A non-interventional study evaluating Kesimpta® (ofatumumab) treatment effects in patients with relapsing multiple sclerosis transitioning from other therapies [KAIROS]
Table of contents

Table of contents ................................................................................................................. 2
List of figures ...................................................................................................................... 3
List of tables ........................................................................................................................ 3
List of abbreviations ............................................................................................................ 4

1 Abstract ................................................................................................................................ 6
2 Amendments and updates .................................................................................................. 11
3 Milestones .......................................................................................................................... 11
4 Rationale and background ................................................................................................. 11
  4.1 Background ............................................................................................................ 11
  4.2 Purpose and Rationale ........................................................................................... 12
5 Research question and objectives ...................................................................................... 13
  5.1 Primary objective ................................................................................................... 13
  5.2 Secondary objectives ............................................................................................. 13
6 Research methods .............................................................................................................. 13
  6.1 Study design ........................................................................................................... 13
    6.1.1 DMTs for RMS observed in this study ................................................. 15
    6.1.2 Enrollment ............................................................................................. 15
    6.1.3 Observational period ............................................................................. 15
    6.1.4 Treatment interruption or discontinuation ............................................ 16
    6.1.5 Early termination ................................................................................... 16
  6.2 Inclusion and Exclusion criteria ............................................................................ 16
    6.2.1 Inclusion criteria .................................................................................... 16
    6.2.2 Exclusion criteria .................................................................................. 17
  6.3 Endpoints ............................................................................................................... 17
    6.3.1 Primary Endpoints ............................................................................... 17
    6.3.2 Secondary Endpoints ......................................................................... 18
    6.3.3 Exploratory Endpoints .......................................................................... 19
  6.4 Variables ................................................................................................................ 19
    6.4.1 Baseline documentation ......................................................................... 19
    6.4.2 Remaining documentations .................................................................... 20
    6.4.3 Description of selected variables .......................................................... 21
  6.5 Data sources ........................................................................................................... 23
  6.6 Study size ............................................................................................................... 26
  6.7 Data management .................................................................................................... 26
  6.8 Data analysis .......................................................................................................... 26
6.8.1 Statistical Analysis Plan
6.8.2 Population to be analyzed
6.9 Quality control
6.9.1 Data quality management
6.9.2 Data recording and document retention
6.9.3 Site monitoring
6.10 Limitations of the research methods
7 Protection of human subjects
8 Management and reporting of adverse events/adverse reactions
8.1 Adverse event collection and reporting
8.1.1 Definition
8.1.2 AE collection
8.1.3 AE reporting of (serious) adverse event and special scenarios
9 Plans of disseminating and communicating study results
10 References

List of figures
Figure 6-1 Study design

List of tables
Table 4-1 Planned dates of study milestones
Table 6-1 Planned study timelines
Table 6-2 Approved injectable DMTs (IFNß and GA) for RMS in Germany
Table 6-3 Criterion for disability worsening based on change in EDSS score
Table 6-4 Criterion for disability improvement based on change in EDSS score
Table 6-5 Data collection
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ARR</td>
<td>Annualized Relapse Rate</td>
</tr>
<tr>
<td>CD</td>
<td>Cluster of Differentiation</td>
</tr>
<tr>
<td>CDI</td>
<td>Confirmed Disability Improvement</td>
</tr>
<tr>
<td>CDP</td>
<td>Confirmed Disability Progression</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report/Record Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>DMP</td>
<td>Data Management Plan</td>
</tr>
<tr>
<td>DMT</td>
<td>Disease-modifying Therapy</td>
</tr>
<tr>
<td>DVP</td>
<td>Data Validation Plan</td>
</tr>
<tr>
<td>EC</td>
<td>Ethic Committee</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>EDSS</td>
<td>Expanded Disability Status Scale</td>
</tr>
<tr>
<td>EPAR</td>
<td>European Public Assessment Report</td>
</tr>
<tr>
<td>FDA</td>
<td>Food &amp; Drug Administration</td>
</tr>
<tr>
<td>FS</td>
<td>Functional System</td>
</tr>
<tr>
<td>FSMC</td>
<td>Fatigue Scale for Motor and Cognitive Functions</td>
</tr>
<tr>
<td>Gd</td>
<td>Gadolinium</td>
</tr>
<tr>
<td>GPP</td>
<td>Good Pharmacoepidemiology Practices</td>
</tr>
<tr>
<td>HCP</td>
<td>Health Care Provider</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>IgM</td>
<td>Immunoglobulin M</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ISPE</td>
<td>International Society for Pharmacoepidemiology</td>
</tr>
<tr>
<td>mAb</td>
<td>Monoclonal Antibody</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MS</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>MS-HRS</td>
<td>Multiple Sclerosis Health Resource Utilization Survey</td>
</tr>
<tr>
<td>MSIS-29</td>
<td>Multiple Sclerosis Impact Scale 29</td>
</tr>
<tr>
<td>MSTKG</td>
<td>Multiple Sclerosis Therapy Consensus Group</td>
</tr>
<tr>
<td>NEDA</td>
<td>No Evidence of Disease Activity</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
<tr>
<td>NFL</td>
<td>Neurofilament light chain</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NI</td>
<td>Non-Interventional</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NIS</td>
<td>Non-Interventional Study</td>
</tr>
<tr>
<td>RMS</td>
<td>Relapsing Multiple Sclerosis</td>
</tr>
<tr>
<td>RRMS</td>
<td>Relapsing-remitting Multiple Sclerosis</td>
</tr>
<tr>
<td>PASS</td>
<td>Post-Authorization Safety Study</td>
</tr>
<tr>
<td>PMS</td>
<td>Post Marketing Surveillance</td>
</tr>
<tr>
<td>PPMS</td>
<td>Primary Progressive Multiple Sclerosis</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient-Reported Outcome</td>
</tr>
<tr>
<td>S2k</td>
<td>Consensus-based clinical guideline</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Severe Acute Respiratory Syndrome Coronavirus 2</td>
</tr>
<tr>
<td>SDV</td>
<td>Source Data Verification</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SOC</td>
<td>Standard of Care</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SPMS</td>
<td>Secondary Progressive Multiple Sclerosis</td>
</tr>
<tr>
<td>STROBE</td>
<td>Strengthening the Reporting of Observational Studies in Epidemiology</td>
</tr>
<tr>
<td>TSQM</td>
<td>Treatment Satisfaction Questionnaire for Medication</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
1 Abstract

Title
A non-interventional study evaluating Kesimpta® (ofatumumab) treatment effects in patients with relapsing multiple sclerosis transitioning from other therapies [KAIROS]

Version and date
v01 (13-OCT-2022)

Name and affiliation of main author

Rationale and background
Multiple sclerosis (MS), one of the most common causes of neurological disability in young adults, is the prototypic acquired inflammatory demyelinating condition of the central nervous system (CNS), characterized by inflammation, demyelination and axonal/neuronal destruction, ultimately leading to severe disability in the majority of patients.

In its pivotal studies, ofatumumab demonstrated significant reduction on inflammatory activities as well as reduction in disability progression in patients with RMS as compared to teriflunomide in both treatment-naive and pre-treated patients, in addition to having a favorable safety profile (Hauser, Bar-Or et al. 2020). Ofatumumab (Kesimpta®) is approved in the EU for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features. This includes both newly diagnosed patients and patients already treated with a different DMT. In real-life clinical routine a treatment switch from another DMT is often triggered not only due to efficacy failure but rather due to safety or tolerability reasons and even poor adherence. For example in real world setting, more than 50% of patients discontinue dimethyl fumarate (DMF) within 2 years due to lack of efficacy and/or tolerability (Eriksson, Cars et al. 2018). Safety or tolerability considerations can occur after some time (as e.g. after at least 6 months of treatment as represented in the ARTIOS clinical trial, NCT: NCT04353492 ) or right after switching to a new therapy (e.g. after switching to Droximelfumarat).

