1. Title Page

Title	Emulation of a phase 3 study of oral BG-12 or glatiramer in multiple sclerosis
Research question & Objectives	The objective is to emulate the comparative effectiveness of oral dimethyl fumarate (BG-12) versus glatiramer acetate in the real-world given the results of a previously published randomized controlled trial
Protocol version	V3
Last update date	7 June 2024
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Study registration	**Site:** n/a **Identifier:** n/a
Sponsor	**Organization:** n/a **Contact:** n/a
Conflict of interest	n/a

Table of contents

2. Abstract

Multiple treatment strategies exist that modify the course of the relapsing-remitting multiple sclerosis (RRMS), for example by reducing the number of relapses. Dimethyl fumarate and glatiramer acetate, both first line disease-modifying therapies, are observed to have a causal effect on decreasing the number of relapses in RRMS patients, and more specifically decreasing the annualized relapse rate at two years. However, not all patient groups have been included in these pivotal randomized controlled trials and as a result, gaps of knowledge of the causal effect for these subpopulations exist.

Therefore, we aim to use observational data from the Swedish Multiple Sclerosis registry (SMSreg) to find causal evidence for the effect of dimethyl fumarate and glatiramer acetate on lowering the two year relapse rate in these neglected subpopulations by emulating the CONFIRM trial using a target trial emulation framework. We will distinguish between a strict scenario – where we emulate the target trial as closely as possible – and a pragmatic scenario, where additional subpopulations (e.g. elderly and paediatric patients) will be included by applying milder in- and exclusion criteria as opposed to the strict scenario. Through the comparison of these two scenarios, we will identify the effect estimates for these subpopulations which would otherwise have been neglected.

This study will lead to novel insights of the use of dimethyl fumarate and glatiramer acetate in real-world settings and their causal effects on the annualized relapse rate at two years for a wider variety of patient.

3. Amendments and updates

Version date	Version number	Section of protocol	Amendment or update	Reason
2023-05-06	V1	All	Creation of the protocol	Prepared draft version
2023-09-29	V2	All	Minor adjustments to whole protocol	Finalize protocol
2024-06-07	V3	All	Switched primary and secondary outcomes due to bias of health seeking behaviour. Added study design diagram in 7.2. Adjusted the variables: we extended the interval for EDSS measurement at baseline to 1 year prior baseline. Some exclusion criteria cannot be found in the dataset and have been removed from this version of the protocol. Updated data management and quality control. Sensitivity analyses have been added. Updated primary & secondary analysis. Analysis for meta objective has been added. Limitations have been extended. Updated milestones.	Update protocol before publishing to EMA's RWD catalogue and before starting data analysis.

4. Milestones

Table 1 Milestones

Milestone	Date
Finalize protocol	1 October 2023
Upload protocol to EMA's RWD catalogue	11 June 2024
Data access	15 June 2024
Finish data analysis	30 July 2024

5. Rationale and background

See Appendix I for a more detailed Rationale and background.

What is known about the condition: Relapsing-remitting multiple sclerosis is a subtype of multiple sclerosis, a demyelinating disease affecting the central nervous system. The relapsing-remitting subtype is characterised by episodes of sudden worsening of neurological symptoms (a relapse or exacerbation), followed by periods of recovery. These neurological symptoms may improve er even disappear completely during the recovery phase. In progressive types of multiple sclerosis, the symptoms are gradually worsening without periods of recovery.

What is known about the exposure of interest:

- Oral dimethyl fumarate is used as an first line disease modifying therapies in relapsing-remitting multiple sclerosis patients to decrease the number of relapses. Dimethyl fumarate has been approved for the European market since 2013 for patients aged 13 years or older. Only limited practical evidence has been produced regarding the effect of dimethyl fumarate on lowering the relapse rate in elderly (55+).
- Subcutaneous glatiramer acetate is used as a first line disease modifying therapies in relapsing-remitting multiple sclerosis patients to decrease the number of relapses. Glatiramer acetate has been approved on national levels within the European Union from 2001 onwards for patients aged 18 years or older. There is limited practical evidence regarding the effect of glatiramer acetate on lowering the relapse rate in children (<18) and elderly (55+).

Gaps in knowledge: It is unknown what the causal effect of the exposure of interest is on the annualized relapse rate in subgroups present in the observational data and absent in the CONFIRM target trial population.

What is the expected contribution of this study? By emulating the CONFIRM target trial in both a strict and pragmatic scenario (see 6. Research question and objectives), the effect of additional subgroups that were not included in the target trial population can be estimated. This way, the emulation approach can provide insights of the added value of observational data for patient subgroups that have not been studied in (pivotal) randomized controlled trials.

