Wuerfel J, *et al.* P2-058: Brain Volume Loss and Cognition in Teriflunomide-Treated Patients in TEMSO

CONTEXT: The primary endpoint (reduction of ARR) and key secondary endpoint (reduction in progression of disability for at least 12 weeks) were reached in the TEMSO core trial.

In the TEMSO core and post-hoc studies, treatment with AUBAGIO 14 mg was associated with improved cognition[1] as well as significant reductions in BVL,[2] MRI lesions,[3] and relapses[3] vs. placebo. In this post-hoc analysis, Wuerfel *et al.* evaluated the relative contributions of the 3 latter factors as surrogates mediating the effect of AUBAGIO on cognition. The PASAT-3 was used to measure cognition, and the Prentice criteria[4] were used to assess the validity of the 3 surrogates: BVL at Year 2 (measured by PBVC), number of new or enlarging T_2w lesions at Week 108, and total number of relapses during the first 2 years.

The analysis suggests that AUBAGIO's effect on cognition in MS may be partially mediated through its effects on slowing BVL and reducing T_2w lesions rather than through reducing relapses.

KEY RESULTS:

Criteria 1: Treatment Effect on Surrogate

- Significant reductions in all potential surrogate markers for AUBAGIO 14 mg vs placebo

Criteria 2: Treatment Effect on Cognition

- Significant increase in PASAT-3 Z-scores with AUBAGIO 14 mg vs placebo over 2 years

Criteria 3: Association Between Potential Surrogate and Cognition

- Significant association between BVL and change in PASAT-3 Z-score (*P*=0.021)
- Significant association between new/enlarging T_2w lesions and PASAT-3 Z-score (*P*=0.0138)
- No significant association between relapse and PASAT-3 Z-score (**Figure 3**; *P*=0.1206)

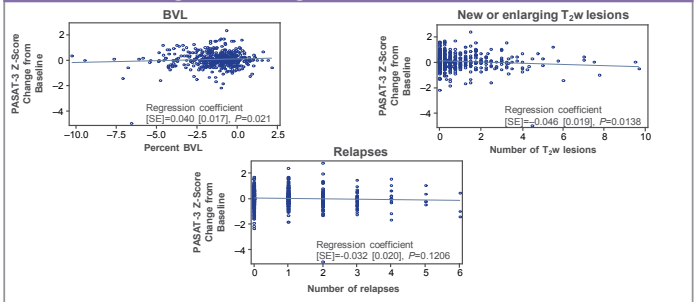
Criteria 4: Adjustment for Potential Surrogate

- Improvement in PASAT-3 performance with AUBAGIO vs placebo:
  - No longer statistically significant after adjusting for BVL (*P*=0.2363) or T_2w lesions (*P*=0.0690)
  - Remained significant after adjusting for relapses (*P*=0.0233)

Proportion of Treatment Effect

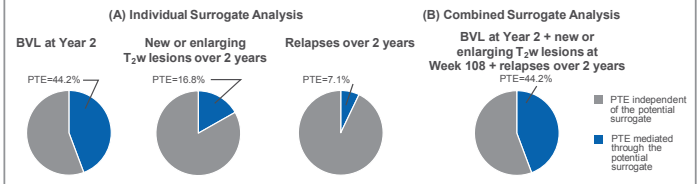
- **44%** of AUBAGIO's effect on cognitive impairment was accounted for by BVL at Year 2 (**Figure 4**)
  - **17%** for new/enlarging T_2w lesions
  - **7%** for relapses

Figure 3: Regression Lines for the Association Between Potential Surrogate and Cognition



BVL, brain volume loss; PASAT-3, Paced Auditory Serial Addition Test 3; SE, standard error; T_2w, T_2-weighted.

Figure 4: Surrogate Analysis



BVL, brain volume loss; PTE, proportion of treatment effect; T_2w, T2-weighted.

These results attribute improved cognition in AUBAGIO-treated patients to significant reductions in BVL

BVL, brain volume loss; MRI, magnetic resonance imaging; PASAT-3, Paced Auditory Serial Addition Test 3; PBVC, percentage brain volume change; T_2W, T2-weighted.

References:

1. Sprenger T, Sormani MP, Wolinsky JS, *et al.* Evaluation of the long-term treatment effect of teriflunomide on cognitive outcomes and association with brain volume change: data from TEMSO and its extension study. Presented at: MSParis2017, 7th joint meeting of the European Committee for Treatment and Research in Multiple Sclerosis and Americas Committee for Treatment and Research in Multiple Sclerosis; October 25–28, 2017; Paris, France; P685. **2.** Radue EW, Sprenger T, Gaetano L, *et al.* Teriflunomide slows BVL in relapsing MS: A reanalysis of the TEMSO MRI data set using SIENA. Neurol Neuroimmunol Neuroinflamm. 2017;4(5):e390. **3.** O'Connor PW, Wolinsky JS, Confavreux C, *et al.* Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med.* 2011;365(14):1293–1303. **4.** Prentice RL. Surrogate endpoints in clinical trials: Definition and operational criteria. *Stat Med.* 1989;8(4):431–440.

