

Study Protocol

Tofacitinib Registry of patients with ulcerative colitis in Germany

(TOFA_{UC}-Registry)

Documentation of Tofacitinib Induction and Maintenance Therapy in conjunction with long-term outcome and predictors of response

Registry design: Investigator initiated non-interventional research (IIR)

Date: Mai 31st 2019

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Initiation: July 01th, 2019

End of recruitment: March 31st, 2021 (scheduled)

Observation period: 2 years of outcome monitoring, until March 31st, 2023

This study project is executed by "Competence Network Intestinal Diseases e.V.", Kiel.

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CEO Competence Network Intestinal Diseases e.V..

Date

1. Introduction

This registry on Tofacitinib and biologics (anti-integrin/anti-TNF) in the treatment of ulcerative colitis (UC) patients in Germany will extend the prospective documentation of safety issues and efficacy in induction and maintenance therapy of Tofacitinib (Xeljanz®) in addition to other biologics used in Germany with a particular interest in predictors of long-term responses and favorable disease outcome or to predict severe side effects caused by therapy with Januskinase(JAK)-inhibitors/biologics.

2. Background to the registry

The use of biologics and other immunomodulatory small molecules in UC patients is increasing; the new therapy with Tofacitinib introduces a new opportunity in UC therapy, however, up to now, no data are available on the efficacy and safety of small molecules like Tofacitinib – a JAK-inhibitor - in Germany in a real world situation. Therefore, a registry documentation of Tofacitinib (Xeljanz) is proposed to evaluate efficacy and potential side effects under real world use as well as predictors of response.

3. Aims of the registry

Primary registry objective

The aim of this registry is the prospective collection of data on the course of patients with Tofacitinib / biologics therapy in the "Real World Setting" to get insights in efficacy and safety which is relevant for the selection of the respective drugs in therapy.

The primary endpoint is steroid-free remission (remission: partial Mayo score ≤ 1 plus a bleeding subscore of 0) in the inductionphase (week 16). For this endpoint it will be only captured if there is a current use of steroids at the time of the visit. So the patient will be asked for current steroid use at time of visit at week 16 and if he has received steroids within the last 4 weeks prior to time point of the visit. As there is no common standard or definition of this endpoint in daily practice this is the most appropriate way to collect this data in non-interventional observational research.

Secondary registry objectives:

The collection of secondary objectives will be done under "Real World Conditions" to the extent that normal ongoing therapy requires normal treatment control.

1. Online documentation of safety and efficacy in induction and maintenance therapy including the occurrence of serious side effects (e.g., death, tumor, tuberculosis, severe infections, or side effects leading to hospitalization)
2. Efficacy (response: partial Mayo Score reduction of ≥ 3 accompanied by a decrease of at least 30% from baseline and remission: partial Mayo score ≤ 1 plus a bleeding subscore of 0) of induction therapy (week 8 and 16) and maintenance therapy (months 6 to 24) and efficacy (response and remission) in different subpopulations, e.g. based on a previous biologic therapy or not.
3. Obtaining health economic data in UC patients on Tofacitinib / biologics therapy (hospitalization, disability, treatment costs, quality of life, early retirement).
4. Obtaining data of the course from UC patients with a new therapy (Tofacitinib / biologics) related to treatment strategy and psychosocial impairments

Data with regard to additional registry objectives (supplementary subgroup analyzes), will only be captured in the normal routine in the course of UC-patients' treatment and in connection with routinely planned contacts at the ibd-center:

This is a non-interventional, observational registry, where patients are treated only regarding the following rules:

- The medicinal product is prescribed in the usual manner in accordance with the approved label,
- The assignment of the patient to a particular treatment has to be done in advance to and independently from the inclusion into this NIS. The decision should be only led by the medical need of the patient and pure medical decision of the treating physician. The in- and exclusion criteria for this registry will be exclusively based on the Summary of Product Characteristics (SmPC).
- The timeframes for visits are non-binding suggestions on the base of recommended timeframes in the SmPC or standard of care procedures.
- No additional diagnostic or monitoring procedures beyond respective recommendations in the SmPC or standard of care procedures will be applied to patients and epidemiological methods are used for the analysis of collected data.