6. Research question and objectives

Table 2 Primary and secondary research questions and objective

A. Primary research question A and objective A: strict scenario

Objective:	The objective is to emulate the comparative effectiveness of oral dimethyl fumarate versus glatiramer acetate in the real-world using strict in- and exclusion criteria, given the results of a previously published randomized controlled trial (CONFIRM trial)
Hypothesis:	The comparative effectiveness of oral dimethyl fumarate versus glatiramer acetate in the real-world using strict in- and exclusion criteria is similar to the comparative efficacy in a previously published randomized controlled trial (CONFIRM trial).
Population ***(mention key inclusion-exclusion criteria):***	Relapsing-remitting multiple sclerosis patients between 18 and 55 years of age and had had at least one documented relapse during the previous year, or at least one gadolinium-enhancing lesion 0 to 6 weeks before the index date, and had a score of 0 to 5 on the Expanded Disability Status Scale (EDSS).
Exposure:	Two-times daily dose of oral dimethyl fumarate 240mg
Comparator:	Daily dose of subcutaneous glatiramer acetate of 20mg
Outcome:	Time to first confirmed relapse. Annualized relapse rate at 2 years (96 weeks), defined as the total number of confirmed relapses experienced in the treatment group, divided by the total number of days and multiplied by 365 days.
Time ***(when follow up begins and ends):***	Follow up starts on the same day as initiation of therapy until the 96 week period has passed or until the date of the last dose in the case of early discontinuation.
Setting:	Outpatient
Main measure of effect:	Time to first event, incidence rate ratio

B. Primary research question B and objective B: pragmatic scenario

Objective:	The objective is to emulate the comparative effectiveness of oral dimethyl fumarate versus glatiramer acetate in the real-world using a pragmatic scenario, given the results of a previously published randomized controlled trial (CONFIRM trial).
Hypothesis:	The comparative effectiveness of oral dimethyl fumarate versus glatiramer acetate in the real-world using a pragmatic scenario is similar to the comparative efficacy in a previously published randomized controlled trial (CONFIRM trial).
Population ***(mention key inclusion-exclusion criteria):***	Relapsing-remitting multiple sclerosis patients between 18 and 55 years of age and had had at least one documented relapse during the previous year, or at least one gadolinium-enhancing lesion 0 to 6 weeks before the index date, and had a score of 0 to 5 on the Expanded Disability Status Scale.
Exposure:	Two-times daily dose of oral dimethyl fumarate 240mg
Comparator:	Daily dose of subcutaneous glatiramer acetate of 20mg
Outcome:	Time to first confirmed relapse. Annualized relapse rate at 2 years (96 weeks), defined as the total number of confirmed relapses experienced in the treatment group, divided by the total number of days and multiplied by 365 days.
Time ***(when follow up begins and ends):***	Follow up starts on the same day as initiation of therapy until the 96 week period has passed or until the date of the last dose in the case of early discontinuation.
Setting:	Outpatient
Main measure of effect:	Time to first event, incidence rate ratio

C. Meta research question and objective: comparing the pragmatic and strict scenarios

Objective:	The meta-objective of this study is to compare the effect estimates from the strict scenario with those obtained from the pragmatic scenario to identify the effect estimates of subpopulations neglected in the strict scenario and in the original CONFIRM trial.
Hypothesis:	Subpopulations neglected in the strict scenario and in the CONFIRM target trial have similar effect estimates as those studied in the main population.
Population ***(mention key inclusion-exclusion criteria):***	n.a. (see objectives in 6A and 6B)
Exposure:	Two-times daily dose of oral dimethyl fumarate 240mg
Comparator:	Daily dose of subcutaneous glatiramer acetate of 20mg
Outcome:	Annualized relapse rate at 2 years (96 weeks), defined as the total number of confirmed relapses experienced in the treatment group, divided by the total number of days and multiplied by 365 days.
Time ***(when follow up begins and ends):***	Follow up starts on the same day as initiation of therapy until the 96 week period has passed or until the date of the last dose in the case of early discontinuation.
Setting:	Outpatient
Main measure of effect:	Comparison of incidence rate ratios, comparison of time to first event data.