Once-daily AUBAGIO® (teriflunomide) 14 mg tablets

Brain Volume Loss and Cognition in Teriflunomide-Treated Patients in TEMSO

2-058

Wuerfel J,[1] Macdonell R,[2] Sormani MP,[3] Miller AE,[4] Kappos L,[5] Lim YM,[6] Ramirez D,[7] Yamout B,[8] Somera-Molina K,[9] Poole EM,[9] Sprenger T[5,10]

[1]Medical Image Analysis Center (MIAC AG) and qbig, Department for Biomedical Engineering, University of Basel, Basel, Switzerland; [2]Department of Neurology, Austin Hospital, Heidelberg, Victoria, Australia; [3]Biostatistics Unit, Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy; [4]Icahn School of Medicine at Mount Sinai, The Corinne Goldsmith Dickinson Center for Multiple Sclerosis, New York, USA; [5]University Hospital Basel, Basel, Switzerland; [6]Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, South Korea; [7]Collaborative Multiple Sclerosis Group of Central America and Spanish Caribbean Region, Dominican Republic; [8]American University of Beirut, Department of Neurology, Beirut, Lebanon; [9]Sanofi, Cambridge, MA, USA; [10]DKD HELIOS Klinik, Department of Neurology, Wiesbaden, Germany

OBJECTIVE

- **To evaluate the relative contribution of relapses, MRI lesions, and brain volume loss (BVL) as surrogates mediating the effect of teriflunomide 14 mg on cognition in the phase 3 TEMSO study (NCT00134563)**

CONCLUSIONS

- **This *post-hoc* analysis suggests that the effects of teriflunomide on cognition in MS may be partially mediated through its effects on slowing BVL as well as reducing T_2w lesions**
- **The effect of teriflunomide on BVL explained the greatest proportion of the treatment effect of teriflunomide on cognition (44.2%), versus new or enlarging T_2w lesions (16.8%) and relapses (7.1%)**
- **The analysis suggests that teriflunomide's effect on cognition is not largely mediated through its reduction of relapses**

INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing forms of MS or relapsing remitting MS, depending on the local label, in over 80 countries, including the United States and countries of the European Union. As of January 2019, over 96,800 patients were being treated with teriflunomide, with a total real-world exposure of approximately 237,400 patient-years as of September 2018
- In clinical trials, the most common adverse events (AEs) associated with teriflunomide treatment were hair thinning, diarrhea, alanine aminotransferase (ALT) elevation, nausea, and headache. These were mostly mild to moderate, resolved spontaneously when patients remained on treatment, and rarely led to treatment discontinuation[1–4]
- In TEMSO, teriflunomide 14 mg demonstrated efficacy versus placebo on relapses, MRI lesions,[2] and cognitive function:[5]
  - Reduced annualized relapse rate risk by 31.5% versus placebo (P<0.001)[2]
  - Lower change in total MRI lesion volume (P<0.001) and fewer gadolinium-enhancing T_1 lesions (P<0.001) from baseline versus placebo[2]
  - Improved Paced Auditory Serial Addition Test 3 (PASAT-3) performance from baseline versus placebo (P=0.04)[5]
- Teriflunomide 14 mg also significantly reduced BVL in TEMSO in a *post-hoc* blinded analysis using Structural Image Evaluation, using Normalisation, of Atrophy (SIENA)[6]
- BVL is associated with cognitive impairment in MS[7–13]
- We aimed to evaluate the relative contribution of relapses, MRI lesions, and BVL (as measured by percent brain volume change [PBVC]) as surrogates mediating the effect of teriflunomide 14 mg on cognition

METHODS

- TEMSO was a multinational, multicenter, randomized, placebo-controlled, double blind, parallel-group phase 3 study in patients with relapsing MS. Details of the patient population and study design have been published previously[2]
- Blinded SIENA analysis was carried out using MRI data collected at baseline, Week 48 (n=808), and Week 108 (n=709), during the core study[6]
  - A longitudinal registration-based technique was used for processing axial pre-contrast T_1-weighted (T_1w) images (3-mm slice thickness without gap)

Evaluation of Teriflunomide on Cognitive Function

- The effect of teriflunomide 14 mg on cognitive function was assessed by change from baseline in PASAT-3 scores
  - The PASAT-3 was assessed at baseline and Weeks 24, 48, 72, and 96
  - Individual component raw scores were transformed into Z-scores[14]

Surrogate Analysis

- The three potential surrogates for cognition evaluated were:
  - BVL (as measured by PBVC) at Year 2
  - Number of new or enlarging T_2-weighted (T_2w) lesions at Week 108
  - Total number of relapses during the first 2 years
- The Prentice criteria were developed to evaluate the validity of a potential surrogate. The four criteria are:[15,16]
  - **Criterion 1** requires the potential surrogate to be significantly associated with treatment
  - **Criterion 2** requires the clinical outcome to be associated with treatment
  - **Criterion 3** requires the clinical outcome to be associated with the potential surrogate
  - **Criterion 4** requires, for an ideal surrogate, that the association of treatment with the clinical outcome (criterion 2) disappears when adjusting for the potential surrogate
- An additional analysis measured the proportion of treatment effect (PTE) on cognition that could be explained by the treatment effect on surrogates. PTE was estimated as the percent attenuation in the adjusted (criterion 4) versus the unadjusted (criterion 2) association between treatment and cognition. Each potential surrogate was evaluated separately and in combination