It is acknowledged in the Kesimpta® EPAR assessment report that patients treated with a different DMT who decide to switch from the current DMT due to safety or tolerability considerations would not formally fulfil the “activity” criterion at the time of switching the DMT. However, the EPAR states the fact that these patients currently receiving a DMT for controlling the MS inflammatory activity could be considered as a “proxy” of fulfilment of an “activity” criterion because it can be assumed that (i) these patients needed to be active at the time the first DMT was prescribed and (ii) a patient whose inflammatory activity is adequately controlled by a DMT intended to control this activity might not be without.

This led to the conclusion in the EPAR that patients switching to ofatumumab from their current DMT due to safety or tolerability considerations could have also a positive benefit-risk profile and thus are commonly considered in-label patients. Furthermore, in the context of siponimod reimbursement, the NHS England also acknowledged treatment with a DMT might mask disease activity which might therefore be undetectable.

However, prospective real-world evidence data on ofatumumab patients switching their current DMT are still lacking. The current study will close this data gap, describe the currently poorly defined population of tolerability/safety switcher in detail and address relevant clinical practice questions on efficacy and safety of ofatumumab in routine clinical practice as well as PRO of patients who are transitioning from other DMTs due to safety or tolerability issues but also lack of efficacy or due to other reasons such as
adherence. This will address increasing numbers of open questions from HCPs and therefore be beneficial for improving optimal patient management not only in Germany but also provide interesting data for other countries.

In addition, we explore the utility of biomarkers (e.g. NfL) of disease progression and for treatment monitoring in MS in centers where this is part of clinical routine.

Research question and objectives

Primary objectives: Description of patient populations depending on the reason for recent treatment switch, e.g. loss of effectiveness of previous DMT, tolerability considerations with previous DMT (e.g. adverse events), or safety concerns with previous DMT (e.g. due to new medical conditions, new laboratory findings or long term DMT effects). The study will further provide data on safety and efficacy of ofatumumab over a period of one year (max 1.5 years) in a routine medical care setting and assess treatment satisfaction and quality of life using patient reported outcomes (PRO) of patients who are transitioning from other DMTs.

Study design

KAIROS is a prospective, multicenter, non-interventional study (NIS) in Germany. Prospective, primary data will be collected via questionnaires and an electronic case report form (eCRF) over a period of one year (max. 1.5 years) of treatment. Additionally, medical history of participants will be collected including disease duration, EDSS, MRI parameters and relapses.

Approximately 300 patients across 40 study sites will be enrolled into the study. Patients who previously received any approved DMT for RMS in Germany, and the decision to transition to ofatumumab therapy due to safety, tolerability, efficacy or other reasons was taken, will be eligible for enrollment.

The decision for ofatumumab as routine medical treatment must be taken independently of and prior to the study start. During the observation phase of the study, data will be collected according to standard of care as recommended by KKNMS (Competence Network Multiple Sclerosis in Germany).

The prospective observational period per patient will be up to approx. one year from the time of consent (1 year ± 2 months visit window + potentially 6 months follow-up to confirm disability worsening in patients who showed increase in EDSS within 6 months prior to EOS). The observational period will not be dictated by the protocol. The follow-up documentation will take place at a frequency defined as per investigator’s discretion. The diagnostic or monitoring procedures are only those ordinarily applied to the therapeutic strategy and to routine clinical care, can be performed as telemedicine visits and will take place as per investigator’s discretion.

Temporary treatment interruption or permanent treatment discontinuation (along with a valid date of last dose) will be recorded in the eCRF. All patients that have not permanently discontinued the treatment shall be counted as being on treatment (except patients that are lost to follow up). A treatment is considered interrupted if one or more injections are missed (according to entry in the adherence questionnaire or eCRF). A treatment is considered to be discontinued permanently if the physician documents this accordingly in the eCRF. Patients, who permanently discontinue ofatumumab treatment will be excluded from the study.

Setting and study population

This study aims to reflect the real-world situation of MS patients who initiate ofatumumab treatment after switching their prior DMT due to efficacy or other reasons (e.g. safety, tolerability, patient wish). 300 adult patients with planned ofatumumab treatment for RMS as routine medical treatment initiation or ofatumumab treatment initiation within the past 14 days may be enrolled in the study upon signing an informed consent.
Outcomes of this study will retrospectively be compared with data of the ARTIOS trial (NCT04353492, virtual comparison). For that purpose, visit time points and relevant endpoints of KAIROS have been aligned to ARTIOS.

Participants eligible for inclusion in this study must meet all of the following criteria:

1. Written informed consent must be obtained before participating in the study
2. Diagnosis of RMS per McDonald Criteria (2017) (Thompson, Banwell et al. 2018)
3. Prior treatment with EU approved DMT for MS other than ofatumumab
4. Decision for treatment initiation of ofatumumab (Kesimpta®) prior to study participation and planned initiation of ofatumumab after respective wash-out period of prior DMT (if applicable) or performed initiation of ofatumumab within the last 14 days
   • Decision for therapy switch mainly due to lack of efficacy of previous DMT based on physicians’ discretion
   • Decision for therapy switch mainly due to other reasons (e.g. safety or tolerability considerations, patient wish, non-adherence with previous DMT or physician’s choice)
5. Ofatumumab treatment in line with the German label

In patients switching due to safety or tolerability considerations, inflammatory activity is often adequately controlled by the DMT therefore the “activity” criterion at the time of switching the DMT might not be formally fulfilled. However, documentation of lack of disease activity resulting from prior DMT can be considered a “proxy” of fulfilment of meeting an “activity” criterion according to EPAR (European Public Assessment Report)

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Use of investigational drugs during the study, OR within 3 months before ofatumumab initiation, OR within 5 half-lives of investigational drug before ofatumumab initiation, OR until the expected pharmacodynamic effect has returned to baseline, whichever is longer
2. Subjects who are not able to provide consent due to incapable judgement
3. Simultaneous participation in any investigational trial or simultaneous participation in another Novartis-sponsored non-interventional study with ofatumumab

Variables

- Demographics
- Anamnesis
- Vital signs
- Physical examination information
- Laboratory outcomes
- MS disease activity status (incl. MRT assessments)
- Reason for recent therapy switch
- Information on study drug
- Concomitant medication
- Adverse events and serious adverse events
- Patient reported outcomes
  - MS Health Resource Utilization Survey (MS-HRS)
  - Fatigue Scale for Motor and Cognitive Functions (FSMC)
  - Multiple Sclerosis Impact Scale 29 (MSIS-29)
  - Treatment Satisfaction Questionnaire for Medication (TSQM, Version 1.4)
Data sources

Overall, a baseline documentation ± 14 days from ofatumumab initiation and up to 3 follow-up
documentations (with the third one being necessary only to confirm disability worsening in patients who
showed increase in EDSS within 6 months prior to EOS) up to 1.5 years (+ 2 months visit window) after
enrollment may be documented.

Designated site staff will enter the clinical data into the eCRF. Patient questionnaires will be completed
by the patient via a tablet at study site, via web-based eCRF or on paper.

Study size

The primary objective of this study is to describe the different patient populations depending on the
reason for their recent treatment switch. 300 patients will be enrolled into this study. All patients will be
treated with ofatumumab.

It is expected that in about 40% of patients the decision for therapy switch might be due to safety or
tolerability issues and in about 30% of patients this decision might be due to lack of efficacy of previous
DMT. Other reasons for treatment switch might include patient wish, physician’s decision, prior non-
compliance, etc. A sample size of 300 patients total allows to estimate these proportions with a precision
(=radius of the 95% confidence interval) of about ±5%. A similar precision will be achieved for the
assessment of adherence and persistence to ofatumumab in a setting of routine medical care.

Data analysis

All data will be analyzed by a designated CRO. Any data analysis carried out independently by the
treating physician(s) should be submitted to Novartis before publication or presentation. Details on the
analysis will be specified in the Statistical Analysis Plan, which will be finalized prior to any data base
lock for any analysis (interim or final).