7. Research methods

7.1. Study design

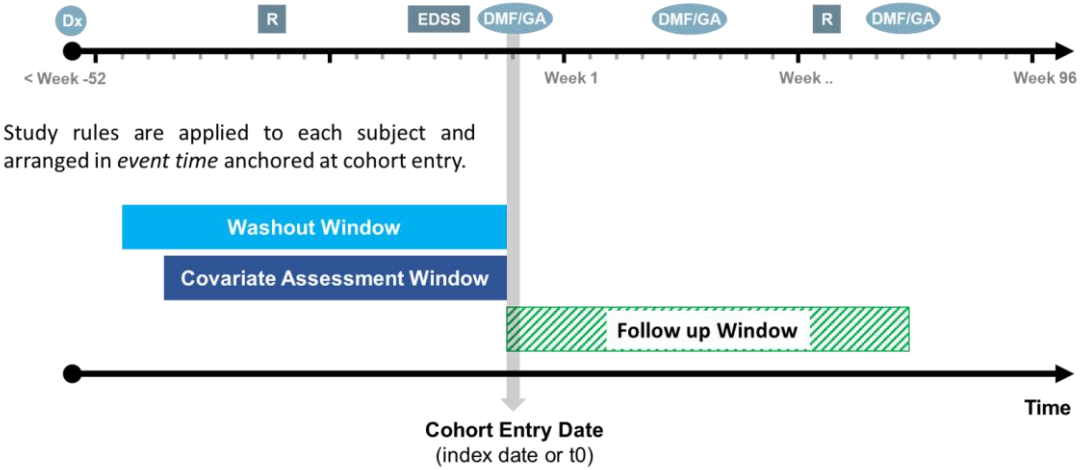
Research design (e.g. cohort, case-control, etc.): Retrospective new user active comparator cohort study

Rationale for study design choice: This study design reduces risk of bias from unmeasured time varying confounding by indication (such as depletion of susceptibles, immortal time bias and adjustment for causal intermediates) and fits neatly into the target trial framework. Patients need to be followed from start of treatment until censoring (death, treatment failure, end of follow-up).

7.2. Study design diagram

Figure 1: From transactional data to study implementation*

Individual-patient is retrieved from SMSreg and documented as encounters from various sources, including diagnoses (Dx), drug dispensings of dimethyl fumarate or glatiramer acetate (DMF/GA), a relapse (R) or visits to measure EDSS. It is arranged in *weeks* from the index date (t0).



7.3. Setting

7.3.1 Context and rationale for definition of time 0 (and other primary time anchors) for entry to the study population

The start of the follow-up, also known as time-zero, is the day of initiation of the dimethyl fumarate or glatiramer acetate therapy.

Table 3 Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting*	Code Type†	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Exposure: dimethyl fumarate (Tecfidera or BG-12)	Date of incident dispensation for dimethyl fumarate (time 0)	Single	Incident	[-365,0][i] [-183,0][ii] [-91,0][iii] [-50,0][iv]	n/a	ATCC	n/a	Dimethyl fumarate (oral, two-times daily 240mg) or glatiramer acetate (SC, once daily 20mg)	No validation study	SMSreg
Comparator: glatiramer acetate (Copaxone or copolymer-1)	Date of incident dispensation for glatiramer acetate (time 0)	Single	Incident	[-365,0][i] [-183,0][ii] [-91,0][iii] [-50,0][iv]	n/a	ATCC	n/a	Dimethyl fumarate (oral, two-times daily 240mg) or glatiramer acetate (SC, once daily 20mg)	No validation study	SMSreg

* IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

† See appendix for listing of clinical codes for each study parameter

7.3.2 Context and rationale for study inclusion criteria:

We will include patients between 18 and 55 years diagnosed with relapsing-remitting multiple sclerosis, have a score between 0 and 5 on the expanded disability status scale (EDSS) confirmed within a time-window of six months from the index date and have had at least one documented relapse in the year before the index date or one gadolinium-enhancing lesion in the 6 weeks prior to the index date.

In the pragmatic scenario we will drop the inclusion criteria to include otherwise neglected subpopulations such as elderly, patients with a low probability of experiencing a relapse, patients with a high EDSS score (>5) and or diagnosed with other phenotypes of multiple sclerosis.

