMS were randomised, 946 of whom were treated with ofatumumab for a median duration of 85 weeks; 33 % of patients receiving ofatumumab were treated for more than 96 weeks (see section 5.1).

The proportion of patients with adverse events (AEs) (83,6 % vs 84,2 %) and the AEs leading to drug discontinuation (5,7 % vs 5,2 %) were similar in the ofatumumab and teriflunomide groups.

Tabulated list of adverse reactions

Adverse drug reactions (ADRs) that have been reported in association with the use of ofatumumab in pivotal RMS clinical studies are listed by MedDRA system organ class in Table 1. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Tabulated list of adverse reactions in Study G2301 and Study G2302 [1]

Adverse drug reactions	**Ofatumumab 20 mg N=946 %**	**Teriflunomide 14 mg N=936 %**	**Frequency category**
Infections and infestations			
Upper respiratory tract infection[2]	39,4	37,8	Very common
General disorders and administration site conditions			
Injection site reactions (local)	10,9	5,6 [3]	Very common
Injury, poisoning and procedural complications			
Injection related reactions (systemic)	20,6	15,3 [3]	Very common
Investigations			
Decreased blood immunoglobulin M	5,9	2,2	Common

1) Pooled data from treatment epochs of G2301 and G2302 (safety set)

2) Grouping of preferred terms (PTs) was considered for ADR frequency determination and includes the following: nasopharyngitis, upper respiratory tract infection, influenza, sinusitis, pharyngitis, rhinitis, viral upper respiratory infection, tonsillitis, acute sinusitis, pharyngotonsillitis, laryngitis, pharyngitis streptococcal, viral rhinitis, sinusitis bacterial, tonsillitis bacterial, viral pharyngitis, viral tonsillitis, chronic sinusitis, nasal herpes, tracheitis.

3) Teriflunomide group received matching placebo injections

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post marketing experience with Bonspri via spontaneous case reports and literature cases. Because these reactions are reported voluntarily

from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Immune system disorders	Hypersensitivity reaction

Description of selected adverse reactions

Upper respiratory tract infections

A higher proportion of ofatumumab-treated patients experienced upper respiratory tract infections compared to teriflunomide-treated patients. In the RMS clinical studies, 39,4 % of ofatumumab-treated patients experienced upper respiratory tract infections compared to 37,8 % of teriflunomide-treated patients. The infections were predominantly mild to moderate and mostly consisted of nasopharyngitis, upper respiratory tract infection and influenza.

Injection-related reactions and injection-site reactions

In the RMS phase III clinical studies, injection-related reactions (systemic) and injection-site reactions (local) were reported in 20,6 % and 10,9 % of patients treated with ofatumumab, respectively.

The incidence of injection-related reactions was highest with the first injection (14,4 %), decreasing significantly with subsequent injections (4,4 % with second, <3 % from third injection). Injection-related reactions were mostly (99,8 %) mild to moderate in severity. Only two (0,2 %) ofatumumab-treated MS patients reported serious injection-related reactions. There were no life-threatening injection-related reactions. The most frequently reported symptoms (≥2 %) included fever, headache, myalgia, chills and fatigue.

Local reactions at the administration site were very common. Injection-site reactions were all mild to moderate in severity and non-serious in nature. The most frequently reported symptoms (≥2 %) included erythema, pain, itching and swelling (see section 4.4).

Laboratory abnormalities

Immunoglobulins

During the course of the RMS phase III clinical studies, decrease in mean value of immunoglobulin M (IgM) was observed and was not associated with risk of infections, including serious infections.

In 14,3 % of patients in RMS phase III clinical studies, treatment with BONSPRI resulted in a decrease in IgM that reached a value below 0,34 g/dL.

There was no decrease in mean values of immunoglobulin G (IgG).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

No cases of overdose have been reported in RMS clinical studies.

Doses up to 700 mg have been administered intravenously in clinical studies with MS patients without dose-limiting toxicity. In the event of overdose, it is recommended that the patient be monitored for any

signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressants, ATC code: L04AG12

Mechanism of action

B cells play an important role in MS pathogenesis due to production of pro-inflammatory cytokines, release of auto-reactive antibodies and activation of pathogenic T cells. Ofatumumab is a fully human anti-CD20 monoclonal antibody (IgG1). It binds to a distinct epitope encompassing both the small and large extracellular loops of the CD20 molecule, giving rise to a slow off-rate and high binding affinity. The CD20 molecule is a transmembrane phosphoprotein expressed on B lymphocytes from the pre-B to mature B lymphocyte stage. The CD20 molecule is also expressed on a small fraction of activated T cells.