All data will be analyzed descriptively. Exploratory subgroup analyses will be applied to identify factors
that may influence primary and secondary endpoints.

Interim analyses will be carried out regularly during the course of the study. These interim analyses
serve as the basis for publications of the first study results. The results of these interim analyses are not
expected to change the conduct of the study. The results might lead to corrective actions with regards
to recruitment if an unbalanced study population (e.g. no variety in reasons for recent treatment switch)
is observed in order to guarantee sufficient data for the primary endpoint.

Additionally, data will retrospectively compared to data from the ARTIOS trial (NCT04353492). This
virtual comparison will be purely descriptive, the aim is to describe and to discuss differences between
the (experimental and therefore possibly somewhat artificial) RCT-setting of the ARTIOS- and the RWE-
setting of the KAIROS population, with respect to both, (baseline-) patient characteristics and outcomes.

Milestones

Planned dates of study milestones:

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Planned date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of data collection</td>
<td>-OCT-2022</td>
</tr>
<tr>
<td>End of data collection</td>
<td>30-JUL-2025</td>
</tr>
<tr>
<td>Interim report 1</td>
<td>1-JUN-2023</td>
</tr>
<tr>
<td>Milestone</td>
<td>Planned date</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Interim report 2</td>
<td>1-FEB-2024</td>
</tr>
<tr>
<td>Final report of study results</td>
<td>31-APR-2026</td>
</tr>
</tbody>
</table>
2 Amendments and updates

None.

3 Milestones

Table 3-1 Planned dates of study milestones

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Planned date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of data collection</td>
<td>OCT-2022</td>
</tr>
<tr>
<td>End of data collection</td>
<td>30-JUL-2025</td>
</tr>
<tr>
<td>Interim report 1</td>
<td>1-JUN-2023</td>
</tr>
<tr>
<td>Interim report 2</td>
<td>1-FEB-2024</td>
</tr>
<tr>
<td>Final report of study results</td>
<td>31-APR-2026</td>
</tr>
</tbody>
</table>

4 Rationale and background

4.1 Background

Multiple sclerosis

Multiple sclerosis (MS), one of the most common causes of neurological disability in young adults, is the prototypic acquired inflammatory demyelinating condition of the central nervous system (CNS), characterized by inflammation, demyelination and axonal/neuronal destruction, ultimately leading to severe disability in the majority of patients. According to the Central Research Institute of Ambulatory Health Care in Germany, a total of 223,000 patients with statutory health insurance were treated for MS in 2015. Assuming that the 8% of privately insured patients in Germany have a similar prevalence, this would add up to around 240,000 MS patients in Germany (Holstiege 2017).

Currently, MS disease course can be grouped into two corresponding main MS categories:

- relapsing MS (RMS), comprising clinically isolated syndrome, relapsing-remitting MS (RRMS) and active secondary progressive MS (SPMS), and
- progressive MS, comprising SPMS and primary progressive MS (PPMS).

Ofatumumab

While the immunopathogenesis of MS remains to be fully elucidated, selectively targeting B cells with anti-CD20 monoclonal antibodies, has been proven highly effective at limiting disease activity in patients with relapsing forms of MS (Hauser, Bar-Or et al. 2017, Bar-Or, Grove et al. 2018, Hauser, Bar-Or et al. 2020).

Ofatumumab is a fully human anti-CD20 monoclonal antibody that selectively depletes CD20+ B- and T-cells, which prevent migration to the CNS and the formation of inflammatory lesions. In its pivotal studies, ofatumumab demonstrated significant reduction on inflammatory activities as well as reduction in disability progression in patients with RMS as compared to
teriflunomide in both treatment-naive and pre-treated patients, in addition to having a favorable safety profile (Hauser, Bar-Or et al. 2020). Ofatumumab (Kesimpta®) is approved in the EU for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features. This includes both newly diagnosed patients and patients already treated with a different DMT.

**Treatment switches**

In real-life clinical routine a treatment switch from another DMT is often triggered not only due to efficacy failure but rather due to safety or tolerability reasons and even poor adherence. For example in real world setting, more than 50% of patients discontinue dimethyl fumarate (DMF) within 2 years due to lack of efficacy and/or tolerability (Eriksson, Cars et al. 2018). Safety or tolerability considerations can occur after some time (as e.g. after at least 6 months of treatment as represented in the ARTIOS clinical trial, NCT04353492) or right after switching to a new therapy (e.g. after switching to Diroximelfumarat).

It is acknowledged in the Kesimpta® EPAR (European public assessment report) assessment report that patients treated with a different DMT who decide to switch from the current DMT due to safety or tolerability considerations would not formally fulfil the “activity” criterion at the time of switching the DMT. However, the EPAR states the fact that these patients currently receiving a DMT for controlling the MS inflammatory activity could be considered as a “proxy” of fulfilment of an “activity” criterion because it can be assumed that (i) these patients needed to be active at the time the first DMT was prescribed and (ii) a patient whose inflammatory activity is adequately controlled by a DMT intended to control this activity might not be without.

This led to the conclusion in the EPAR that patients switching to ofatumumab from their current DMT due to safety or tolerability considerations could have also a positive benefit/risk profile and thus are commonly considered in-label patients. Furthermore, in the context of siponimod reimbursement, the NHS England also acknowledged treatment with a DMT might mask disease activity which might therefore be undetectable.

### 4.2 Purpose and Rationale

Prospective real-world evidence data on ofatumumab patients switching their current DMT (especially for reasons other than loss of effectiveness of previous DMT) are still lacking. The current study will close this data gap, describe the currently poorly defined population of tolerability/safety switcher in detail and address relevant clinical practice questions on efficacy and safety of ofatumumab in routine clinical practice. The study will further assess patient reported outcomes (PRO) of patients who are transitioning from other DMTs due to safety or tolerability issues but also lack of efficacy or due to other reasons such as adherence. This will address increasing numbers of open questions from HCPs and therefore be beneficial for improving optimal patient management.

In addition, we explore the utility of biomarkers (e.g. NfL) of disease progression and for treatment monitoring in MS in centers where this is part of clinical routine.
5 Research question and objectives

5.1 Primary objective

- Description of patient population depending on the reason for recent treatment switch as well as comprehensive description of switch reasons, e.g. loss of effectiveness of previous DMT, tolerability considerations with previous DMT (e.g. adverse events), or safety concerns with previous DMT (e.g. due to new medical conditions, new laboratory findings or long term DMT effects)

5.2 Secondary objectives

- To assess adherence and persistence to ofatumumab in a setting of routine medical care
- To evaluate the impact of ofatumumab on quality of life and treatment satisfaction of RMS patients using PROs (MSIS, FSMC, TSQM V1.4) after switch from the prior DMT in a routine medical care setting depending on reason for treatment switch
- To assess resource utilization of RMS patients after switch from the prior DMT using PROs (MS-HRS)
- To assess the effect of ofatumumab on clinical parameters of MS in a routine medical care setting depending on reason for treatment switch
- To assess the effect of ofatumumab on NEDA-3 and its individual components depending on reason for treatment switch
- To confirm and evaluate the safety of ofatumumab routine medical care setting
- Characterization of serum biomarkers including NfL and immunophenotyping in patients treated with ofatumumab

6 Research methods

6.1 Study design

KAIROS is a prospective, multicenter, non-interventional study (NIS) in patients being treated for RMS with ofatumumab in clinical routine in Germany. Prospective, primary data will be collected via questionnaires and an electronic case report form (eCRF) over a period of one year (max. 1.5 years) of treatment (for more details refer to 6.1.3). Additionally, medical history of participants will be collected including disease duration, EDSS, MRI parameters and relapses. The current assumption is that the study cohort will include

- Patients switching mainly due to lack of effectiveness of prior DMT
- Patients switching mainly due to other reasons (e.g. safety considerations, tolerability issues, patient wish, non-compliance with prior DMT or physician’s choice)

Approximately 300 patients across 40 study sites who previously received any approved DMT for RMS in Germany, and for who the decision to transition to ofatumumab therapy due to
efficacy or other reasons (e.g. safety considerations, tolerability issues, patient wish, non-compliance with prior DMT or physician’s choice) was taken independently of and prior to study start, will be eligible for enrollment upon signing an informed consent.