Table 4. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Age between 18 and 55 years		Before selection of index date	[0,0]	n/a	n/a	n/a	Exposure (dimethyl fumarate), comparator (glatiramer acetate)	No validation study	SMSreg
Diagnosed with relapsing-remitting multiple sclerosis		Before selection of index date	[0,0]	Any	ICD-10-CM	Any	Exposure (dimethyl fumarate), comparator (glatiramer acetate)	No validation study	SMSreg
EDSS between 0 and 5		Before selection of index date	[-365,0]	n/a	n/a	n/a	Exposure (dimethyl fumarate), comparator (glatiramer acetate)	No validation study	SMSreg
At least one documented relapse in previous year or at least one gadolinium-enhancing lesion 0 to 6 weeks before the index date		Before selection of index date	[-365,0] [-42,0]	n/a		Any	Exposure (dimethyl fumarate), comparator (glatiramer acetate)	No validation study	SMSreg

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.3.3 Context and rationale for study exclusion criteria

We exclude patients with a documented relapse within 50 days prior to the index date and patients who have not stabilized since their last relapse at the time zero. Patients with a missing age and/or sex are excluded. Patients who do not meet the different wash-out criteria in Table 5 are excluded. Patients with a history of alcohol and drug abuse are excluded if possible to identify in SMSreg. Patients with a history of malignancy, human immunodeficiency virus (HIV), severe allergic or anaphylactic reactions or known drug hypersensitivity are excluded if possible to identify in SMSreg.

Table 5. Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Sex missing/unknown		Before selection of index date	[0,0]	n/a	n/a	n/a	Exposure (dimethyl fumarate), comparator (glatiramer acetate)		SMSreg
Age missing/unknown		Before selection of index date	[0,0]	n/a	n/a	n/a	Exposure (dimethyl fumarate), comparator (glatiramer acetate)		SMSreg
A documented relapse within the 50 days prior to the index date AND/OR the subject has not stabilized from a previous relapse prior to the index date.		Before selection of index date	[-50, 0]	Any		Any	Exposure (dimethyl fumarate), comparator (glatiramer acetate)		SMSreg
Corticosteroid treatment within 30 days before the index date		Before selection of index date	[-30, 0]	Any	ATCC	Any	Exposure (dimethyl fumarate), comparator (glatiramer acetate)		SMSreg

History of malignancy	Subjects with basal cell carcinoma that has been completely excised prior to study entry remain eligible	Before selection of index date	[-∞, 0]	Any	ICD-10-CM	Any	Exposure (dimethyl fumarate), comparator (glatiramer acetate)		SMSreg
History of severe allergic or anaphylactic reactions or known drug hypersensitivity		Before selection of index date	[-∞, 0]	Any	ICD-10-CM	Any	Exposure (dimethyl fumarate), comparator (glatiramer acetate)		?
Any history of treatment with total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination AND/OR any therapeutic monoclonal antibody	Subjects with prior treatment of the monoclonal antibody natalizumab remain eligible.	Before selection of index date	[-∞, 0]	Any	ATCC	Any	Exposure (dimethyl fumarate), comparator (glatiramer acetate)		Cladribine and non-natlizumab monoclonal antibodies in SMSreg
Treatment within 1 year prior to the index date with mitoxantrone ANR/OR cyclophsphamide		Before selection of index date	[-365,0]	Any	ATCC		Exposure (dimethyl fumarate), comparator (glatiramer acetate)		Mitoxantrone in SMSreg
Treatment within 6 months prior to the index date with cyclosporine, azathioprine, methotrexate, natalizumab, immunoglobin (IV), plasmapheresis, cytapheresis AND/OR any treatment used for investigational purposes		Before selection of index date	[-183,0]	Any	ATCC		Exposure (dimethyl fumarate), comparator (glatiramer acetate)		Natalizumab and investigational drugs in SMSreg

Prior treatment within 3 months prior to the index date with any interferon-α AND/OR interferon-β		Before selection of index date	[-91,0]	Any	ATCC		Exposure (dimethyl fumarate), comparator (glatiramer acetate)		SMSreg
Prior treatment within 50 days prior to the index date with steroids AND/OR 4-aminopyridine or related products		Before selection of index date	[-50,0]	Any	ATCC		Exposure (dimethyl fumarate), comparator (glatiramer acetate)		(cortico)steroids and fampridine in SMSreg.

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.4. Variables

7.4.1 Context and rationale for exposure(s) of interest

We focus on new treatment initiators to avoid bias related to depletion of the susceptibles and confounding by time varying indication. The use of an active comparator of glatiramer acetate will allow us to compare initiators who are in need of a similar line of therapy and at a similar stage of multiple sclerosis disease severity. Both dimethyl fumarate and glatiramer acetate are used as first line disease modifying therapies.

Algorithm to define duration of exposure effect:

If a refill occurs before the end of days supply dispensed, add overlapping days to the end of the subsequent dispensing's day supply. Assume that the effect of a pill lasts for 7 days. Therefore, we allow up to a 7 day gap between a dispensation + days supply and refill. We also add 15 days to the last dispensation + days supply in a treatment episode and consider this "exposed" time.