The binding of ofatumumab to CD20 induces lysis of CD20+ B cells primarily through complement-dependent cytotoxicity (CDC) and, to a lesser extent, through antibody-dependent cell-mediated cytotoxicity (ADCC). Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells. CD20-expressing T cells are also depleted by ofatumumab.

Pharmacodynamic effects

B-cell depletion

In the RMS phase III studies, ofatumumab 20 mg every 4 weeks, after an initial dose regimen of 20 mg on days 1, 7, and 14, resulted in a rapid and sustained reduction of B cells to below the lower limit of normal as early as two weeks after treatment initiation, and sustained for as long as 120 weeks while on treatment.

Similar results were observed in a study of bioequivalence using the same dosing regimen as in the phase III studies. Before initiation of the maintenance phase starting at week 4, total B-cell levels of <10 cells/µl were reached in 94 % of patients, increasing to 98 % of patients at week 12.

B-cell repletion

Data from RMS Phase 3 studies indicate a median time to B-cell recovery to LLN or baseline value of 24,6 weeks post treatment discontinuation. PK-B-cell modelling and simulation for B-cell repletion corroborate this data, predicting median time to B-cell recovery to LLN of 23 weeks post treatment discontinuation.

Immunogenicity

As a fully human monoclonal antibody, ofatumumab has a low potential of inducing anti-drug antibodies (ADA). In RMS phase III studies, the overall incidence of ADAs was very low: treatment-induced ADA were detected in 2 of 914 ofatumumab-treated patients and no patients with treatment enhancing or neutralising ADA were identified. There was no impact of positive ADA titers on PK, safety profile or B-cell kinetics in any patient.

Clinical efficacy and safety

The efficacy and safety of BONSPRI were evaluated in two randomised, double-blind, active-controlled phase III pivotal studies of identical design (G2301 [ASCLEPIOS I] and G2302 [ASCLEPIOS II]) in patients with relapsing forms of MS (RMS) aged 18 to 55 years, a disability status at screening with an Expanded Disability Status Scale (EDSS) score from 0 to 5.5, and who had experienced at least one documented relapse during the previous year or two relapses during the previous two years or positive

gadolinium (Gd)-enhancing MRI scan during the previous year. Both newly diagnosed patients and patients switching from their current treatment were enrolled.

In the two studies, 927 and 955 patients with RMS, respectively, were randomised 1:1 to receive either ofatumumab 20 mg subcutaneous injections every 4 weeks starting at week 4 after an initial dosing regimen of three weekly 20 mg doses in the first 14 days (on days 1, 7 and 14) or teriflunomide 14 mg capsules orally once daily. Patients also received matching placebo corresponding to the other treatment arm to ensure blinding (double-dummy design).

The treatment duration for individual patients was variable based on when the end of study criteria were met. Across both studies, the median treatment duration was 85 weeks, 33,0 % of patients in the ofatumumab group vs 23,2 % of patients in the teriflunomide group were treated more than 96 weeks.

Demographics and baseline characteristics were well-balanced across treatment arms and both studies (see Table 2). Mean age was 38 years, mean disease duration was 8,2 years since onset of first symptom, and mean EDSS score was 2.9; 40 % of patients had not been previously treated with a disease-modifying therapy (DMT) and 40 % had gadolinium (Gd)-enhancing T1 lesions on their baseline MRI scan.

The primary efficacy endpoint of both studies was the annualised rate of confirmed relapses (ARR) based on EDSS. Key secondary efficacy endpoints included the time to disability worsening on EDSS (confirmed at 3 months and 6 months), defined as an increase in EDSS of ≥1.5, ≥1, or ≥0.5 in patients with a baseline EDSS of 0, 1 to 5, or ≥5.5, respectively. Further key secondary endpoints were the time to disability improvement on EDSS (confirmed at 6 months), the number of Gd-enhancing T1 lesions per MRI scan, the annualised rate of new or enlarging T2 lesions, the neurofilament light chain (NfL) concentration in serum and the rate of brain volume loss (BVL). Disability-related key secondary

endpoints were evaluated in a meta-analysis of combined data from studies G3201 and G2302, as defined in the study protocols.