The safety and efficacy of induction and maintenance therapy of Tofacitinib and other biologics are assessed in several relevant subgroups of UC patients. Most planned analyzes are descriptive:

1. Safety and efficacy of Tofacitinib in comparison with other biologics: comparison of groups with different pretreatments (e.g., biologics-naïve and biologics-experienced UC-patients or also compared to immunosuppressive drugs in pre-treatment).
2. Effects of Tofacitinib and other biologic therapies on the number of proctocolectomies and hospitalizations

3. Treatment dynamics according to the mode of treatment over time (e.g., change in proportion of Tofacitinib and first-time use of biologics in biologic naive UC patients)

4. Registry design

This is an Investigator-initiated non-randomized, non-interventional observational prospective long-term research (IIR) as part of the normal treatment of UC patients for the safety and efficacy of Tofacitinib / biologic therapies. As of 01st July 2019, UC patients who have been provided Tofacitinib / biologics for UC according the respective label by the treating physician may be prospectively included in an online database by the participating study centers by 31st March 2021.

An interim analysis is planned at the end of patients' recruitment with respect of the induction phase (week 16) for October 2021 with a first publication of the data in a peer-reviewed journal (e.g., JCC, GUT, UEG Journal).

Up to 480 patients (including about 360 UC patients with Tofacitinib and about 120 UC patients with biologics) will be included in the online documentation. A specification to the study centers regarding the group inclusion (patients treated with Tofacitinib (group 1) or a biologics (group 2)) will not be made; this means, each study center can include patients in both groups.

We assume that approximately 20-30% of Tofacitinib patients will be biologic-naïve UC patients, many of whom will represent early disease patients (< 2 years after first diagnosis).

5. Registry conduction

Data will be documented in an online registry-like database. Follow-up documentation in an abbreviated online follow-up form takes place every 6 months during the prospective registry (M6-M24) according to the normal planned clinical visits. In group 1 and 2, the induction phase, (if patient contact occurs within the framework of normal care) will be followed by up to three additional visits (W2, 8, 16) in the first three months after initiation of Tofacitinib / biological therapy. Any medication side effects are also recorded online in an AE / SAE sheet. About 15% of documented cases are monitored by in-house or on-site monitoring. In addition, in the context of the usual care patient contacts, the supervising physician carries out a prospective documentation of the course of the disease at intervals of approximately six months.

6. Selection of registry population

The diagnosis UC is made in accordance with current DGVS/ECCO UC guidelines. Patients for whom the indication of Tofacitinib / biologics therapy has been submitted for medical indication by the treating physician can be entered in the registry. The therapy decision is made by the physician, regardless of and in advance to a potential registry participation.

There are the following inclusion and exclusion criteria:

Inclusion Criteria:

- Patients with moderate to severe Ulcerative Colitis aged 18-80 years at enrollment
- Written informed consent is given

Exclusion Criteria:

- Malignant disease in history (except for non-melanoma skin cancer)
- Any contraindication according to the SmPC of the respective medication

There are two subpopulations:

1. UC-patients (age at enrollment: 18-80 years) receiving a newly introduced Tofacitinib therapy (n=360). Previous treatment(s) with biologics or immunosuppressants is (are) permitted. About 20-30% of the Tofacitinib patients will biologic-naiv.
2. UC-patients (age at enrollment: 18-80 years) receiving a newly introduced biologics therapy (n=120). Previous treatment(s) with biologics or immunosuppressants is (are) allowed.

7. Criteria for selecting participating study sites

The investigator initiated non-interventional research (IIR) is conducted at sites in hospitals or gastroenterology practice sites that have special experience in the treatment of inflammatory bowel disease. Site selection will be directed by the principal investigator.

8. Sample size calculation, Data Monitoring, Data acquisition and statistical evaluation

Sample size calculation:

The sample size calculation is based on the achievement of the primary endpoint (steroid-free remission) at the end of the induction phase. The steroid-free remission rates between a tofacitinib therapy in "real word setting" are compared with a control group in an allocation ratio of 3:1. A total drop out rate of 10% is assumed.

Basic statistical determinations:

- Two independent groups
- Comparison of two unequal ratios to each other (proportions)
- Two-sided test problem (Fisher's exact test)
- Global alpha error of 5%.
- Power 80%
- No adjustment for multiple testing

Group allocation and acceptance of securities

The steroid-free remission rate in the control group is assumed to be 0.45.

The clinically relevant odds ratio (OR) for the primary endpoint was set to at least 1.9.