RESULTS

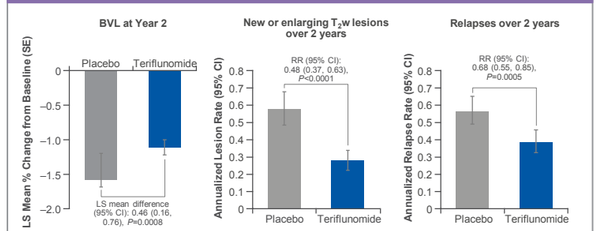
Treatment Effect on Surrogate (Criterion 1)

- Teriflunomide was associated with significant reductions in all potential surrogate markers of cognition compared with placebo (**Figure 1**)
  - The least squares (LS) mean difference in BVL from baseline to Year 2 was 0.46% (95% confidence interval, CI: 0.16, 0.76), P=0.0008
  - The number of new or enlarging T_2w lesions at Week 108 was reduced by 52%; relative risk (RR)=0.48 (95% CI: 0.37, 0.63), P<0.0001
  - The number of relapses over 2 years was reduced by 32%; RR=0.68 (95% CI: 0.55, 0.85), P=0.0005

Treatment Effect on Cognition (Criterion 2)

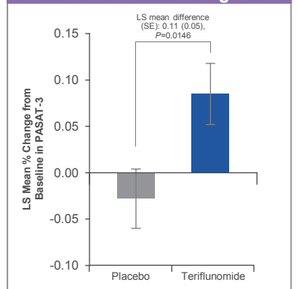
- PASAT-3 Z-scores were significantly increased with teriflunomide compared with placebo over 2 years; LS mean difference=0.11 (standard error; SE: 0.05), P=0.0146 (**Figure 2**)

Figure 1: Teriflunomide Treatment Effect on Surrogate Markers



BVL, brain volume loss; CI, confidence interval; LS, least squares; RR, relative risk; T_2w, T_2-weighted.

Figure 2: Teriflunomide Treatment Effect on Cognition



LS, least squares; PASAT-3, Paced Auditory Serial Addition Test-3; RR, relative risk; SE, standard error.

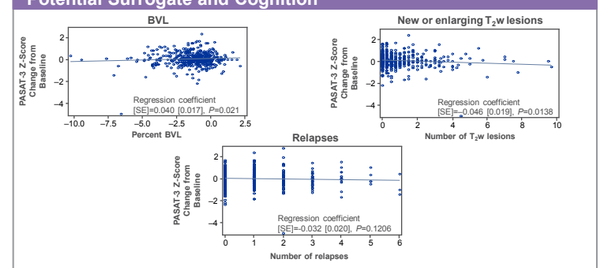
Association between Potential Surrogate and Cognition (Criterion 3)

- There was a significant association between BVL and change in PASAT-3 Z-score; regression coefficient=0.040 (SE: 0.017), P=0.021; and between new or enlarging T_2w lesions and PASAT-3 Z-score; regression coefficient=−0.046 (SE: 0.019), P=0.0138
- Relapses were not significantly associated with PASAT-3 Z-score; regression coefficient=−0.032, (SE: 0.020), P=0.1206 (**Figure 3**)

Association between Treatment and the Clinical Outcome Disappears when Adjusting for the Potential Surrogate (Criterion 4)

- The improvement in PASAT-3 performance with teriflunomide versus placebo was no longer statistically significant after adjusting for BVL (P=0.2363) or T_2w lesions (P=0.0690), but remained significant after adjusting for relapses (P=0.0233)

Figure 3: Regression Lines for the Association Between Potential Surrogate and Cognition

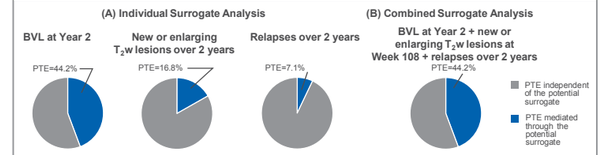


BVL, brain volume loss; PASAT-3, Paced Auditory Serial Addition Test 3; SE, standard error; T_2w, T_2-weighted.

Proportion of Treatment Effect

- When surrogate markers were analyzed separately, BVL accounted for the largest proportion (44.2%) of the effect of teriflunomide on cognitive impairment. New or enlarging T_2w lesions and relapses accounted for 16.8% and 7.1% of the effect, respectively (**Figure 4**)
- Combined, the three potential surrogate markers explained no more of the treatment effect on cognition than BVL alone (44.2%)

Figure 4: Surrogate Analysis



BVL, brain volume loss; PTE, proportion of treatment effect; T_2w, T2-weighted.