Table 2 Demographics and baseline characteristics

Characteristics	**Study G2301 (ASCLEPIOS I)**		**Study G2302 (ASCLEPIOS II)**	
	Ofatumumab (N=465)	Teriflunomide (N=462)	Ofatumumab (N=481)	Teriflunomide (N=474)
Mean age (years)	38.9	37.8	38.0	38.2
Age range (years)	19 - 55	18 - 55	18 - 55	18 - 55
Female (%)	68.4	68.6	66.3	67.3
Mean/Median duration of MS since first symptoms (years)	8.36 / 6.41	8.18 / 6.69	8.20 / 5.70	8.19 / 6.30
Mean/Median duration of MS since diagnosis (years)	5.77 / 3.94	5.64 / 3.49	5.59 / 3.15	5.48 / 3.10
Previously treated with DMTs (%)	58.9	60.6	59.5	61.8
Number of relapses in last 12 months	1.2	1.3	1.3	1.3
Mean/Median EDSS score	2.97 / 3.00	2.94 / 3.00	2.90 / 3.00	2.86 / 2.50
Mean total T2 lesion volume (cm^3)	13.2	13.1	14.3	12.0
Patients free of Gd+ T1 lesions (%)	62.6	63.4	56.1	61.4
Number of Gd+ T1 lesions (mean)	1.7	1.2	1.6	1.5

The efficacy results for both studies are summarised in Table 3, Figure 1 and Figure 3.

In both phase III studies (G2301 and G2302), BONSPRI demonstrated a significant reduction in the annualised relapse rate of 50,5 % and 58,4 %, respectively (both $p<0.001$) compared to teriflunomide.

The pre-specified meta-analysis of combined data showed that BONSPRI significantly reduced the risk of 3-month confirmed disability worsening (CDW) (risk reduction = 34,3 %, $p = 0.003$) and 6-month CDW (risk reduction = 32,4 %, $p = 0.012$) compared to teriflunomide (see Figure 1).

BONSPRI significantly reduced the number of Gd-enhancing T1 lesions and the rate of new or enlarging T2 lesions by 95,9 % and 83,6 %, respectively (both studies combined).

Efficacy results were consistent across the two phase III studies (G2301 and G2302) and across subgroups defined based on gender, age, prior MS therapy, baseline and on-study relapse activity,

baseline MRI disease activity, baseline EDSS, and RRMS/SPMS diagnosis.