This results in the following remission rates:

Group 1: IBD on Tofacitinib proportion $p_1 = 0,61$

Group 2: IBD on control proportion $p_2 = 0,45$

Sample size:

Group	Percentage	Sample size	Sample size inclusive 10% „drop out“ Rate*
Tofacitinib	75%	325	360
Control	25%	108	120
Total	100%	433	480

Note: Due to rounding, deviations may occur in the table.

Data Monitoring: A spot-monitoring with full source data verification will be carried out in 10-15% of documented using internal, trained and certified monitors. A site monitoring plan will be drawn up by the principal investigator together with the sponsor. In the induction period, there will be an additional in-house/on-site data probability check. Selected high recruiting study centers will be subjected to an additional on-site monitoring supported by external monitoring personnel. Monitoring will start in a center when at least 10 patients will be recruited.

Data acquisition will be done online on a central server (FORGA Solutions GmbH). Data transfer and evaluation is pseudonymized. Statistical evaluation will be done by FORGA Solutions, Berlin, with the support of the institutes of the principal investigators for specific additional issues and stratification with regard to the number of prior biologics therapies (an appropriate sample size analysis will be performed before each sub-analysis).

Data evaluation is also supported by the Competence Network Intestinal Diseases e.V.. The boxes in the online documentation form are equipped by input logic settings to prevent false entries. The cumulative data, especially the side effects reports, are sent by the study coordinator in a timely manner to the biologics companies funding the registry and semiannually for internal information.

Statistical evaluation will be performed by applying the descriptive methods in terms of frequency tables and statistical values, as average values, standard deviation and quantiles. As graphical methods bar diagrams will be shown with box-and-whisker-plots for quantitative data. Furthermore,

univariate significance tests and inferential statistical methods will be done supported by applicable two-sided asymptotic significance tests and confidence intervals, including chi-square test and Wilcoxon-W test and McNemar's test for comparison of dependent variables. During the analysis of evaluation criteria local significance levels of $\alpha=0.05$ will be controlled instead of global significance levels. No adjustment for multiple tests will be proceeded. Complete evaluation criteria will be exploratory analyzed with no proceeded testing of in advance formulated hypotheses. Accordingly, to these mentioned methods the obtained p-values will be interpreted in terms of Fisher's method: a p-value will be considered as a metric data and the effect is higher the smaller is the p-value. Missing data will not be replaced.

9. Duration of the registry

The registry is planned for a 3.75-year period as a longitudinal investigation. In consultation with study coordination personnel and the funding pharmaceutical company, the registry period may be extended to a longer period than 3.75 years.

10. Study flow of the registry

Starting from July 01th, 2019, patients with UC on a Tofacitinib therapy will be documented in a prospective online documentation form at the participating study sites.

The data will be documented in an online documentation form. After initial documentation at enrollment and during induction (0, 2, 8 and 16 weeks), follow-up documentation using an abbreviated online follow-up form will be requested every 6 months during the longitudinal investigation. Any drug side effects are also captured online on a side effects form.

Endpoints:

The primary endpoint is steroid-free remission (remission: partial Mayo score ≤ 1 plus a bleeding subscore of 0) in the inductionphase (week 16) phase. For this endpoint it will be only captured if there is a current use of steroids at the time of the visit. So the patient will be asked for current steroid use at time of visit at week 16 and if he has received steroids within the last 4 weeks prior to time point of the visit. As there is no common standard or definition of this endpoint in daily practice this is the most appropriate way to collect this data in non-interventional observational research.

Efficacy (response: partial Mayo Score reduction of ≥ 3 accompanied by a decrease of at least 30% from baseline and remission: partial Mayo score ≤ 1 plus a bleeding subscore of 0) of induction therapy (week 8 and 16) and maintenance therapy (months 6 to 24) and efficacy (response and remission) in different subpopulations, e.g. based on a previous biologic therapy or not.

Consecutive patients will be enrolled at the study sites, taking the organizational conditions at the

study sites into account. The main data to be documented is as follows:

1. **Baseline documentation** including demographic data, age, gender, height, weight, nicotine consumption and country of origin:
 - 1.1. History data: date of first diagnosis, involvement pattern (endoscopy and/or capsule endoscopy), extraintestinal manifestations, fistulas, strictures and past surgery.
 - 1.2. Drug history: treatments performed to date, including treatment period and any intolerances.
 - 1.3. Current state of health: symptoms, disease activity, and classification (partial Mayo Score).
 - 1.4. Current medication: documentation of current medication (including NSAIDs), including dosage to calculate drug treatment cost.
 - 1.5. Laboratory markers: documentation of existing laboratory markers like CRP, calprotectin.
 - 1.6. Data from the patient questionnaire on disease course, social impairment, mental situation and medical support.
 - 1.7. Patient quality of life questionnaire.
 - 1.8. vaccination status.