References

1. O'Connor *et al. Neurol*. 2006;66:894–900.
2. O'Connor *et al. N Engl J Med*. 2011;365:1293–303.
3. Confavreux *et al. Lancet Neurol*. 2014;13:247–56.
4. Vermersch *et al. Mult Scler*. 2014;20:705–16.
5. Sprenger *et al.* Poster P685, ECTRIMS 2017.
6. Radue *et al. Neurol Neuroimmunol Neuroinflamm*. 2017;4:e390.
7. Furby *et al. Mult Scler*. 2008;14:1068–75.
8. Ingle *et al. Brain*. 2003;126:2528–36.
9. Jasperse *et al. NeuroImage*. 2007;38:529–37.
10. Locatelli *et al. Mult Scler*. 2004;10:562–68.
11. Mineev *et al. Neurosci Behav Physiol*. 2009;3:35–38.
12. Sastre-Garriga *et al. NeuroImage*. 2004;22:353–59.
13. Lazeron *et al. Mult Scler*. 2005;11:524–31.
14. Cohen *et al. Arch Neurol*. 2001;58:961–67.
15. Sormani *et al. Mult Scler*. 2015;21:916–24.
16. Prentice *et al. Stat Med*. 1989;8:431–40.

Acknowledgments and Disclosures

This poster was reviewed by Darren P Baker, PhD, Karyn Liu, PhD, and Jonathan Valenzano, PharmD, of Sanofi. Medical writing support for this poster was provided by Beth Fisher, PhD, for Onyx, Knutsford, UK, and was funded by Sanofi.
JW: CEO of Medical Image Analysis Center (MIAC AG), Basel, Switzerland; received speaker honoraria in the past (Bayer, Biogen, Genzyme-Sanofi, Novartis, and Teva); served on advisory boards and has received research grants (Biogen, Novartis, Roche, and Sanofi Genzyme); supported by the German Ministry of Science (BMBF/KKNMS) and German Ministry of Economy (BMWi) and EU (Horizon 2020). **RM:** Consulting/speaker fees from Bayer, Biogen, Genzyme, Merck, Sanofi, Serono, Novartis, and Roche. **MPS:** Consulting fees (Biogen, Genzyme, Merck Serono, Novartis, Roche, Synthon, and Teva). **AEM:** Consulting fees from Accordant Health Services, Adamas, Biogen, Celgene, EMD Serono, Genentech/Roche, Mallinckrodt Pharmaceuticals [Questcor], Mapi-Pharma, and Novartis; contracted research for Biogen, Genentech, Novartis, Questcor, Roche, and Sanofi. **LK:** Author's institution (University Hospital Basel) has received in the last 3 years and used exclusively for research support: steering committee, advisory board, and consultancy fees (Actelion, Addex, Bayer HealthCare, Biogen Idec, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi, Santhera, Siemens, Teva, UCB, and XenoPort); speaker fees (Bayer HealthCare, Biogen Idec, Merck, Novartis, Sanofi, and Teva); support of educational activities (Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi, and Teva); license fees for Neurostatus products; grants (Bayer HealthCare, Biogen Idec, European Union, Merck, Novartis, Roche Research Foundation, Swiss MS Society, and Swiss National Research Foundation). **YML:** Nothing to disclose. **DR:** Nothing to disclose. **BY:** Speaker honoraria (Biogen Idec, Merck Serono, and Novartis). **KSM:** Employee of Sanofi, with ownership interest. **EMP:** Employee of Sanofi, with ownership interest. **TS:** Author's current and previous institutions have received compensation for author serving on scientific advisory boards/consultation and speaking (Actelion, ATI, Biogen, Desitin, Electrocore, Novartis, Sanofi Genzyme, and Teva); research support (Novartis Pharmaceuticals Switzerland, Swiss MS Society, and Swiss National Science Foundation).
Teriflunomide is approved in many countries, including the US and countries of the European Union, for the treatment of relapsing MS or relapsing remitting MS, depending on the local label. This material may contain information that is outside of the approved labeling in some countries.

Presented at the 71st Annual Meeting of the American Academy of Neurology (AAN), May 4–10, 2019, Philadelphia, USA
Funding provided by Sanofi