Table 6. Operational Definitions of Exposure

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Exposure (dimethyl fumarate)		[-365,0][i] [-183,0][ii] [-91,0][iii] [-50,0][iv]	[1, censor]	n/a	ATCC	n/a	Exposure, control	Dimethyl fumarate (oral), glatiramer acetate (SC)	No validation study	SMSreg
Control (glatiramer acetate)		[-365,0][i] [-183,0][ii] [-91,0][iii] [-50,0][iv]	[1, censor]	n/a	ATCC	n/a	Exposure, control	Dimethyl fumarate (oral), glatiramer acetate (SC)	No validation study	SMSreg

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.4.2 Context and rationale for outcome(s) of interest

The outcome is the annualized relapse rate ratio, where the annualized relapse rate is defined as the total number of confirmed relapses experienced in the treatment group, divided by the total number of days and multiplied by 365 days. This is the unadjusted relapse rate. The rate ratio is defined as the unadjusted annualized relapse rate of the exposure group divided by the unadjusted annualized relapse rate of the control group.

In addition, the relapse rate for an individual subject will be calculated as the number of relapses for that subject divided by the number of days the subject participated in the study, and the ratio multiplied by 365. Based on these individual relapse rates, the mean and median for each treatment group will be presented.

Table 7. Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
Relapse		Yes	Incidence rate ratio, Time-to-event	n/a	Any	ICD-10-CM	Any	Exposure (dimethyl fumarate), control (glatiramer acetate)	No validation study	SMSreg

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.4.3 Context and rationale for follow up

We focus on an on-treatment analysis as the primary analysis to emulate the per-protocol estimate for the primary outcome from CONFIRM.

Moreover, we focus on treatment-initiators to emulate the observational analogue of the intention-to-treat estimate. However, if patients switched from glatiramer acetate to a newer treatment for the sole reason of the newer treatment being more effective they will still be censored, i.e., loss to follow-up in this case must be for reasons related to the safety and efficacy of glatiramer acetate itself (e.g., loss to follow-up must be similar to reasons expected in the target trial).

Table 8. Operational Definitions of Follow Up

Follow up start	Week 0, Day 1	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome	No	n/a
Date of death	Yes	Discharged dead or registry recorded death, whichever came 1st
End of observation in data	Yes	Allow 30 day gaps in enrolment
Day X following index date *(specify day)*	Yes	672 (week 96)
End of study period (specify date)	No	n/a
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	Yes	**Stockpiling algorithm:** If refill occurs before end of days supply, count overlapping days at the end of the subsequent dispensing's day supply. **Grace period:** -A strict grace period of 15 days to refill the prescription is used, as non-adherence is not expected here.
Date of add to/switch from exposure *(specify algorithm)*	Yes	Date that patient in exposed group is dispensed comparator drug or vice versa.
Other date *(specify)*	No	n/a

[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

7.4.4 Context and rationale for covariates (confounding variables and effect modifiers, e.g. risk factors, comorbidities, comedications)

Baseline age, baseline EDSS score and baseline relapse rate (number of relapses in the year prior to the index date) are considered the main covariates, as this was also the case in the CONFIRM target trial. If EDSS score at baseline as missing, we will take the EDSS score closest to the index date, within a time-window of -12 or +6 months from the index date. The other covariates (sex and history of disease-modifying therapies usage) are therefore automatically considered as exploratory covariates. Region is not considered as a covariate due to the limited geographical variance expected in the Swedish multiple sclerosis registry (SMSreg).

Table 9. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Age at baseline	*Primary covariate, also a covariate in the CONFIRM target trial*	*Continuous*	[0,0]	n/a	n/a	n/a	Exposure (dimethyl fumarate), control (glatiramer acetate)		SMSreg
EDSS score at baseline or within a time-window of ±6 months from the index date	*Primary covariate, also a covariate in the CONFIRM target trial*	*Ordinal (non-linear)*	[-365,0]	n/a	n/a	n/a	Exposure (dimethyl fumarate), control (glatiramer acetate)		SMSreg
Annualized relapse rate at baseline	*Primary covariate, also a covariate in the CONFIRM target trial*	*Continuous*	[-365,0]	n/a	n/a	n/a	Exposure (dimethyl fumarate), control (glatiramer acetate)		SMSreg
Sex	*Exploratory covariate (not used in the covariate-adjusted analysis in CONFIRM target trial)*	*Binary*	[0,0]	n/a	n/a	n/a	Exposure (dimethyl fumarate), control (glatiramer acetate)		SMSreg
History of disease-modifying therapy usage	*Exploratory covariate (not used in the covariate-adjusted analysis in CONFIRM target trial)*	*Categorical*	[-∞, 0]	n/a	n/a	n/a	Exposure (dimethyl fumarate), control (glatiramer acetate)		SMSreg