Table 3 Overview of results from phase III studies in RMS

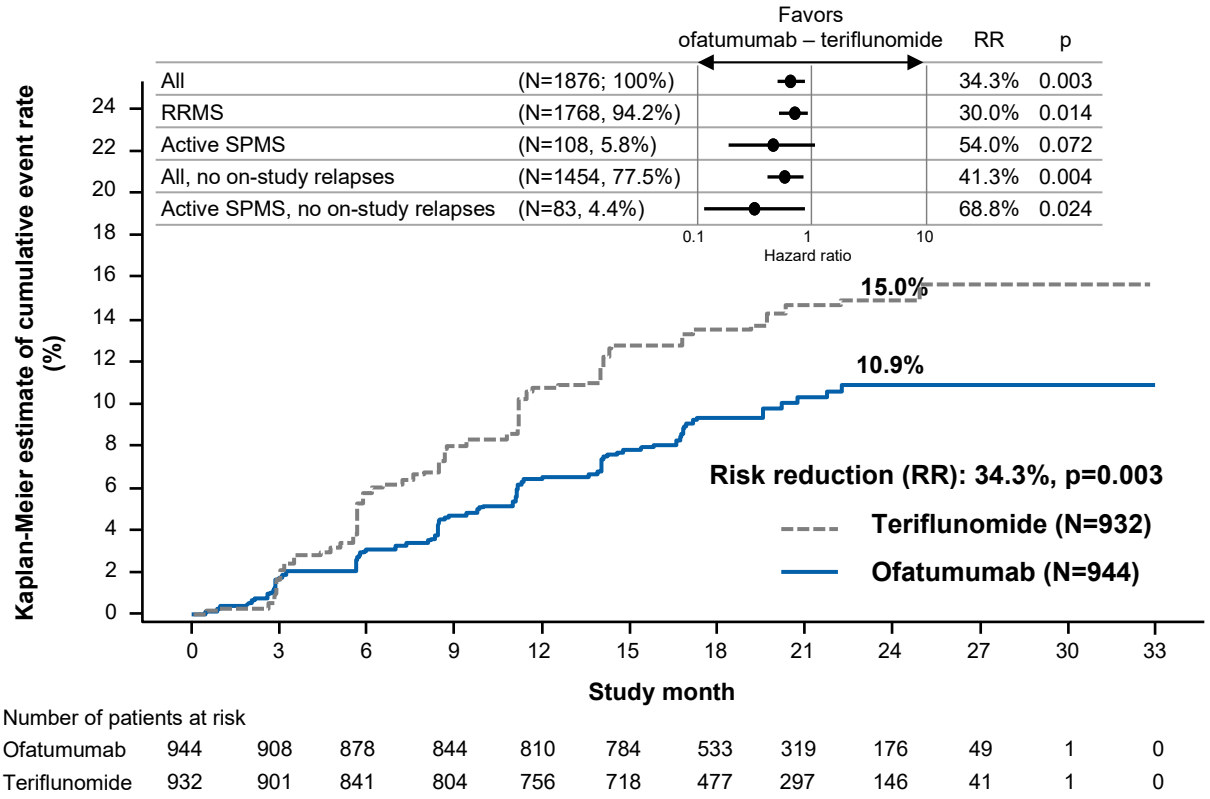
Endpoints	**Study G2301 (ASCLEPIOS I)**		**Study G2302 (ASCLEPIOS II)**	
	Ofatumumab 20 mg (n=465)	Teriflunomide 14 mg (n=462)	Ofatumumab 20 mg (n=481)	Teriflunomide 14 mg (n=474)
Endpoints based on separate studies				
Annualised relapse rate (ARR) (primary endpoint)[1]	0.11	0.22	0.10	0.25
Rate reduction	50,5 % (p<0.001)		58,4 % (p<0.001)	
Mean number of T1 Gd-enhancing lesions per MRI scan	0.0115	0.4555	0.0317	0.5172
Relative reduction	97,5 % (p<0.001)		93,9 % (p<0.001)	
Number of new or enlarging T2 lesions per year	0.72	4.00	0.64	4.16
Relative reduction	81,9 % (p<0.001)		84,6 % (p<0.001)	
NfL[2] at month 3 (pg/ml)	8.80	9.41	8.92	10.02
Relative reduction	7 % (p=0.011)		11 % (p<0.001)	
NfL[2] at month 12 (pg/ml)	7.02	9.63	7.06	9.53
Relative reduction	27 % (p<0.001)		26 % (p<0.001)	
NfL[2] at month 24 (pg/ml)	6.90	8.99	6.80	8.99
Relative reduction	23 % (p<0.001)		24 % (p<0.001)	
Endpoints based on pre-specified meta-analyses				
Proportion of patients with 3-month confirmed disability worsening[3] Risk reduction (meta-analysis)	10,9 % ofatumumab vs. 15,0 % teriflunomide 34,3 % (p=0.003)			
Proportion of patients with 6-month confirmed disability worsening[4] Risk reduction (meta-analysis)	8,1 % ofatumumab vs. 12,0 % teriflunomide 32,4 % (p=0.012)			

[1] Confirmed relapses (accompanied by a clinically relevant change in the EDSS).

[2] In serum

[3] Disability worsening was defined as an increase in EDSS of at least 1.5, 1 or 0.5 points in patients with baseline EDSS of 0, 1 to 5, or 5.5 or greater, respectively.

Figure 1 Time to first 3-month CDW by treatment (G2301 and G2302 combined, full analysis set) and subgroups



Elevated levels of neurofilament light chain (NfL) in serum are a specific marker of neuronal injury. In both phase III studies (G2301 and G2302), BONSPRI significantly reduced NfL concentrations at month 3 and in all post-baseline visits compared with teriflunomide (see Table 3).