The decision for treatment switch must be taken independently to and prior to the study start and the reason for this recent treatment switch will be documented by the physician based on the patient’s medical history. During the observation phase of the study, data will be collected according to standard of care as recommended by KKNMS (Competence Network Multiple Sclerosis in Germany).

Data will retrospectively be compared to data from the ARTIOS trial (NCT: NCT04353492). This virtual comparison will be purely descriptive, the aim is to describe and to discuss differences between the (experimental and therefore possibly somewhat artificial) RCT-setting of the ARTIOS- and the RWE-setting of the KAIROS population, with respect to both, (baseline-) patient characteristics and outcomes.

**Figure 6-1  Study design**

Non-interventional study to observe patients switching due to safety or tolerability considerations vs. disease activity. Outcomes of all subgroups will be retrospectively compared with data of the ARTIOS trial (NCT: NCT04353492; virtual comparison). For this purpose, visit time points and relevant endpoints of KAIROS have been aligned with ARTIOS.

* Start of ofatumumab 14 days prior to 14 days after ICF possible
**Additional follow-up visit only to confirm disability worsening in patients who showed increase in EDSS within 6 months prior to 48-week EOS visit. Visit not necessary for patients discontinuing the study early.

**Table 6-1  Planned study timelines**

| Planned start of the observational phase | October 2022 |
| Planned end of the enrollment phase     | October 2023 |
| Planned end of the observational phase  | Juli 2025    |
6.1.1 **DMTs for RMS observed in this study**

Ofatumumab will be observed within this study.

<table>
<thead>
<tr>
<th>Table 6-2 Study treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name and Strength</strong></td>
</tr>
<tr>
<td>Ofatumumab 20 mg</td>
</tr>
</tbody>
</table>

6.1.2 **Enrollment**

The prerequisite for participation in this observational study is the independent decision of the treating physician and patient to start ofatumumab therapy for RMS as routine medical treatment. This decision must have been made prior to enrollment in this study.

Only patients who are treated according to local SmPC are admitted to this study.

Enrollment for this study is limited to 1 year or 300 patients, whichever occurs first.

In case of unbalanced representation of switch reasons, Novartis reserves the right to limit enrollment of patients switching due to specific reasons (e.g. disease activity) in order to obtain sufficient numbers of patients with other switch reasons for a meaningful analysis.

6.1.3 **Observational period**

The prospective observational period per patient will be up to approx. one year from the time of consent (1 year ± 2 months visit window + potentially 6 months follow-up to confirm disability worsening in patients who showed increase in EDSS within 6 months prior to 48-weeks visit). The observational period will not be dictated by the protocol. The follow-up documentation will take place at a frequency defined as per investigator’s discretion. The diagnostic or monitoring procedures are only those ordinarily applied to the therapeutic strategy and to routine clinical care, they can be performed as telemedicine visits and will take place as per investigator’s discretion.

Temporary treatment interruption or permanent treatment discontinuation (along with a valid date of last dose) will be recorded in the eCRF. All patients that have not permanently discontinued the treatment shall be counted as being on treatment (except patients that are lost to follow up). A treatment is considered interrupted if one or more injections are missed (according to entry in the adherence questionnaire or eCRF). A treatment is considered to be discontinued permanently if the physician documents this accordingly in the eCRF. Patients, who permanently discontinue ofatumumab treatment will be excluded from the study.

During the observation phase, clinical parameters, the results of patient reported outcomes on quality of life, treatment satisfaction and health-economic parameters and further parameters as described in Table 6-5 are recorded. The observational period for a single patient ends with the end of study documentation approx. 1 year after enrollment (1 year ± 2 months visit window) or 1.5 years after enrollment, in case a follow-up visit is needed (1 year ± 2 months visit window + potentially 6 months follow-up to confirm disability worsening in patients who showed
increase in EDSS within 6 months prior to EOS). The overall study ends when there is no longer any active patient in the observational phase, at the latest 1.5 years after the last patient has been enrolled. This means that patients included at the end of the enrollment period will have a shorter visit window for documentation of their last visit and that the last patient enrolled can be documented until exactly 1.5 years after enrollment. Given that the safety reporting period is 100 calendar days after the patient’s last visit, any safety related event can be reported in the eCRF up to 100 days after the patient’s last visit.

6.1.4 Treatment interruption or discontinuation
Temporary treatment interruption or permanent treatment discontinuation (along with a valid date of last dose) will be recorded in the eCRF. All patients that have not permanently discontinued the treatment shall be counted as being on treatment (except patients that are lost to follow up). A treatment is considered interrupted if one or more injections are missed (according to entry in the adherence questionnaire or eCRF). A treatment is considered to be discontinued permanently if the physician documents this accordingly in the eCRF. Patients, who interrupt ofatumumab treatment should remain in this study. Patients, who permanently discontinue ofatumumab treatment cannot be documented any further in this study.

6.1.5 Early termination
Patients must be excluded from the observational study if:
- they withdraw their consent/oppose to use their data
- they permanently discontinue ofatumumab treatment
- they have not been to the practice or clinic for at least 12 months and no phone contact was performed

Should the participation of a patient be terminated prematurely, the date of the termination, the reason for the termination, the date of the last ofatumumab injection, the (planned) follow-up therapy and any adverse events in the following 100 days after the therapy discontinuation should be noted.

For participants whose status is unclear because e.g. they fail to appear for visits (“lost to follow up”), the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to contact the patient in order to understand the primary reason for the patient’s decision and record this information.

6.2 Inclusion and Exclusion criteria

6.2.1 Inclusion criteria
Participants eligible for inclusion in this study must meet all of the following criteria:
1. Written informed consent must be obtained before participating in the study.

2. Diagnosis of RMS per McDonald Criteria (2017) (Thompson, Banwell et al. 2018)

3. Prior treatment with EU approved DMT for MS other than ofatumumab

4. Decision for treatment initiation of ofatumumab (Kesimpta®) prior to study participation and planned initiation of ofatumumab after respective wash-out period of prior DMT (if applicable) or performed initiation of ofatumumab within the last 14 days
   a. Decision for therapy switch mainly due to lack of efficacy of previous DMT based on physicians' discretion
   b. Decision for therapy switch mainly due to other reasons (e.g. safety or tolerability considerations, patient wish, non-adherence with previous DMT or physician’s choice)

5. Ofatumumab treatment in line with the German label
   In patients switching due to safety or tolerability considerations, inflammatory activity is often adequately controlled by the DMT therefore the “activity” criterion at the time of switching the DMT might not be formally fulfilled. However, documentation of lack of disease activity resulting from prior DMT can be considered a “proxy” of fulfilment of meeting an “activity” criterion according to EPAR (European Public Assessment Report)

6.2.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Use of investigational drugs during the study, OR within 3 months before ofatumumab initiation, OR within 5 half-lives of investigational drug before ofatumumab initiation, OR until the expected pharmacodynamic effect has returned to baseline, whichever is longer

2. Subjects who are not able to provide consent due to incapable judgement

3. Simultaneous participation in any investigational trial or simultaneous participation in another Novartis-sponsored non-interventional study with ofatumumab

6.3 Endpoints

6.3.1 Primary Endpoints

- Description of reasons for recent therapy switch to ofatumumab as well as description of the respective patient populations

Description of reasons for recent therapy switch will focus on qualitative aspects including the summary and comprehensive characterization of main reasons for therapy switch and listing of additional supporting reasons.
6.3.2 Secondary Endpoints

