# Advanced treatment of ulcerative colitis using an Italian healthcare administrative database: drug utilization patterns, healthcare resource use and costs

## The MICHELANGELO study

**Version 1.1**

**26/04/2021**

## STUDY ESSENTIAL INFORMATION

| | |
|---|---|
| **Title** | **Advanced treatMent of ulceratIve Colitis using an Italian HEaLthcAre admiNistrative database: druG utilization pattErns, heaLthcare resOurce use and costs (the MICHELANGELO study)** |
| **Protocol version** | 1.0 |
| **EU PAS REGISTRY NUMBER** | To be assigned |
| **Version date** | February 28th, 2021 |
| **Active substance object of the study** | o Adalimumab<br>o Infliximab<br>o Golimumab<br>o Vedolizumab<br>o Tofacitinib |
| **Promoter** | Galapagos Biopharma Italy S.r.l. |
| **Research question and objectives** | This study will describe the population of users of advanced treatments for Ulcerative Colitis in Tuscany (Italy) between January 1st 2015 to December 31st 2019, including history of disease modifying anti rheumatic drugs (DMARDs) use, accesses to Emergency Department (ED), hospitalizations, access to specialist gastroenterology encounters by means of real world data. This study will also analyze health direct costs associated with the management of this population when treated with advanced treatment. |
| **Country of study** | Italy |
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# I. List of Abbreviations

ARS: agenzia Regionale di Sanità
ATC: anatomical therapeutic chemical
bDMARD: biologic disease modifying anti-rheumatic drug
csDMARD: conventional synthetic disease modifying anti-rheumatic drug
DMARD: disease modifying anti-rheumatic drug
ED: Emergency department
ENCEPP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ICD: international classification of diseases
IMID: Immuno-mediated inflammatory diseases
JAK: Janus Kinase
JAKi: Janus Kinase Inhibitor
RA: Rheumatoid Arthritis
SSSA: Scuola Superiore Sant'Anna
TNF: tumor necrosis factor
UADRM: Unit of Adverse Drug Reaction Monitoring
UniPi: University of Pisa

## II. Investigators and institutions

| Name | Role in the study | Institution |
|---|---|---|
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| Ersilia Lucenteforte | Principal Investigator | Department of Clinical and Experimental Medicine, University of Pisa (UniPi), Pisa, Italy |

*UADRM and UniPi represent the coordinating centre

## III. Milestones

This is a study conducted on administrative healthcare database. Prospective collection of data is not scheduled. Below a summary of the timeline based on activities and responsibilities.

| **Activity** | **Responsability** | **Expected timeline** |
|---|---|---|
| Complete study protocol | UniPi, SSSA, ARS | April 15th, 2021 |
| Data extraction and data processing | ARS | April 17th, 2021 |
| Data analysis | UniPi, SSSA | April 20th, 2021 |
| Report drafting | UniPi, SSSA | April 25th, 2021 |
| Report reviewing | ARS | April 30th, 2021 |
| Report comments | Galapagos | May 5th 2021 |
| Report finalisation | UniPi, SSSA, ARS | May 15th 2021 |

# 1. BACKGROUND

Ulcerative colitis (UC) is an inflammatory chronic disease primarily affecting the colonic mucosa; the extent and severity of colonic involvement are variable. In its most limited form, it may be restricted to the distal rectum, while in its most extended form the entire colon is involved. However, 80% of the patients present with disease extending from the rectum to the splenic flexure, and only 20% have panicolitis. UC is usually associated with recurrent attacks with complete remission of symptoms in the interim. The disease is more common in Caucasians than in Blacks or Orientals with an increased incidence (three to six fold) in Jewish. Both sexes are equally affected. In Western Europe and in the USA, UC has an incidence of approximately 6 to 8 cases per 100.000 populations and an estimated prevalence of approximately 70 to 150 per 100.000 populations.