2. **Follow-up documentation** (2, 8 and 16 weeks, 6, 12, 18, 24 months; real times, which are as close as possible to these predetermined by the infusion, injection or control frequency visits in the center). Patients will not be recalled for this observation but will visit the center at these times to receive their infusion / injection / control.

In cases of acute flare or SAE an extra documentation will be triggered (flare-up documentation):

 - 2.1. Current disease findings: clinical picture (and documented endoscopic findings), disease activity (partial Mayo Score).
 - 2.2. Current medication: documentation of current medication (including NSAIDS's), including dosage to calculate cost of drug treatment.
 - 2.3. Laboratory markers: documentation of existing laboratory markers like CRP, calprotectin.
 - 2.4. Data from the patient questionnaire on disease course, social impairment, mental situation and medical care.
 - 2.5. Patient quality of life questionnaire.

3. **AE/SAE report form:** Any adverse events (AEs) or serious adverse events (SAEs) are documented promptly in a dedicated AE/SAE follow-up form. SAE trigger an extra follow up documentation.

11. Registry outline: flow chart

	Baseline documentation	Follow-up documentation	Flare-up documentation	AE / SAE report
Time in months	0	months 6, 12, 18, 24 (+/- 4 wks) (and 3 additional visits (week 2, 8, 16) in the induction therapy)		
Informed consent	√			
Inclusion criteria	√			
Exclusion criteria	√			
Demographics	√			
Case History	√			
Drug history	√			
Patient questionnaire	√	√	(√)	(√)
Current lab markers	√	√	(√)	(√)
Clinical findings	√	√	(√)	(√)
Current medication + dosage	√	√	(√)	(√)
Part. Mayo Score	√	√	(√)	-
Quality of life (EQ-5D)	√	√	(√)	-
AE/SAE-report	√	√	(√)	√
Final evaluation	√	√	√	(√)

12. Adverse events (AEs/SAEs)

Any adverse events (AEs) or serious adverse events (SAEs) are documented immediately at the study site using the AE/SAE follow-up form (SAE-reporting within 24 hours). The physician treating the patient is also obliged to report important drug side effects centrally to the medicines authority (BfArM). The relevant legal requirements (German Drug Law § 29 and 63b following enforcement of the 14th amendment to the German Drug Law) apply in terms of processing adverse drug reactions.

Documented serious adverse events (SAEs) are forwarded within 24 hours (only working days count) to the manufacturer by the documentation center (FORGA Solutions GmbH), stating the treating

documentation center. The companies are also forwarded the anonymized initials of the patient in addition to the relevant study site data in order to enable the companies to ask the study site for any necessary additional data.

12.1. Serious adverse event

An adverse event meeting any of the following criteria qualifies as a serious adverse event (SAE):

Death – An event leading to a patient's death.

Life-threatening – An event that would be fatal without medical intervention. Events that might have been fatal had they been more severe are not serious adverse events.

Hospitalization – An event results in hospitalization for an indefinite period. Outpatient treatment in an emergency room or doctor's office does not count as hospitalization.

Prolongation of hospital stay – An event occurs in a patient during a hospital stay and prolongs the hospital stay.

Genetic damage – Genetic defects discovered during or after birth or defects resulting in miscarriage.

Permanent or significant disability – An event causing major impairment of activities of daily living. Manifestations of minor medical relevance such as headaches, nausea, vomiting, diarrhea, flu and accidents (e.g. a sprained ankle) do not meet this definition of disability.

Conditions requiring medical or surgical intervention to prevent complications – A condition that is not immediately life-threatening or fatal and does not result in hospitalization but which constitutes a medical threat and requires medical treatment to prevent any of the stated complications (e.g. asthma attack, blood condition or seizure).

Spontaneous abortion – A patient sustains a spontaneous abortion.

Planned termination of pregnancy – A patient has a termination of pregnancy.

Investigator's judgment – If an adverse event is very serious in the Investigator's view, this is an SAE.

12.2 Severity rating

The following definitions are used for evaluation of the severity of an adverse event if it is rated as a study endpoint and for all serious adverse events:

Mild – The adverse event is temporary and does not impair the patient.