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.5. Data analysis

7.5.1 Context and rationale for analysis plan

For both the primary and secondary analysis, weights will be calculated using the stabilized version of inverse probability of treatment weighting (IPtW) method to balance baseline confounders between the two cohorts. For the primary analysis, we will study the time to first confirmed relapse using a Cox proportional hazards model to create hazard ratios, similar to the CONFIRM target trial. For the secondary analysis, we will study the annualized relapse rate ratio at 2 years (96 weeks) using a negative binomial regression model. In both analyses, our approach is doubly robust. Moreover, several sensitivity analysis will be performed to assess robustness of our primary and secondary analysis.

The meta objective will also be analysed by 1) comparing the direction and magnitude of the estimated study effect obtained from the strict scenario with those provided by the original target trial, and 2) comparing the direction and magnitude of the estimated study effect obtained from the pragmatic scenario with those provided by the strict scenario and the original target trial. Successful comparison will be expressed through clinical relevance, which is determined by consulted neurologists.

Table 10. Primary, secondary, and subgroup analysis specification

A. Primary analysis

Hypothesis strict scenario:	The comparative effectiveness of oral dimethyl fumarate versus glatiramer acetate in the real-world using strict in- and exclusion criteria is similar to the comparative efficacy in a previously published randomized controlled trial (CONFIRM trial).
Hypothesis pragmatic scenario:	The comparative effectiveness of oral dimethyl fumarate versus glatiramer acetate in the real-world using a pragmatic scenario is similar to the comparative efficacy in a previously published randomized controlled trial (CONFIRM trial).
Outcome:	Time to first confirmed relapse
Analytic software:	R
Model(s): *(provide details or code)*	Cox proportional hazards model to calculate hazard rates of the DMF and GA cohorts, and the hazard ratio between the two cohorts.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	The Hazard ratios of dimethyl fumarate compared to placebo and glatiramer acetate compared to placebo have been reported in the CONFIRM trial, predicted using a single Cox proportional hazards model using a term for treatment strategy and adjusting for baseline EDSS, age, baseline ARR and region. Since they have been predicted from a single model, we were able to calculate the hazard ratio of dimethyl fumarate compared to glatiramer acetate, which will be used to compare the emulations. For each subject, stabilized weights will be calculated using the stabilized IPtW approach to balance baseline confounders between the two cohorts. Stabilized weights will be calculated taking the following covariates in mind: • Age at baseline

	• Gender • EDSS at baseline • ARR at baseline • History of DMT usage (categorical which DMT) • Calendar year (weeks since start of data collection) The Cox proportional hazards model will be applied on the study population, using a term for treatment and adjusting for baseline EDSS, age and baseline ARR and the stabilized IPt weights (doubly robust estimation). Region is not expected to be a confounder due to only studying the Swedish MS population.
Missing data methods	*Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.*
	Patients with missing or unknown age or sex will be excluded. Patients with a missing EDSS score within 1 year prior or 6 months after the index date will be excluded. We assume that no relapse occurred when it is not documented as such in SMSreg. If a variable is missing at random (MAR), we will apply multiple imputation. If a variable is missing not at random (MNAR), the possible confounding effect will be estimated to assess robustness.
Subgroup Analyses	*List all subgroups*

	If a baseline characteristic differs ±20% from the value reported in the original CONFIRM target trial:
	• Subgroup where the baseline value is similar to the reported value in the original CONFIRM target trial
	  • Age
	  • EDSS
	  • Sex
	  • Previous disease-modifying therapy usage
	
	Otherwise similar subgroup analysis as reported in the original CONFIRM target trial:
	• baseline EDSS (EDSS ≤2.0 vs. EDSS > 2.0)
	• age at baseline (age < 40 vs. age ≥40)
	• sex
	• baseline weight (by quartiles)
	• Previous disease-modifying therapy usage