- Proportion of missed ofatumumab doses within one year, defined as the difference between number of planned doses and number of administered doses
- Reasons for, number of and duration of treatment interruptions per patient
- Characterization of patient subgroups with and without 100% adherence, defined as patients with matching number of planned doses and number of administered doses within 1 year (e.g., previous experience with sub-cutaneous therapy)
- Proportion of patients permanently discontinuing ofatumumab during the study, reasons for discontinuation and planned next DMT
- Treatment effect of ofatumumab on the impact of multiple sclerosis as measured by MSIS-29 as compared to baseline in general and depending on reasons for treatment switch
- Treatment satisfaction with ofatumumab as measured by TSQM 1.4 as compared to baseline in general and depending on reasons for treatment switch
- Changes in fatigue scores as measured by fatigue questionnaire (FSMC) compared to baseline in general and depending on reasons for treatment switch
- Percentage of patients with no clinical evidence of disease activity (clinical NEDA; NEDA is defined by no confirmed MS relapse, no new or enlarging T2 lesions, no Gadolinium-positive T1 lesions, and no six-month confirmed disability worsening) at 6 and 12 months as compared to baseline
- Proportion of patients demonstrating NEDA-3 and its individual components at 12 months as compared to baseline
- The proportion of subjects discontinuing treatment due to insufficient effectiveness (lack of effectiveness) or tolerability/safety reasons
- Description of general safety and tolerability
- Occurrence, proportion and persistence of drug-related adverse events (AEs) including those of special interest (main focus on injection site reactions such as scarring, skin reactions, influenza-like symptoms)
- Specific safety assessment of injection related AEs (i.e. injection site reaction AEs vs. injection systemic reaction AEs) summarized by providing the number and percentage of patients with each of the symptoms and pre-specified grouping of symptoms as well as overall. These summaries will be provided for each injection and cumulatively for all injections.
6.3.3 Exploratory Endpoints

- *Only in centers where this test is clinical routine:* To describe population dynamics of the innate and adaptive immune cell repertoire under ofatumumab treatment
- *Only in centers where this test is clinical routine:* To characterize the dynamic of serum biomarkers in patients treated with ofatumumab
- Mean annual health care resource utilization cost, annual direct medical costs, annual direct nonmedical costs and annual indirect costs as measured by MS Health Resource Utilization Survey [MS-HRS] (Ness, Haase et al. 2020)

6.4 Variables

6.4.1 Baseline documentation

The following variables may be documented at baseline:

- Demographics including age, sex, ethnicity, working status, and status of health insurance
- Anamnesis including
  - Date of first MS symptoms
  - Date of first MS diagnosis
  - Number and date of previous MS relapses
  - Medical history and current medical conditions
- Vital signs including
  - Height
  - Weight
  - Pulse rate
  - Systolic and diastolic blood pressure
- Physical examination information
- Laboratory outcomes
- MS disease activity status
  - EDSS total score or per functional domain
  - MRI parameters (number of T1 and T2 lesions, presence of spinal lesions)
  - Relapse status
  - NEDA3 status
- Information on recent treatment switch
  - Main reason for recent treatment switch (loss of effectiveness of previous DMT, safety considerations, tolerability consideration, patient wish, physician’s decision, etc.)
  - Specification of main reason for recent treatment switch
  - Additional reasons supporting treatment switch decision
- Information on study treatment
• Reason for choosing ofatumumab
• Dose, frequency and route of administration
• Start date
• Batch number

• Concomitant medication
• Adverse events and serious adverse events

6.4.2 Remaining documentations

The following variables may be documented at documentation time points after the baseline documentation.

• Changes in demographics (working status only)
• Vital signs including
  • Weight
  • Pulse rate
  • Systolic and diastolic blood pressure
• Physical examination information
• Laboratory outcomes
• MS disease activity status
  • EDSS total score or per functional domain
  • MRI parameters (number of T1 and T2 lesions, presence of spinal lesions)
  • Relapse status including date, duration, treatment, intensity and recovery of relapses
  • NEDA3 status

• Information on study treatment
  • Date of last injection
  • Batch number
  • Changes, interruptions and permanent discontinuation of treatment (if applicable)
    • Number and duration of temporary treatment interruptions
    • Reasons for temporary treatment interruptions
    • Date of permanent discontinuation of treatment
    • Reasons for permanent discontinuation of treatment
    • Name, dose, frequency, route of administration, start date of planned DMT (for switch patients only)
• Concomitant medication
• Adverse events and serious adverse events
• Patient reported outcomes
  • MS Health Resource Utilization Survey (MS-HRS)
  • Fatigue Scale for Motor and Cognitive Functions (FSMC)
  • Multiple Sclerosis Impact Scale 29 (MSIS-29)
  • Treatment Satisfaction Questionnaire for Medication (TSQM, Version 1.4)
  • performed injections and batch number

6.4.3 Description of selected variables

MS relapse definition

Appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event (Polman et al 2011). The abnormality must have been present for at least 24 hours and occurred in the absence of fever (< 37.5°C) or a known infection.

Expanded Disability Status Scale (EDSS)

EDSS is a widely used and accepted instrument to evaluate disability status at a given time and, longitudinally, to assess accumulation of disability in clinical studies in MS. The EDSS scale consists of scores in each of seven functional systems (FSs) and an ambulation score that are then combined to determine the EDSS steps (ranging from 0 (normal) to 10 (death due to MS)). The FSs are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral functions (Fatigue contributes) (Kurtzke, 1983).

A 3-month confirmed disability worsening (3mCDW) is defined as an increase from Baseline in EDSS sustained for at least 3 months (Table 6-3). Analogously, a 6-month confirmed disability worsening (6mCDW) is defined as an increase from Baseline in EDSS sustained for at least 6 months.

A 6-month confirmed disability improvement (6mCDI) is defined as a decrease from baseline EDSS sustained for at least 6 months (Table 6-4).

EDSS values to confirm progression or improvement must not be determined during an relapse. The maximum duration of a relapse is limited to 90 days.

<table>
<thead>
<tr>
<th>Table 6-3</th>
<th>Criterion for disability worsening based on change in EDSS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total EDSS at Baseline</td>
<td>“Disability worsening” criterion</td>
</tr>
<tr>
<td>0</td>
<td>≥ +1.5</td>
</tr>
<tr>
<td>1 to 5</td>
<td>≥ +1</td>
</tr>
<tr>
<td>≥ 5.5</td>
<td>≥ +0.5</td>
</tr>
</tbody>
</table>
Table 6-4  
Criterion for disability improvement based on change in EDSS score

<table>
<thead>
<tr>
<th>Total EDSS at Baseline</th>
<th>“Disability improvement” criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1.5</td>
<td>No improvement possible</td>
</tr>
<tr>
<td>≥2 to 6</td>
<td>≤ -1</td>
</tr>
<tr>
<td>≥6.5 to 9.5</td>
<td>≤ -0.5</td>
</tr>
</tbody>
</table>

Multiple sclerosis health resource utilization survey (MS-HRS)

The MS-HRS is a validated questionnaire that allows for a holistic and longitudinal assessment of resource utilization of MS patients (Ness, Haase et al. 2020).

This 24-item questionnaire covers societal resource use, regardless of the issue of reimbursement, as well as impact of the disease on work, family and leisure. With the help of this questionnaire a monetary value can be assigned to e.g. the stage of MS, a relapse or a therapy.

Fatigue Scale for Motor and Cognitive Functions (FSMC)

Fatigue in the context of multiple sclerosis (MS) is a complex symptom with still unknown pathophysiology. The Fatigue Scale for Motor and Cognitive Functions (FSMC) is a 20 item scale developed as a measure of cognitive and motor fatigue for people with MS. Sensitivity and specificity scores allow reliable assessment and the statistically identified cutoff values provide detailed quantification of fatigue in clinical routine. The tool has been extensively validated in different languages, and practice settings. Improving fatigue in patients with MS is difficult and drug trials have shown mixed results. Given the high impact on employment and quality of life, the scale will be utilized.