Moderate – The adverse event causes the patient distress and affects the patient's everyday activities.

Severe – The adverse event significantly impairs the patient's normal activities and causes disability or is life-threatening.

12.3 Rating of causality

Investigators can use the following definitions to rate the causal relationship between an adverse event and a drug, if the event is rated as an endpoint in a study and for all serious adverse events:

Likely – The adverse event occurs in a close temporal association with administration of the drug or recurs after rechallenge, or another cause is less likely or is unlikely.

Possible – The adverse event occurs in a close temporal association with administration of the drug, but, in addition to the potential relationship with the drug, an alternative cause is possible too.

Unlikely – There is no definite temporal association with administration of the drug and/or other causes are more likely.

Unrelated – The adverse event is due to an underlying disease or other drug and is unrelated to the study drug (e.g. there is no temporal association with administration of study drug or another likely cause exists).

If the doctor arrives at a rating of "possible", "unlikely" or "unrelated", an alternative cause needs to be stated.

12.4 Adverse events (AEs)

An adverse event (AE) is any untoward phenomenon occurring in a temporal association with use of a drug/medical device, whether or not it is believed to be related to the drug/medical device. It can also be an untoward and unfavorable phenomenon, for example abnormal blood values.

Starting from the date of onset, all adverse events (AEs) are forwarded within 90 days in a collective report to the relevant pharmaceutical company by the study coordinators (Competence Network Intestinal Diseases e.V.) on the basis of the AE documentation lists of the documentation site (FORGA Solutions GmbH).

13. Documentation fees

The study sites receive a documentation fee per complete baseline/follow-up documentation at the scheduled regular semiannual documentations, which includes payment for blood sampling and

sample shipment for baseline documentation. The cost of any necessary interim flare-up or AE/SAE reports is included in the fee for regular semiannual follow-up documentation. The documentation fee represents fair market value and is based on GOÄ (German physician fee scale) rates. Fees will be paid regardless of the documentation group.

14. Ethics and data protection

The principal investigator and the “Competence Network Intestinal Diseases e.V.”, Kiel, are responsible for the relevant ethics committee opinions and for compliance with data protection requirements. The ethics committee opinion will be elicited from the Ethics Committee of medical faculty of the University of Kiel.

15. Publication of data

It is planned to evaluate and publish the data on a regular basis while the registry is ongoing. An interim analysis will be planned in October 2021 with a first publication of the data in a peer review paper (e.g. JCC, GUT, UEG-Journal). Choice of authors follows the standards of “good scientific practice” (Safeguarding Good Scientific Practice, DFG 2013). The sites with the highest recruitment figures will serve as co-authors in the scientific publication. The data will be presented 1-2 times annually at a symposium or with abstracts at the annual conferences of the DGVs/DGIM or ECCO/UEGW.

16. Appendix

16.1 Partial Mayo Score

English version of the partial Mayo score:

Parameter	Clinical evaluation (single choice)	Score
1. Stool frequency (per day)	<ul style="list-style-type: none">normal number of stools1-2 more than normal3-4 more than normal≥ 5 more than normal	<ul style="list-style-type: none">0123
2. Rectal bleeding (indicate the most severe bleeding of the day)	<ul style="list-style-type: none">nonestreaks of blood with stool in less than half of the casesobvious blood with stools in most casesblood alone passes	<ul style="list-style-type: none">0123
3. Physician's global assessment	<ul style="list-style-type: none">normalmild diseasemoderate diseasesevere disease	<ul style="list-style-type: none">0123

16.2. EQ-5D

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

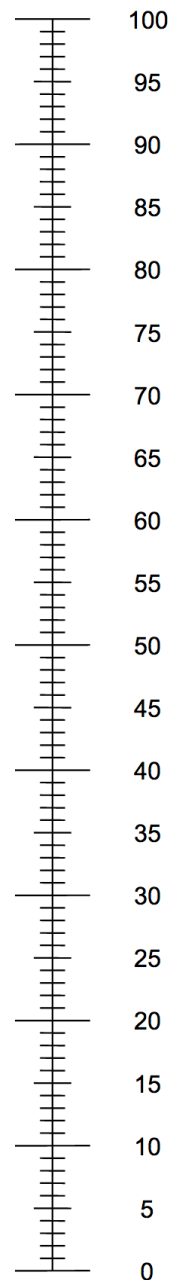
ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

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