B. Secondary Analysis

Hypothesis strict scenario:	The comparative effectiveness of oral dimethyl fumarate versus glatiramer acetate in the real-world using strict in- and exclusion criteria is similar to the comparative efficacy in a previously published randomized controlled trial (CONFIRM trial).
Hypothesis pragmatic scenario:	The comparative effectiveness of oral dimethyl fumarate versus glatiramer acetate in the real-world using a pragmatic scenario is similar to the comparative efficacy in a previously published randomized controlled trial (CONFIRM trial).
Exposure contrast:	Dimethyl fumarate vs. glatiramer acetate
Outcome:	Annualized relapse rates at 2 years (96 weeks), defined as the total number of confirmed relapses experienced in the treatment group, divided by the total number of days and multiplied by 365 days.
Analytic software:	R
Model(s): *(provide details or code)*	Negative binomial regression model to calculate incidence rates of the DMF and GA cohorts, and the incidence rate ratio between the two cohorts.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	Stabilized inverse probability of treatment weighting (IPtW) will be applied to weigh subjects on their covariates. Stabilized weights will be calculated taking the following covariates in mind: • Age at baseline • Gender • EDSS at baseline • ARR at baseline • History of DMT usage (categorical which DMT) • Calendar year (weeks since start of data collection) A negative binomial regression model will be used to estimate the adjusted annualized relapse rate at 2 years, taking into account a term for treatment, baseline EDSS, baseline relapse rate and the IPt weights (doubly robust estimation).
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	See primary analysis.
Subgroup Analyses	***List all subgroups***
	See primary analysis.

C. analysis for meta objective (1.1C)

Hypothesis meta objective:	The comparative effectiveness of oral dimethyl fumarate versus glatiramer acetate in the real-world using strict in- and exclusion criteria is similar to the comparative effectiveness in the real-world using less stringent in- and exclusion criteria.
Outcome:	Time to first confirmed relapse, annualized relapse rate at 2 years (96 weeks).
Analytic software:	R
Model(s): *(provide details or code)*	Comparison of the absolute estimates (hazard rates and annualized relapse rates) and the relative estimates (hazard ratios and annualized relapse rate ratios), where similarity is expressed through clinical relevance. Clinical relevance of both absolute and relative outcomes is determined by expert knowledge, for which at least three neurologists will be consulted.

Table 11. Sensitivity analyses – rationale, strengths and limitations

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Sensitivity analysis 1	The study period will be restricted from the authorization date of glatiramer acetate (12/01/2004) to the authorization date of dimethyl fumarate (30/01/2014)	The glatiramer acetate population prior to 2014 is potentially intransitive with the post 2014 population due to reasons provided in "8. Limitation of the methods"	Glatiramer acetate and dimethyl fumarate patients can be weighted on their treatment initiation date leading to less biased estimates.	Subjects having initiated glatiramer acetate in between 2004 and 2014 will now be excluded from analysis, leading to smaller sample sizes and less power.
Sensitivity analysis 2	Patients diagnosed with Secondary progressive multiple sclerosis (SPMS) will be included in the analysis	The conversion from RRMS to SPMS is hard to distinguish, and, therefore, it is expected that some	Besides leading to a bigger sample size, we now include subjects in this grey area as well and most likely have covered all RRMS patients.	Some subjects may have converted to SPMS and therefore may not experience clear relapses anymore, these are now included in the analysis.
Sensitivity analysis 3	The g-formula will be applied instead of stabilized IPtW.	Application of the g-formula as an alternative weighing strategy to IPtW.	The combination of both weighing strategies leads to bigger confidence in the provided estimate and accompanied confidence interval.	The parametric survival model has the assumption that the baseline hazard follows a certain parametric distribution.
Sensitivity analysis 4	Poisson regression model instead of negative binomial regression model	Relapses tend to follow a Poisson distribution, hence the deviation from the analysis as performed in the CONFIRM target trial (i.e., negative binomial regression).	Better suitable for analysing relapses, as relapses tend to follow a Poisson distribution.	Deviation from CONFIRM target trial statistical analysis protocol. Moreover, Poisson models are collapsible and thereby deviate from the non-collapsible models used in the target trial.
Sensitivity analysis 5	Adding the covariates gender, history of DMT usage and calendar year.	These are expected to have a confounding effect on the exposure and the outcome.	Adjusting for these additional confounders will lead to a more trustworthy estimate	Deviation from CONFIRM target trial statistical analysis protocol.
Sensitivity analysis 6	Adjusting the assessment window of the EDSS score	To investigate potential differences between subjects having their EDSS measured between [-365, -180] and [-180, 0] days from the index date.	Robustness will be assessed between the two different patient groups	Less patients will be eligible for inclusion in the study due to not having their baseline EDSS assessed within the assessment window.
Sensitivity analysis 7	Time to first confirmed relapse to time to first relapse	A certain fraction of the relapse documented in SMSreg are self-reported, and not confirmed by the treating physician / neurologist.	Including more data.	Including self-reported data.

7.6. Data sources

7.6.1 Context and rationale for data sources

Reason for selection: We will be using the Swedish multiple sclerosis registry (SMSreg).