AUBAGIO PI – GB

Prescribing Information: AUBAGIO® 14 mg (teriflunomide) film-coated tablets Please refer to the Summary of Product Characteristics (SmPC) before prescribing. Presentation: Each film-coated tablet contains 14 mg of teriflunomide. **Indication:** AUBAGIO is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS). **Dosage and administration:** The treatment should be initiated and supervised by a physician experienced in the management of MS. In adults, the recommended dose of teriflunomide is 14 mg once daily. In paediatric patients (10 years of age and above), the recommended dose is 14mg once daily with body weight >40 kg. AUBAGIO should be taken orally and swallowed whole with some water. AUBAGIO can be taken with or without food. *Elderly (≥65 years):* AUBAGIO should be used with caution due to insufficient data on safety and efficacy. *Renal impairment:* No dose adjustment is necessary for patients with mild, moderate or severe renal impairment not undergoing dialysis. *Hepatic impairment:* No dose adjustment is necessary for patients with mild and moderate hepatic impairment. *Paediatric:* The safety and efficacy in children aged below 10 years have not been established. No data are available. **Contraindications:** Hypersensitivity to the active ingredient or excipients. Patients with severe hepatic impairment (Child-Pugh class C). Pregnant women, or women of childbearing potential not using reliable contraception during treatment and thereafter as long as plasma levels are above 0.02 mg/l. Breastfeeding women. Pregnancy must be excluded before start of treatment. Patients with severe immunodeficiency states, e.g. AIDS. Significantly impaired bone marrow function or significant anaemia, leucopoenia, neutropenia or thrombocytopenia. Severe active infection until resolution. Severe renal impairment undergoing dialysis, because insufficient clinical experience is available in this patient group. Severe hypoproteinaemia, e.g. in nephrotic syndrome. **Warnings and precautions:** *Monitoring: Before starting treatment*: blood pressure, alanine aminotransferase (ALT/SGPT), complete blood cell count (CBC) including differential white blood cell (WBC) and platelet count. Pregnancy should be excluded. *During treatment* the following should be monitored: blood pressure periodically, ALT/SGPT assessed at least every 4 weeks for the first 6 months of treatment and regularly thereafter. Consider additional monitoring when AUBAGIO is given in patients with pre-existing liver disorders, given with other potentially hepatotoxic drugs or as indicated by clinical symptoms such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. Liver enzymes should be assessed every 2 weeks during the first 6 months of treatment, and at least every 8 weeks thereafter for at least 2 years from initiation of treatment. For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly. CBC should be performed based on clinical signs and symptoms. *Accelerated elimination procedure (AEP):* Without an AEP, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/l and may take up to 2 years. An AEP can be used at any time after discontinuation of teriflunomide. *Hepatic effects:* Elevations of liver enzymes have been observed in patients receiving teriflunomide. These elevations occurred mostly within the first 6 months of treatment. Cases of drug-induced liver injury (DILI) have been observed during treatment with teriflunomide, sometimes life-threatening. Most cases of DILI occurred with time to onset of several weeks or several months after treatment initiation of teriflunomide, but DILI can also occur with prolonged use. The risk for liver enzyme increases and DILI with teriflunomide might be higher in patients with pre-existing liver disorder, concomitant treatment with other hepatotoxic drugs, and/or consumption of substantial quantities of alcohol. Patients should be closely monitored for signs and symptoms of liver injury. Teriflunomide therapy should be discontinued and accelerated elimination procedure considered if liver injury is suspected. If liver enzymes are confirmed as >3x ULN, teriflunomide therapy should be discontinued. In case of treatment discontinuation, liver tests should be pursued until normalisation of transaminase levels. *Infections:* Patients receiving AUBAGIO should be instructed to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment with AUBAGIO until the infection(s) is resolved. Patients tested positive in tuberculosis screening should be treated by standard medical practice prior to therapy. *Respiratory reactions:* Interstitial lung disease (ILD) as well as cases of pulmonary hypertension have been reported with teriflunomide in the post-marketing setting. The risk might be increased in patients with a history of ILD. Due to the potential risk of ILD, pulmonary symptoms, such as persistent cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate. *Haematological effects*: A mean decrease of <15% from baseline affecting WBC counts have been observed. Obtain CBC including differential white blood cell count and platelets prior to initiation of treatment, thereafter CBC should be assessed as indicated by clinical signs and symptoms. Patients with pre-existing cytopenias may have a higher risk of haematological disorders. In cases of severe haematological reactions, including pancytopenia, AUBAGIO and all concomitant myelosuppressive treatment must be discontinued and the AEP be considered. *Skin reactions:* Cases of serious skin reactions, sometimes fatal, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported with AUBAGIO. If skin and /or mucosal reactions (ulcerative stomatitis) are observed which raise the suspicion of severe generalised major skin reactions, teriflunomide must be discontinued and an accelerated procedure initiated immediately. New onset of psoriasis (including pustular psoriasis) and worsening of pre-existing psoriasis have been