Furthermore, in both studies higher NfL concentrations at baseline were correlated with higher number of new or enlarging T2 lesions by the end of study, i.e. NfL had prognostic value ($p<0.001$) for on-study lesion formation (see Figure 2). BONSPRI reduced the number of on-study lesions, irrespective of the baseline NfL level.

Figure 2 Number of new or enlarging T2 lesions per year (at the end of the study relative to baseline), by NfL baseline quartiles

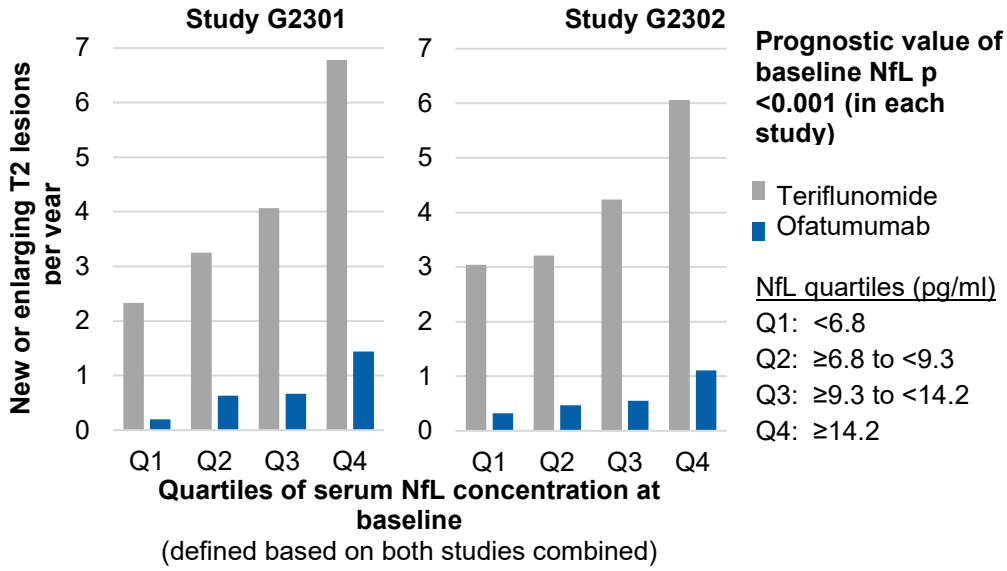
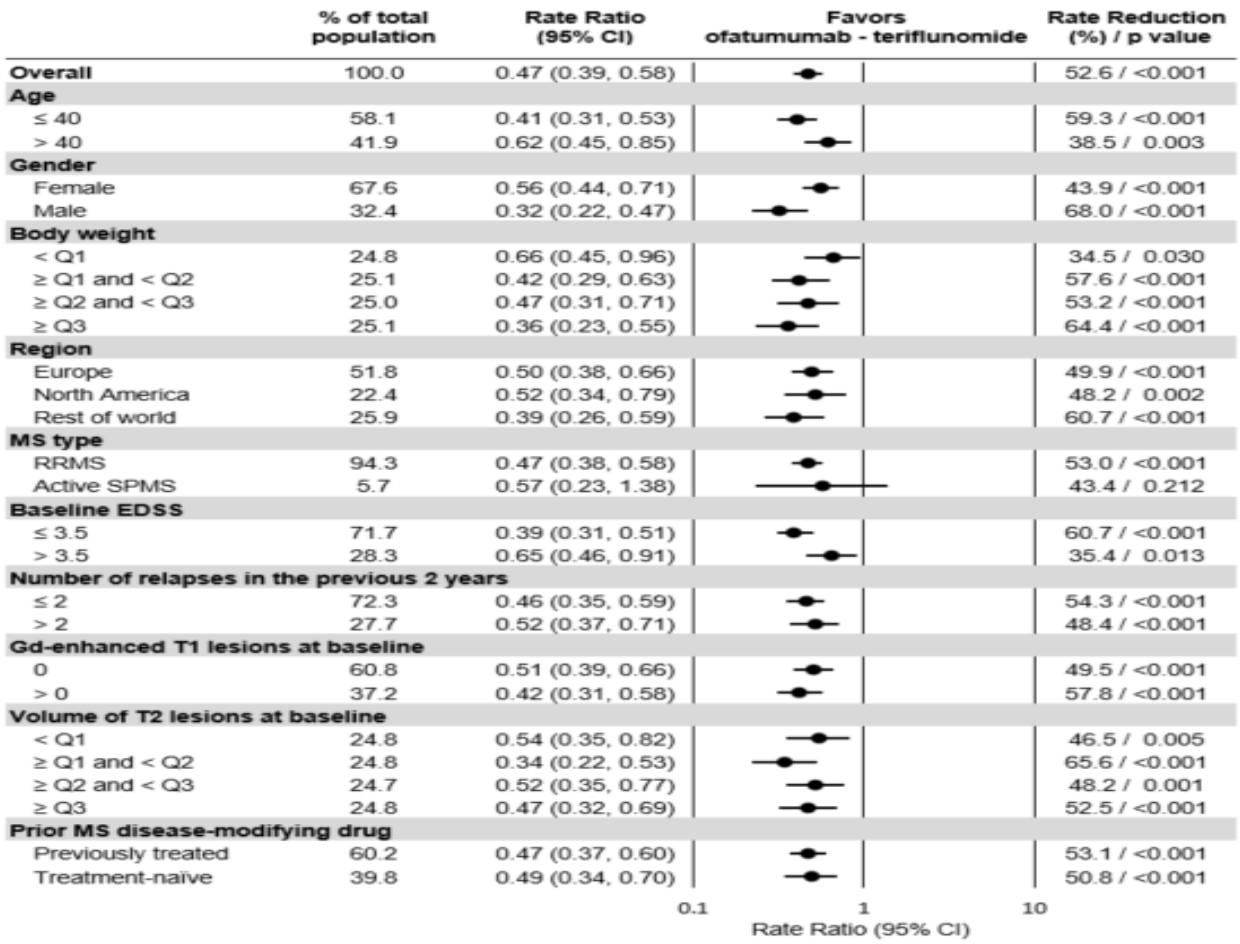