Strengths of data source(s): The SMSreg is specifically designed to register (relapsing-remitting) multiple sclerosis patients. The registry is therefore of high quality given our objectives.

Limitations of data source(s): Not all covariates may be included in SMSreg, these fall outside the scope of this study proposal. Not all subpopulations may be identifiable in SMSreg, these fall outside the scope of this study proposal.

Data source provenance/curation: SMSreg is widely used for research with almost 200 scientific publications. The data holder provides thorough documentation of data contents, assumptions and limitations

Table 12. Metadata about data sources and software

	Data 1
Data Source(s):	Swedish multiple sclerosis registry (SMSreg)
Study Period:	1 April 2024 – 31 December 2026
Eligible Cohort Entry Period:	First prescription date of Glatiramer acetate in the database (12/01/2004) until 31/12/2023).
Data Version (or date of last update):	
Data sampling/extraction criteria:	All enrollees in data source
Type(s) of data:	Disease registry
Data linkage:	n/a
Conversion to CDM*:	n/a
Software for data management:	R

*CDM = Common Data Model

7.7. Data management

Data will be anonymized by the SMSreg team and transferred to the secured analytics environment of the University of Groningen where it will be further analysed. The data will be deleted from the secured servers of the University of Groningen after completion of the study.

7.8. Quality control

Subjects with missing age and gender will be excluded. Outliers are checked by the value being bigger then 1.5*IQR, and replaced by last observation carried forwards (LOCF). Subjects having received investigational drugs without details will be deleted from the study. Subjects having received a particular treatment before its authorization date will be removed from the study, since these are assumed to have been administered for investigational purposes. Subjects with baseline values as defined in Table 9 outside the provided time window will be excluded.

Multiple imputation will be used for missing values if the missing data mechanism is assumed to be missing at random (MAR). Typos in self-reported data (e.g. reporting a bodyweight of 600 kg as opposed to having consistently reported 60 kg before) will be replaced by LOCF for the particular subject.

7.9. Study size and feasibility

The same reasoning as compared to the CONFIRM target trial will be followed. However, if we obtain a smaller sample size, we will still continue the study under a lower power. Similarly, we will continue the study if we obtain a higher sample size, the analysis will be continued with higher power.

Table 13. Power and sample size

See 7.9.

8. Limitation of the methods

- Relapses tend to be underreported in observational data as compared to experimental settings.
- Gradual progression from RRMS to SPMS may happen at or around the index date, which may remain unrecognized/undiagnosed and could therefore lead to bias. This bias is not applicable to the CONFIRM target trial, due to the controlled and experimental setting of the trial at baseline.
- The comparator treatment, i.e., GA, has been available on the Swedish market since 2004, while DMF has been available since 2014. There are multiple ways this discrepancy in authorisation date and availability may lead to bias. This bias is not applicable to the target trial
    - Patients on glatiramer acetate may switch to other first line therapies when they become available and may therefore disrupt the observational analogue of the intention-to-treat analysis, i.e., patients may switch therapies for reasons not possible in the CONFIRM target trial.
    - Patients on glatiramer acetate before 2006, when natalizumab was authorized, may have had a higher disease severity as opposed to patients on glatiramer after 2006 due to second line DMTs being unavailable prior to 2006.
    - Patients on glatiramer acetate before 2014, when dimethyl fumarate was authorized, may have experienced a different level of standard-of-care which may affect both the treatment and the outcomes.
- EDSS score may not have been measured exactly at baseline, i.e., the index date. The real EDSS score at baseline may therefore differ from the one used in this study that falls within the time-window of ±6 months from the index date.

9. Protection of human subjects

Patient data will be anonymized before data transfer and analysis.

10. Reporting of adverse events

n/a

11. References

1. Fox, R.J., et al., *Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis.* New England Journal of Medicine, 2012. **367**(12): p. 1087-1097.

12. Appendices

Appendix 1: Rationale and background for the emulation of the CONFIRM target trial using SMSreg

[i] Washout of 1 year prior to randomization for mitoxantrone, cyclosphosphamide as prior treatment.
[ii] Washout of 6 months prior to randomization for cyclosporine, azathioprine, methotrexate, natalizumab, intravenous immunoglobulin, plasmapheresis or cytapheresis as prior treatment or treatment with any drug for investigational purposes.
[iii] Washout of 3 months prior to randomization for interferon beta or interferon alpha as prior treatment.
[iv] Washout of 50 days prior to randomization for steroids (IV or oral corticosteroid treatment or agents that may act though the corticosteroid pathway) or 4-aminpridine and related products as prior treatment.