reported during the use of teriflunomide. Treatment withdrawal and initiation of an AEP may be considered. *Peripheral neuropathy:* Discontinuing AUBAGIO therapy and performing the AEP should be considered. *Vaccination:* Live attenuated vaccines should be avoided. *Interference with determination of ionised calcium levels:* The measurement of ionised calcium levels might show falsely decreased values under treatment with teriflunomide. The plausibility of observed values should be questioned and in case of doubtful measurements, it is recommended to determine the total albumin adjusted serum calcium concentration. *Immunosuppressive/ Immunomodulating therapies:* Co-administration with leflunomide is not recommended. Co-administration with antineoplastic or immunosuppressive therapies has not been evaluated. *SWITCHING to/from AUBAGIO:* No waiting period is required when initiating teriflunomide after interferon beta or glatiramer acetate. Due to the risk of concomitant immune effects for up to 2-3 months, caution is required when switching patients immediately from natalizumab to teriflunomide. To avoid concomitant immune effects when switching from fingolimod, 10-14 weeks is needed for lymphocytes to return to the normal range. If a decision is made to stop treatment with AUBAGIO, during the interval of 5 half-lives (approximately 3.5 months, although may be longer in some patients), starting other therapies will result in concomitant exposure to AUBAGIO. This may lead to an additive effect on the immune system and caution is, therefore, indicated. Paediatric population: Cases of pancreatitis have been observed. Clinical symptoms included abdominal pain, nausea and/or vomiting. Serum amylase and lipase were elevated in these patients. The time to onset ranged from a few months up to three years. Patients should be informed of the characteristic symptoms of pancreatitis. If pancreatitis is suspected, pancreatic enzymes and related laboratory parameters should be obtained. If pancreatitis is confirmed, teriflunomide should be discontinued and an accelerated elimination procedure should be initiated. *Lactose:* Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product. *Sodium:* This medicine contains less than 1 mmol sodium (23 mg per tablet), that is to say essentially "sodium free". *Interactions:* Rifampicin and other known potent CYP and transporter inducers; medicinal products metabolised by CYP1A2 or CYP2C8; substrates of OAT3; substrates of BCRP and the OATP family, especially HMG-Co reductase inhibitors, should be used with caution during the treatment with teriflunomide. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered. Co-administration with cholestyramine or activated charcoal is not recommended unless an accelerated elimination is desired. Whilst the interaction of teriflunomide is not expected to adversely impact the efficacy of oral contraceptives, it should be considered when selecting or adjusting oral contraceptive treatment. A 25% decrease in peak international normalised ratio (INR) was observed when teriflunomide was co-administered with warfarin as compared with warfarin alone. Close INR follow-up and monitoring is recommended. **Pregnancy and lactation:** Women of childbearing potential must use effective contraception during treatment and after treatment as long as teriflunomide plasma concentration is >0.02 mg/l. Female children and/or parents/ caregivers of female children should be informed about the need to contact the treating physician once the female child under AUBAGIO treatment experiences menses. Counselling should be provided to the new patients of child-bearing potential about contraception and the potential risk to the foetus. Referral to a gynaecologist should be considered. Plans to stop or change contraception, or in the case of suspected pregnancy, patient must discontinue AUBAGIO and notify the physician immediately. In case of pregnancy, the physician and patient must discuss the risk to the pregnancy and the AEP. In women wishing to become pregnant, teriflunomide should be stopped and an AEP is recommended. Please see SmPC for more details. Lactation is contraindicated. **Adverse effects:** ***Very common (≥1/10):*** Headache, diarrhoea, nausea, alopecia and ALT increase. ***Common (≥1/100 to <1/10):*** Influenza, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis, neutropenia, anaemia, mild allergic reactions, anxiety, paraesthesia, sciatica, carpal tunnel syndrome, palpitations, hypertension, pancreatitis in the paediatric population, upper abdominal pain, vomiting, toothache, Gamma-glutamyltransferase increase, aspartate aminotransferase increase, rash, acne, musculoskeletal pain, myalgia, arthralgia, pollakiuria, menorrhagia, pain, asthenia, weight decrease, neutrophil count decrease, WBC decrease and blood creatine phosphokinase increase. ***Uncommon (≥1/1000 to <1/100):*** Severe infections including sepsis, mild thrombocytopenia (platelets <100G/l), hypersensitivity reactions (immediate or delayed) including anaphylaxis and angioedema, hyperaesthesia, neuralgia, peripheral neuropathy, interstitial lung disease, pancreatitis in the adult population, stomatitis, colitis, dyslipidaemia, nail disorders psoriasis (including pustular), severe skin reactions and post-traumatic pain. ***Rare:*** (≥1/10,000 to <1/1,000): Acute hepatitis. ***Frequency not known:*** Pulmonary hypertension, drug-induced liver injury (DILI. Please see SPC for full details. **Legal Classification:** POM. **List Price: UK:** £1037.84 (28x tablets). **Marketing authorisation number:** PLGB 04425/0819. **Marketing authorisation holder:** Aventis Pharma Ltd, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK. **For more information please contact:** Medical Information, Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK. Or uk-medicalinformation@sanofi.com. **Date of preparation:** December 2021. **Document No.** MAT-GB-2105646 (v1.0)