Figure 3 Annualised relapse rates (G2301 and G2302 combined, full analysis set) by subgroup



5.2 Pharmacokinetic properties

Ofatumumab exhibits a long half-life and low volume of distribution similar to that of other monoclonal antibodies. Ofatumumab is eliminated through a non-linear target-mediated route as well as a target-independent route mediated by non-specific endocytosis followed by intracellular catabolism. Higher baseline B-cell count results in greater component of target-mediated elimination clearance and shorter ofatumumab half-life at the start of therapy. Subsequent ofatumumab dosing leads to potent depletion of B cells resulting in reduced overall clearance.

Absorption

A monthly subcutaneous dose of 20 mg leads to a mean AUC_{tau} of 483 µg·h/ml and a mean C_{max} of 1,43 µg/ml at steady state.

After subcutaneous administration, ofatumumab is believed to be predominantly absorbed via the lymphatic system similarly to other therapeutic monoclonal antibodies.

Distribution

The volume of distribution at steady state was estimated to be 5,42 liters following repeated subcutaneous administration of BONSPRI at a dose of 20 mg.

Biotransformation/metabolism

Ofatumumab is a protein for which the expected metabolic pathway is degradation to small peptides and amino acids by ubiquitous proteolytic enzymes.

Elimination

Ofatumumab is eliminated in two ways: a target-independent route mediated by non-specific endocytosis followed by intracellular catabolism, as with other IgG molecules and a target-mediated route that is related to binding to B cells. B-cells present at baseline result in a greater component of target-mediated clearance of ofatumumab at the start of therapy. Ofatumumab dosing leads to potent depletion of B-cells resulting in reduced overall clearance. The half-life at steady state was estimated to be approximately 16 days following repeated subcutaneous administration of BONSPRI at a dose of 20 mg.

Linearity/non-linearity

Ofatumumab had non-linear pharmacokinetics related to its decreasing clearance over time.

Special populations

Adults over 55 years old

There are no dedicated pharmacokinetic studies of ofatumumab in patients over 55 years old due to limited clinical experience (see section 4.2).

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of ofatumumab in paediatric patients below the age of 18 years.