Multiple Sclerosis Impact Scale (MSIS-29)

The Multiple Sclerosis Impact Scale (MSIS-29) version 2 (Hobart and Cano 2009) will be used to assess health-related quality of life. MSIS-29 is a 29-item, self administered questionnaire that includes two domains, physical and psychological. Responses are captured on a 4-point scale ranging from “not at all” (1) to “extremely” (4), where higher scores reflect greater impact on day-to-day life.

It is a clinically useful and scientifically sound measure of the impact of MS from the subject's perspective suitable for clinical trials and epidemiological studies (Hobart, Lamping et al. 2001). It is considered a reliable, valid and responsive PRO measure that complements other indicators of disease activity used to improve the understanding of the impact of MS.

The questions in the scale ask the subjects for their views about the impact of MS on their day-to-day life during the past 2 weeks. The MSIS-29 takes approximately 5 minutes to complete, and will be translated into the appropriate language of the subject.

Treatment Satisfaction Questionnaire for Medication (TSQM, Version 1.4)

The Treatment Satisfaction Questionnaire for Medication (TSQM, Version 1.4) will be used to psychometrically evaluate the patients’ satisfaction with ofatumumab treatment. The TSQM is
a sound and valid measure of the major dimensions of patients’ satisfaction with medication and a good predictor of adherence across different types of medication and patient population. The TSQM Version 1.4 comprises 14 items across four domains focusing on effectiveness (3 items), side effects (5 items), convenience (3 items), and global satisfaction (3 items) of the medication over the previous 2–3 weeks, or since the subject’s last use. With the exception of item 4 (presence of side effects; yes or no), all items have 5 or 7 responses, scored from 1 (least satisfied) to 5 or 7 (most satisfied). The 7-item scales had a non-neutral midpoint, such that there were more positive response options than negative response options, to allow precise information to be obtained at the upper end of the score distribution. Item scores are summarized to give four domain scores, which are in turn transformed to a scale of 0–100. For the purpose of the study, medication side effects will be only captured via the AE reporting form to avoid inconsistency in data capture.

6.5 Data sources

This is an observational, non-interventional study where prospective, primary data of clinical routine is documented. Additionally, as part of anamnesis, retrospective data on medical history is documented from patient files.

Overall, a baseline documentation ±14 days from ofatumumab initiation and up to 3 follow-up documentations (with the third one being necessary only to confirm disability worsening in patients who showed increase in EDSS within 6 months prior to EOS) up to 1.5 years (+2 months visit window) after enrollment may be documented.

Intervals for documentation in this study protocol may not reflect actual visits at the center.

Patients fulfilling the study criteria will be enrolled on a consecutive basis. Patient records at the sites will be regarded as source data. Sites will be monitored as described in the monitoring plan. No additional laboratory tests or physical examinations that exceed the regular treatment of the patient will be needed.

Designated site staff will enter the clinical data into the eCRF. The investigator must certify that the data entered are complete and accurate.

Patient questionnaires will be completed by the patient via a tablet at study site, via web-based eCRF or on paper. Questionnaires will be checked by the investigator for remarks hinting at an otherwise unreported adverse event. In case of such an adverse event the investigator needs to follow the procedures of adverse event reporting within 24 hours.

Patients will be asked to report adverse events to their treating physician/study site.

Concomitant or prior medications entered into the database will be coded using the World Health Organisation (WHO) Drug Reference List. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Safety data will be transferred to Novartis at a frequency as defined in Section 8.1.3 of this protocol and/or CRO contract. Clinical data will be transferred to Novartis after closure of the study.
Data collection schedule

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study. The treating physician is asked to complete the appropriate eCRF at every patient visit recommended by the data collection schedule.

Below is the recommended data collection schedule that most likely mirrors the patterns of routine clinical care of most patients being treated with ofatumumab.

For patients who discontinue prematurely, the reason for discontinuation should be determined.
## Table 6-5  Data collection

<table>
<thead>
<tr>
<th>Documentation number</th>
<th>Baseline</th>
<th>Visit 2</th>
<th>Visit 3 (EOS)</th>
<th>Additional follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timepoint (relative to Baseline)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/Exclusion criteria</td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information &amp; Informed consent</td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demography¹</td>
<td>X</td>
<td>(X)</td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td>Anamnesis²</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vital signs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td>Pulse rate</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td><strong>Physical examination³</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory examination⁴</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(X)**</td>
<td>(X)</td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td><strong>MS disease activity status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS⁵</td>
<td>(X)**</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)***</td>
</tr>
<tr>
<td>Relapses⁵</td>
<td>(X)**</td>
<td>(X)</td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>(X)**</td>
<td>(X)</td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td>NEDA</td>
<td>(X)**</td>
<td>when MRI is available</td>
<td>when MRI is available</td>
<td></td>
</tr>
<tr>
<td><strong>Concomitant medication</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X*****</td>
</tr>
</tbody>
</table>

(X) upon discretion of the treating physician

¹ Demographics include age, sex, ethnicity, working status and status of health insurance.

² Anamnesis includes date of first MS symptoms and diagnosis, medical history, current medical conditions and reason for recent treatment switch of MS therapy to ofatumumab.

³ Physical examination includes an assessment of skin, head and neck, lymph nodes, heart, lungs, abdomen, back, neurological function and comments on general appearance.

⁴ Laboratory evaluations may include e.g. (differential) blood count, serology (Hepatitis B, SARS-CoV2), immune status (CD19+ B cells, CD20+ cells, CD3+ cells, CD4+ T-cells, CD8+ T-cells, immunophenotyping, total IgG, total IgM) and NfL if assessed in clinical routine at study site. For baseline visit, laboratory values collected no more than 6 months before and +2 months after the informed consent signature can be documented. For follow-up visits, values collected no more than ±2 month to the visit date can be documented.

⁵ For baseline visit, the EDSS score evaluation no more than 4 months before and +2 months after the informed consent signature can be documented. For follow-up visits, the EDSS evaluation no more than ±2 month to the visit date can be documented.

⁶ Relapse status includes information of date, duration, treatment, intensity and recovery of relapse.
7 = Working status only.
* To be done before any study-related activities
** Prior ofatumumab treatment.
*** Only to confirm disability worsening in patients who showed increase in EDSS
**** If patients stop ofatumumab treatment during follow-up period, AEs need to be reported until 100 calendar days after the patient discontinued ofatumumab treatment

6.6 Study size

300 patients will be enrolled into this study. All patients will be treated with ofatumumab.

It is expected that in about 40% of patients the decision for therapy switch might be due to safety or tolerability issues and in about 30% of patients this decision might be due to lack of efficacy of previous DMT. Other reasons for treatment switch might include patient wish, physician’s decision, prior non-compliance, etc. A sample size of 300 patients total allows to estimate these proportions with a precision (= radius of the 95% confidence interval) of about ±5%. A similar precision will be achieved for the assessment of adherence and persistence to ofatumumab in a setting of routine medical care.

6.7 Data management

Designated site staff will enter the clinical data into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff. The Investigator must certify that the data entered into the eCRF is complete and accurate.

Patient questionnaires will be completed by the patient via a tablet at the study site or via a web-based eCRF. The patient adherence questionnaire can be completed by the patient on paper. Further details will be defined in the Data Management Plan.