Adverse events should be reported. Reporting forms and information can be found at:
In the UK: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to the Sanofi drug safety department on Tel: 0800 0902314. Alternatively, send via email to UK-drugsafety@sanofi.com

Prescribing Information: AUBAGIO® 14 mg (teriflunomide) film-coated tablets
Please refer to the Summary of Product Characteristics (SmPC) before prescribing.
Presentation: Each film-coated tablet contains 14 mg of teriflunomide. **Indication:** AUBAGIO is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS). **Dosage and administration:** The treatment should be initiated and supervised by a physician experienced in the management of MS. In adults, the recommended dose of teriflunomide is 14 mg once daily. In paediatric patients (10 years of age and above), the recommended dose is 14mg once daily with body weight >40 kg. AUBAGIO should be taken orally and swallowed whole with some water. AUBAGIO can be taken with or without food. *Elderly (≥65 years):* AUBAGIO should be used with caution due to insufficient data on safety and efficacy. *Renal impairment:* No dose adjustment is necessary for patients with mild, moderate or severe renal impairment not undergoing dialysis. *Hepatic impairment:* No dose adjustment is necessary for patients with mild and moderate hepatic impairment. *Paediatric:* The safety and efficacy in children aged below 10 years have not been established. No data are available. **Contraindications:** Hypersensitivity to the active ingredient or excipients. Patients with severe hepatic impairment (Child-Pugh class C). Pregnant women, or women of childbearing potential not using reliable contraception during treatment and thereafter as long as plasma levels are above 0.02 mg/l. Breastfeeding women. Pregnancy must be excluded before start of treatment. Patients with severe immunodeficiency states, e.g. AIDS, significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia. Severe active infection until resolution. Severe renal impairment undergoing dialysis, because insufficient clinical experience is available in this patient group. Severe hypoproteinaemia, e.g. in nephrotic syndrome. **Warnings and precautions:** *Monitoring: Before starting treatment:* blood pressure, alanine aminotransferase (ALT/SGPT), complete blood cell count (CBC) including differential white blood cell (WBC) and platelet count. Pregnancy should be excluded. *During treatment* the following should be monitored: blood pressure periodically, ALT/SGPT assessed at least every 4 weeks for the first 6 months of treatment and regularly thereafter. Consider additional monitoring when AUBAGIO is given in patients with pre-existing liver disorders, given with other potentially hepatotoxic drugs or as indicated by clinical symptoms such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. Liver enzymes should be assessed every 2 weeks during the first 6 months of treatment, and at least every 8 weeks thereafter for at least 2 years from initiation of treatment. For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly. CBC should be performed based on clinical signs and symptoms. *Accelerated elimination procedure (AEP):* Without an AEP, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/l and may take up to 2 years. An AEP can be used at any time after discontinuation of teriflunomide. *Hepatic effects:* Elevations of liver enzymes have been observed in patients receiving teriflunomide. These elevations occurred mostly within the first 6 months of treatment. Cases of drug-induced liver injury (DILI) have been observed during treatment with teriflunomide, sometimes life-threatening. Most cases of DILI occurred with time to onset of several weeks or several months after treatment initiation of teriflunomide, but DILI can also occur with prolonged use. The risk for liver enzyme increases and DILI with teriflunomide might be higher in patients with pre-existing liver disorder, concomitant treatment with other hepatotoxic drugs, and/or consumption of substantial quantities of alcohol. Patients should be closely monitored for signs and symptoms of liver injury. Teriflunomide therapy should be discontinued and accelerated elimination procedure considered if liver injury is suspected. If liver enzymes are confirmed as >3x ULN, teriflunomide should be discontinued. In case of treatment discontinuation, liver tests should be pursued until normalisation of transaminase levels. *Infections:* Patients receiving AUBAGIO should be instructed to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment with AUBAGIO until the infection(s) is resolved. Patients tested positive in tuberculosis screening should be treated by standard medical practice prior to therapy. *Respiratory reactions:* Interstitial lung disease (ILD) as well as cases of pulmonary hypertension have been reported with teriflunomide in the postmarketing setting. The risk might be increased in patients with a history of ILD. Due to the potential risk of ILD, pulmonary symptoms, such as persistent cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate. *Haematological effects:* A mean decrease of <15% from baseline affecting WBC counts have been observed. Obtain CBC including differential white blood cell count and platelets prior to initiation of treatment, thereafter CBC should be assessed as indicated by clinical signs and symptoms. Patients with pre-existing cytopenias may have a higher risk of haematological disorders. In cases of severe haematological reactions, including pancytopenia, AUBAGIO and all concomitant myelosuppressive treatment must be discontinued and the AEP be considered. *Skin reactions:* Cases of serious skin reactions, sometimes fatal, (including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)) and drug reaction with eoseinophilia and systemic symptoms (DRESS), have been reported with AUBAGIO. If skin and /or mucosal reactions (ulcerative stomatitis) are observed which raise the suspicion of severe generalised major skin reactions, teriflunomide must be discontinued and an accelerated procedure initiated immediately. New onset of psoriasis (including pustular psoriasis) and worsening of pre-existing psoriasis have been reported during the use of teriflunomide. Treatment withdrawal and initiation of an