Gender

Gender had a modest (12 %) effect on ofatumumab central volume of distribution in a cross-study population analysis, with higher C_{max} and AUC values observed in female patients (48 % of the patients in this analysis were male and 52 % were female); these effects are not considered clinically relevant, and no dose adjustment is recommended.

Renal impairment

Ofatumumab is not excreted via urine; therefore, it is not expected that patients with renal impairment require dose modification.

Hepatic impairment

Since hepatic metabolism of monoclonal antibodies such as ofatumumab is negligible, hepatic impairment is not expected to impact its pharmacokinetics. Therefore, it is not expected that patients with hepatic impairment require dose modification.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of repeated dose toxicity including safety pharmacology endpoints.

In all pivotal repeat-dose toxicity studies, the highest dose of 100 mg/kg ofatumumab was defined as the no observed adverse effect level (NOAEL). This corresponds to safety margins of at least 110-fold when compared with the clinical exposure at the therapeutic dose of 20 mg monthly.

Neither carcinogenicity nor mutagenicity studies have been conducted with ofatumumab. As an antibody, ofatumumab is not expected to interact directly with DNA.

The embryo-foetal development (EFD) and the enhanced pre/post-natal development (ePPND) studies in monkeys showed that exposure to ofatumumab given intravenously during gestation caused no maternal toxicity, no teratogenicity, and no adverse effects on embryo-foetal and pre/post-natal development. The NOAEL for these parameters leads to AUC-based safety margins of at least 160-fold when compared with human exposure at the therapeutic dose of 20 mg monthly.

In these studies, ofatumumab was detected in the blood of the foetuses and infants, confirming placental transfer and foetal exposure to ofatumumab persisting post-natally (long half-life of the monoclonal antibody). Exposure to ofatumumab during gestation led to the expected depletion of CD20+ B cells in maternal animals and their foetuses and infants, along with a reduced spleen weight (without histological correlate) in foetuses and a reduced humoral immune response to keyhole limpet haemocyanin (KLH) in infants at high doses. All these changes were reversible during the 6-month post-natal period. In infants, early post-natal mortality was observed at a dose 160 times higher than the therapeutic dose (on AUC basis) and was likely due to potential infections secondary to immunomodulation. The NOAEL related to the pharmacological activity of ofatumumab in infants of the ePPND study leads to an AUC-based safety margin of at least 22-fold when maternal exposure at the NOAEL is compared with human exposure at the therapeutic dose of 20 mg monthly.

In a dedicated monkey fertility study, male and female fertility endpoints were unaffected. The NOEL-related exposure is at least 260 times higher than the human exposure at the therapeutic dose of 20 mg monthly in terms of AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine

Sodium acetate trihydrate

Sodium chloride

Polysorbate 80

Disodium edetate dihydrate

Hydrochloric acid (for pH adjustment)

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.

If necessary, BONSPRI may be stored unrefrigerated for a single period of up to 7 days at room temperature (not above 30 °C). If not used during this period, BONSPRI can then be returned to the refrigerator for a maximum of 7 days.

Keep the pre-filled syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

BONSPRI is supplied in a single-use glass syringe, equipped with a stainless steel needle, a plunger stopper and a rigid needle shield, containing 0,4 mL solution. The syringe is assembled with a plunger rod and a needle safety device.

BONSPRI is available in unit packs containing 1 pre-filled syringe and in multipacks containing

3 (3 packs of 1) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before injection, the pre-filled syringe should be taken out of the refrigerator for about 15 to 30 minutes to allow it to reach room temperature. The pre-filled syringe should be kept in the original carton until ready to use, and the needle cap should not be removed until just before the injection is performed. Prior to use, the solution should be inspected visually by looking through the viewing window. The solution should be clear to slightly cloudy. The pre-filled syringe should not be used if the liquid contains visible particles or is cloudy.

Comprehensive instructions for administration are given in the PATIENT INFORMATION LEAFLET "Instructions for use of BONSPRI pre-filled syringe."

Disposal

Pre-filled syringes are for single use only. Dispose used pre-filled syringes in a sharps disposal container (closable, puncture resistant container). For the safety and health of you and others, pre-filled syringes must never be re-used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

55/32.12/0368

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

28 September 2021

10. DATE OF REVISION OF THE TEXT

13 February 2025