6.8 Data analysis

As this is an observational study, data analysis will based on descriptive methods. Mean, median, standard deviation and range will be displayed for continuous variables (e.g. PROs) and proportions with (descriptive CIs) will be displayed for proportions/categorical variables (e.g. proportion of patients who switch for certain reasons). Exploratory subgroup analyses will be applied to identify factors that may influence primary and secondary endpoints. Additionally, data will retrospectively compared to data from the ARTIOS trial (NCT04353492). This virtual comparison will be purely descriptive, the aim is to describe and to discuss differences between the (experimental and therefore possibly somewhat artificial) RCT-setting of the ARTIOS- and the RWE-setting of the KAIROS population, with respect to both, (baseline-) patient characteristics and outcomes. Details on the analysis will be specified in the Statistical Analysis Plan, which will be finalized prior to any data base lock for any analysis (interim or final).
All data will be analyzed by a designated CRO. Any data analysis carried out independently by the treating physician(s) should be submitted to Novartis before publication or presentation. Interim analyses will be carried out regularly during the course of the study. These interim analyses serve as the basis for publications of the first study results. The results of these interim analyses are not expected to change the conduct of the study or the patient population. The results might lead to corrective actions with regards to recruitment if an unbalanced study population (e.g. no variety in reasons for recent treatment switch) is observed in order to guarantee sufficient data for the primary endpoint.

6.8.1 Statistical Analysis Plan
The designated CRO will provide a detailed statistical analysis plan prior to the first data base lock of the study including
- Specification of statistical database on which analysis is based
- Definition of subcohorts to be analyzed
- Specification of (interference) statistical procedures

6.8.2 Population to be analyzed
All patients who have received at least one ofatumumab injection and for whom at least one documentation is available are included in the evaluation.

For Per-Protocol set efficiency analyses of permanently discontinued patients, a definition for “on treatment” as data till last dose of the drug + dosing frequency shall be applied (ofatumumab last dose date + 30 days). If a patient is switching treatments and the switch happens earlier than the dosing frequency window, then one should include data until the switch date.

For safety analysis of permanently discontinued patients, a +100 days cutoff (as used in all ofatumumab global studies) should be applied. If the patient switches to another treatment, then the cutoff will be the day before the switch treatment initiation (if earlier).

6.9 Quality control
All quality assuring measures as part of data management will be defined in a separate data management plan (DMP) and data validation plan (DVP) and specified for the following phases:
- Automated plausibility check as part of data entry
- Data query plan, catalogue with questions leading to queries at the study site
- Implementation of audit trail according to FDA CFR21 part 11 standard
- Securing of data integrity by documented database lock
- Data handling report to handle database lock. This will be part of the SAP
- All data management processes are based on the CROs SOPs which must fulfill GxP standards
6.9.1 Data quality management

The designated CRO will assure database quality processes are followed including review of the data entered into the eCRF by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

6.9.2 Data recording and document retention

In all scenarios, the physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the CRF must be traceable to these source documents in the patient’s file.

The physician must give Novartis (or designee) access to all relevant source documents to confirm their consistency with the CRF entries. No information in source documents about the identity of the patients will be disclosed.

The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant). Informed consent forms must not be shared with the sponsor and local data privacy policies apply.

6.9.3 Site monitoring

Formal site monitoring will be performed as described in the Monitoring Plan for this study.

On-site monitoring is performed at least once a year for each participating active study center in compliance with the applicable data protection legislation to assure the confidentiality of the patient's personal data. Objectives of the Source Data Verification (SDV) to be performed as part of the monitoring are:

- Check for the presence of the patient's written informed consent
- Reconciliation of documentation data and source data for the following variables:
  - Demographic data
  - Medical history, mainly reason for switch of recent MS therapy
  - Date of visits inclusive the performed assessments
  - PROs
  - Documentation of (S)AEs
  - Concomitant medications

Remote monitoring will also be performed as described in the Monitoring Plan for this study.

Monitoring is performed by representatives of Novartis. All Field Monitors will be trained, mentored, and managed according to Novartis policies and procedures. The results of the SDV are documented in the monitoring report.

6.10 Limitations of the research methods

For this non-interventional study general limitations of non-interventional studies apply. This includes interpretation of the data, heterogeneity, and bias of the study population as well as incomplete data. By applying narrow inclusion and exclusion criteria the heterogeneity of the
study population shall be reduced to a minimum. Through the visit schedule as a suggestion for a structured and regular documentation of data as well as monitoring visits to check data integrity, the best possible data quality and least possible bias shall be ensured.

7 Protection of human subjects

This is a non-interventional study where data is documented during routine visits of participating patients. No additional visits, examinations or treatments are performed for the purpose of this study. Therefore, it is to be expected that no additional risk exists for participants.

Data privacy

Protection of data privacy is assured in this study. All documented parameters of this study will be documented in pseudonymized form in the eCRF i.e. with a unique patient identifier not containing name, initials, date of birth or address of the participant.

In case of publication, personal data may only be used in anonymized form.

Personal data may only be accessed by authorized persons with confidentiality obligations of the sponsor or authorities if this is required to ensure an orderly performance of the study.

Personnel documenting data from patient files in the eCRF has to be informed of their data privacy obligations.

Patient numbering

Novartis or the designated CRO will assign a unique number to the study site.

Each participating patient will be identified by a unique patient number. This patient number will be automatically generated when documenting basic parameters of the baseline visit in the eCRF. Each patient number will only be assigned to one patient.

For the identification of a patient within the scope of monitoring processes, the investigator must keep a separate identification list enabling linking patient numbers with name, age and date of birth of the patients. This list must remain at the study site.

Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2007), and with the ethical principles laid down in the Declaration of Helsinki.
Informed consent procedures

The physician must keep the original informed consent form signed by the patient (a signed copy is given to the patient).

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/EC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient’s representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to treating physicians or other involved medical professionals in a separate document a proposed informed consent form that complies with the Declaration of Helsinki principle and regulatory requirements and is considered appropriate for this study.

8 Management and reporting of adverse events/adverse reactions

8.1 Adverse event collection and reporting

8.1.1 Definition

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A serious adverse event (SAE) is defined as an AE which:

- Results in death or is life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
  - Social reasons and respite care in the absence of any deterioration in the patient’s general condition
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g.
may require treatment on an emergency outpatient basis for an event not fulfilling any of
the definitions of a SAE given above and not resulting in hospital admission

Note: Transmission of infectious disease via medication is considered to be a serious adverse
reaction and should be reported and assessed as medically significant in the absence of other
seriousness criteria.

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and
unintended. An ADR implies at least a reasonable possibility of a causal relationship between
a medicinal product and an adverse event.

The Novartis drug of interest evaluated in this study is: Kesimpta® (ofatumumab).

8.1.2 AE collection

All AEs from all patients enrolled in the study must be collected and recorded in the study
database, irrespective of seriousness or causal association.

The occurrence of AEs should be sought by non-directive questioning of the patient at each
visit during the study. AEs may also be detected when they are volunteered by the patient during
or between visits or through physical examination, laboratory test, or other assessments.
Medical conditions/ diseases ongoing before starting treatment with a study drug are only
considered AEs if they worsen after starting the study drug.

All AEs must be recorded on the AE case report form (eCRF) with the following information:
1. the severity grade (mild, moderate, severe)
2. its relationship to the drugs of interest (suspected/not suspected)

For assessment of causality between a drug and the reported adverse event, the following
options could be chosen: “not suspected” or “suspected”. Causality assessment must be
performed and documented by a physician for every event. In addition, we would like to
draw your attention to the fact that several different aspects could play a role in causality
assessment, e.g. individual patient, underlying disease(s), concurrent diseases as well as
concomitant medication or even drug-free treatments.

Not suspected: There is no reasonable possibility of causal relationship between
adverse event and medicinal product.
Suspected: There is a reasonable possibility of causal relationship between adverse
event and medicinal product.