AEP may be considered. *Peripheral neuropathy:* Discontinuing AUBAGIO therapy and performing the AEP should be considered. *Vaccination:* Live attenuated vaccines should be avoided. *Interference with determination of ionised calcium levels:* The measurement of ionised calcium levels might show falsely decreased values under treatment with teriflunomide. The plausibility of observed values should be questioned and in case of doubtful measurements, it is recommended to determine the total albumin adjusted serum calcium concentration. *Immunosuppressive/ Immunomodulating therapies:* Co-administration with leflunomide is not recommended. Co-administration with antineoplastic or immunosuppressive therapies has not been evaluated. *SWITCHING to/from AUBAGIO:* No waiting period is required when initiating teriflunomide after interferon beta or glatiramer acetate. Due to the risk of concomitant immune effects for up to 2-3 months, caution is required when switching patients immediately from natalizumab to teriflunomide. To avoid concomitant immune effects when switching from fingolimod, 10-14 weeks is needed for lymphocytes to return to the normal range. If a decision is made to stop treatment with AUBAGIO, during the interval of 5 half-lives (approximately 3.5 months, although may be longer in some patients), starting other therapies will result in concomitant exposure to AUBAGIO. This may lead to an additive effect on the immune system and caution is, therefore, indicated. Paediatric population: Cases of pancreatitis have been observed. Clinical symptoms included abdominal pain, nausea and/or vomiting. Serum amylase and lipase were elevated in these patients. The time to onset ranged from a few months up to three years. Patients should be informed of the characteristic symptoms of pancreatitis. If pancreatitis is suspected, pancreatic enzymes and related laboratory parameters should be obtained. If pancreatitis is confirmed, teriflunomide should be discontinued and an accelerated elimination procedure should be initiated. *Lactose:* Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product. *Sodium:* This medicine contains less than 1 mmol sodium (23 mg per tablet), that is to say essentially "sodium free". *Interactions:* Rifampicin and other known potent CYP and transporter inducers; medicinal products metabolised by CYP1A2 or CYP2C8; substrates of OAT3; substrates of BCRP and the OATP family, especially HMG-Co reductase inhibitors, should be used with caution during the treatment with teriflunomide. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered. Co-administration with cholestyramine or activated charcoal is not recommended unless an accelerated elimination is desired. Whilst the interaction of teriflunomide is not expected to adversely impact the efficacy of oral contraceptives, it should be considered when selecting or adjusting oral contraceptive treatment. A 25% decrease in peak international normalised ratio (INR) was observed when teriflunomide was co-administered with warfarin as compared with warfarin alone. Close INR follow-up and monitoring is recommended. **Pregnancy and lactation:** Women of childbearing potential must use effective contraception during treatment and after treatment as long as teriflunomide plasma concentration is >0.02 mg/l. Female children and/or parents/caregivers of female children should be informed about the need to contact the treating physician once the female child under AUBAGIO treatment experiences menses. Counselling should be provided to the new patients of child-bearing potential about contraception and the potential risk to the foetus. Referral to a gynaecologist should be considered. Plans to stop or change contraception, or in the case of suspected pregnancy, patient must discontinue AUBAGIO and notify the physician immediately. In case of pregnancy, the physician and patient must discuss the risk to the pregnancy and the AEP. In women wishing to become pregnant, teriflunomide should be stopped and an AEP is recommended. Please see SmPC for more details. Lactation is contraindicated. **Adverse effects:** ***Very common (≥1/10):*** Headache, diarrhoea, nausea, alopecia and ALT increase. ***Common (≥1/100 to <1/10):*** Influenza, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis, neutropenia, anaemia, mild allergic reactions, anxiety, paraesthesia, sciatica, carpal tunnel syndrome, palpitations, hypertension, pancreatitis in the paediatric population, upper abdominal pain, vomiting, toothache, Gamma-glutamyltransferase increase, aspartate aminotransferase increase, rash, acne, musculoskeletal pain, myalgia, arthralgia, pollakiuria, menorrhagia, pain, asthenia, weight decrease, neutrophil count decrease, WBC decrease and blood creatine phosphokinase increase. ***Uncommon (≥1/1000 to <1/100):*** Severe infections including sepsis, mild thrombocytopenia (platelets <100G/l), hypersensitivity reactions (immediate or delayed) including anaphylaxis and angioedema, hyperaesthesia, neuralgia, peripheral neuropathy, interstitial lung disease, pancreatitis in the adult population, stomatitis, colitis, dyslipidaemia, nail disorders, psoriasis (including pustular), severe skin reactions and post-traumatic pain. ***Rare: (≥1/10,000 to <1/1,000):*** Acute hepatitis. ***Frequency not known:*** Pulmonary hypertension, drug-induced liver injury (DILI). Please see SPC for full details. **Legal Classification:** POM. **List Price: UK:** £1037.84 (28x tablets). **Marketing authorisation numbers:** EU/1/13/838/001-005. **Marketing authorisation holder:** Sanofi-Aventis Groupe. 54, Rue La Boétie. F-75008 Paris. France. **For more information please contact:** ***UK:*** Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK or uk-medicalinformation@sanofi.com ***IE:*** Sanofi, 18 Riverwalk, Citywest Business Campus, Dublin 24. Tel: 01 403 5600, email: IEmedinfo@sanofi.com. **Date of preparation:** August 2021. Document no.: MAT-IE-2101114 (v1.0)

Adverse events should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Sanofi Tel: 0800 0902314. Alternatively, send via email to UK-drugsafety@sanofi.com

In Ireland: www.hpra.ie; email: medsafety@hpra.ie. Adverse events should also be reported to Sanofi Ireland Ltd. Tel: 01 403 5600. Alternatively, send via email to IEPharmacovigilance@sanofi.com