3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a SAE
5. whether it constitutes an injection reaction related (S)AE

Injection reaction related (S)AEs could be assessed as either injection site reaction (S)AE
or injection systemic reaction (S)AE. Only reactions/symptoms within 24 hours after
injections should be assessed as injection reaction related (S)AE (i.e., time to onset of
reaction <= 24 hours).
In addition, all reports of the following special scenarios, whether or not associated with AEs, are also collected and reported in the same manner as AEs:

- Drug-drug or drug-food interaction
- Drug use during lactation
- Lack of efficacy
- Overdose
- Intentional drug abuse and misuse
- Medication errors including drug maladministration
- Dispensing or prescribing errors
- Drug dependence or addiction
- Withdrawal reaction/ syndrome or rebound symptoms
- Unexpected beneficial effect
- Treatment non-compliance (with clinical symptoms)

**Note:** Occupational or accidental exposure, for example of study personnel or family members of the patient should be reported to Novartis as a spontaneous report as well as, if required, to the responsible drug commission according to code of medical ethics.

Any action taken with study drug or addition of treatment medication as a result of an AE should be recorded on the AE form in the eCRF. Some examples to be recorded are: no action taken (i.e., further observation only); study drug dosage adjusted/ temporarily interrupted; study drug permanently discontinued due to this AE.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common adverse effects already known about the study drugs can be found in the locally available labeling document for the approved indication under evaluation in this study.

Batch number of the drug taken at the time of the AE must be recorded on the AE form in the eCRF.

In case an SAE is not previously documented in the labeling document for the study, a Novartis Patient Safety associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

Hospital discharge summaries as well other reports or lab value reports in the context of an adverse event should be sent on request only.

### 8.1.3 AE reporting of (serious) adverse event and special scenarios

Information about all AEs (serious and non-serious) that occurred in patients exposed to the Novartis drug of interest, irrespective of causality, is captured in individual eCRF of each patient. Study site documents all SAE within 24 hours of becoming aware of it, non-serious events within 10 calendar days of becoming aware of it.
Information about SAE would be forwarded to Novartis Patient Safety or responsible CRO directly after saving the information in eCRF by study site. Information about non-serious AEs is forwarded by responsible CRO to Novartis Patient Safety through periodic batch extraction of non-serious AEs from the study database (at least weekly).

Batch number of the DMT taken at the time of the AE must be provided on the (S)AE reporting form in the eCRF.

Exception: If SAE documentation within eCRF is not possible due to technical reasons or other reasons, complete the SAE Report Form and send the completed, signed form by fax/ email within 24 hours to the responsible CRO:

The original copy of the SAE Report Form and the fax confirmation sheet or the email must be kept with the CRF documentation at the study site.

In case of incomplete information at the time of initial knowledge, this information should be completed as soon as possible and reported as follow-up report.

In case an adverse event is incomplete or is considered to be of particular interest, a Novartis Patient Safety associate or associate of responsible may seek additional information concerning the event. Corresponding questionnaires will then be provided by Novartis Patient Safety to the treating physician or other involved health care professional on a case-by-case basis.

In case an SAE is not previously documented in the labeling document for the study, a Novartis Patient Safety associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

Hospital discharge summaries as well other reports or lab value reports in the context of an adverse event should be sent on request only.

**Exposure during pregnancy**

Any occurrence of a pregnancy in a patient exposed to the Novartis drug of interest must be reported to within 24 hours of learning of its occurrence. The pregnancy should be followed-up to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.
Information about the pregnancy should be recorded on the Pregnancy Form and reported by the treating physician or other involved HCP to [BLANK]. In case of any congenital abnormality, birth defect or maternal and newborn complications, the possible relationship to the Novartis drug should be reported.

Additionally, any SAE/non-serious AE experienced during pregnancy must be collected in the eCRF and reported to [BLANK] following the respective reporting routes described in this section.

**Abnormal lab values and test results**

Abnormal lab values and test results should be reported as **adverse event** only if:

- there is deterioration of the relevant parameter in comparison to baseline finding (baseline visit). This condition is not relevant in case there is no value in baseline visit.

AND

- changed lab value
  - is assessed as medically significant **OR**
  - is in conjunction with clinical signs or symptoms **OR**
  - requires therapeutic intervention **OR**
  - results in dosage reduction and/or temporary halt or permanent discontinuation of drug if interest.

In these scenarios it should be documented as adverse events within the eCRF.

Abnormal lab values should be documented as **SAE** if

- formal criteria of SAE are fulfilled (see SAE definition)
- defined limits of the relevant parameter were undershot or exceeded.

**Protocol-exempt events**

The following events are defined as “exempt” from collection and entry into the safety database because they are anticipated in the patient population and/or represent study endpoints:

- Disease progression of underlying disease which is investigated in the context of this NIS has not to be documented as AE or SAE in the context of this NIS except there is a fatal outcome.

- Occurrence of MS relapses during treatment with Novartis drug of interest has to be documented as adverse event only in case a causal relationship with disease-modifying treatment is suspected. MS relapses have to be documented as serious adverse events (SAE) only if treating physician assessed MS relapse as exceptionally severe, atypical or with unexpected clinical course although formal SAE criteria (e.g. hospitalization) were fulfilled.

Any exempted event which is suspected to the Novartis drug of interest (i.e. an Adverse Drug Reactions, ADR) may be reported by the investigator to Novartis Patient Safety as a
spontaneous report as well as to the responsible drug commission according to code of medical ethics.

**Patient questionnaires (e.g. quality of life questionnaires)**

Answers to the validated and standardized patient questionnaires (MS-HRS, MSIS-29, TSQM Version 1.4, FSMC, and adherence questionnaire) have not to be documented additionally as adverse event. These answers are describing the underlying clinical picture as well as clinical course of the disease and will be analyzed and presented separately. Participating physician, however, will review filled questionnaires - also in comparison to filled questionnaire in previous visit - regarding additional (hidden) adverse events which have to be documented as adverse events.

Additional information provided by patient (beyond the questionnaire layout) has to be screened by participating physician and, if required, (S)AEs have to be documented in eCRF.

**Safety reporting for Novartis drugs other than the Novartis drugs of interest and for non-Novartis drugs**

Adverse Drug Reactions (ADRs) occurring in patients exposed to a Novartis drug other than the Novartis drugs of interest, can be reported to the responsible drug commission according to code of medical ethics or to Novartis Patient Safety as a spontaneous report.

All adverse reactions identified for non-Novartis drugs should be reported to the responsible drug commission according to code of medical ethics or the Marketing Authorization Holder as these will not be recorded in the Novartis safety database.

**Follow-up information**

Recurrent episodes, complications, or progression of the initial event must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within the same timelines as defined for initial information. Any event that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Follow-up information is sent to the same contact person to whom the initial information was sent, stating, where an AE report form is used, that this is a follow-up to the previously reported event and providing the date of the original report. If known, the information missing from the initial report should be completed. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

In case an SAE is not previously documented in the labeling document for the study a Novartis Patient Safety associate or [redacted] associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

In case an adverse event is considered to be of particular interest, a Novartis Patient Safety associate or [redacted] associate may seek additional information concerning the event. Corresponding questionnaires will then be provided by Novartis Patient Safety or
to the treating physician or other involved health care professional on a case-by-case basis.

### Safety reporting period

Every SAE, exposure during pregnancy, non-serious AE and special scenario, regardless of causality assessment must be reported within the eCRF:

- after the patient has provided informed consent. If treatment with ofatumumab was already started up to 14 days before informed consent, every above mentioned event must be reported retrospectively since treatment start date.
- until 100 calendar days after the patient discontinued the Novartis drug of interest during the study conduct or until 100 calendar days after the last patient last visit if the patient is still receiving the Novartis drug of interest.

Special scenario for exposure during pregnancy during treatment with Kesimpta® (ofatumumab):

- Reports about exposure during pregnancy during treatment with Kesimpta® (ofatumumab) must be reported to Novartis/CRO after informed consent is obtained until 6 months after patient discontinued treatment with Kesimpta® (ofatumumab).

Any SAEs, pregnancies, non-serious AEs and special scenarios experienced after the period mentioned above should only be reported to Novartis if the investigator suspects a causal relationship to the Novartis drugs of interest.

### 9 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines. Additionally several interim analyses will be performed and results will be published at medical congresses and/or in medical journals.

### 10 References