While the cause of UC remains unknown, a number of findings in recent years point to an overstimulation or inadequate regulation of the mucosal immune system as a major pathophysiologic pathway, and particular emphasis has been given to either the study of mucosal inflammation or immunologic reactions. When the disease is active, the *lamina propria* of the mucosa becomes heavily infiltrated with a mixture of acute and chronic inflammatory cells. There is a predominant increase in mucosal IgG production, evidence of complement activation, and activation of macrophages and T cells. This immunological activity is associated with the release of a vast array of cytokines, kinins, leukotrienes, platelet activating factor (PAF) and reactive oxygen metabolites. These mediators not only serve to amplify the immune and inflammatory response, but they also have direct effects on epithelial function, on endothelial function, and on repair mechanisms, thus increasing collagen synthesis. In addition, many of the cytokines (IL-1, IL-6, TNF) will activate an acute phase response, resulting in fever and a rise in serum acute phase proteins. [Ungaro et al., 2017; Gajendran et al., 2019]

Treatment of UC should be guided by severity, behavior, disease localization, appearance of complications, treatment refractoriness and dependency to steroids. In addition, the treatment of UC is divided also into drugs inducing remission and those for maintenance of remission. Traditional pharmacological therapies of UC are based on synthetic small molecules, which include: mesalazine and other derivatives of the 5-aminosalycilic acid; corticosteroids; thiopurines (azathioprine, 6-mercaptopurine); methotrexate; cyclosporine [Burri et al., 2020; Danese et al., 2020]. Based on the available data, patients with mild-to-moderate distal UC may be treated with either oral mesalazine, topical mesalazine, or topical steroids. Patients refractory to all of the above agents may require treatment with oral prednisone in doses up to 40-60 mg/day. For maintenance of remission, mesalazine suppositories or enemas are effective, as well as oral mesalazine or sulfasalazine, whereas topical corticosteroids have not proven effective for maintaining remission in distal UC. Patients with mild-to-moderate extensive UC should begin therapy with oral sulfasalazine or mesalazine. Oral corticosteroids are generally useful for patients who are refractory to oral mesalazine with or without topical therapy. 6-Mercaptopurine or azathioprine are effective for patients who do not respond to oral prednisone, but are not so acutely ill as to require intravenous therapy. In these patients, when the acute attack is controlled, a maintenance regimen is usually required. Sulfasalazine or mesalazine are effective in reducing relapses. As a rule, patients should not be treated chronically with corticosteroids. Azathioprine or 6-mercaptopurine may be useful as steroid-sparing agents for steroid-dependent and steroid-resistant patients, and for maintenance of remission not adequately sustained by mesalazine. Patients with severe UC refractory to maximal oral treatment with prednisone, oral salicylates, and topical medications, or patients, who present with toxicity, should be treated for 7-10 days with intravenous corticosteroids. Failure to demonstrate significant improvement within 7-10 days is an indication for either colectomy or treatment with intravenous cyclosporine [Burri et al., 2020; Danese et al., 2020].

At present, several biologics are also available ads advanced therapy for the treatment of UC. These include: TNF inhibitors (infliximab, adalimumab, golimumab); anti-integrin (vedolizumab) and JAk inhibitors (tofacitinib)[Burri et al., 2020; Danese et al., 2020; Gledhill & Bodger, 2013; Scribano, 2018].

There exists only limited knowledge about the real-world treatment of UC patients with biologics and other advanced therapies in Italy. This relates to the proportion of patients receiving such a treatment, previous treatments prescribed before the start of such a therapy, specific agents prescribed, agents' dosage in the induction as well as the maintenance phase, and treatment associated healthcare resources utilization and cost. A recent Ingress-Health claims data study looked at rates of treatment discontinuations of biologics by specifically comparing anti-TNFs with Vedolizumab and described respective treatment patterns [Mevius 2018; Brandes 2019]. A substantial percentage of patients discontinued the therapy early, 12-month persistence was not higher than 60-70% of the patients, and in up to 40% of patients it could be assumed that even after start of a biologic therapy there was still substantial IBD disease activity observable, as measured primarily by concomitant corticosteroid use. However, very recent data including tofacitinib covering above topics are not available.

This study aims to report these data of UC-patients on advanced therapies in Tuscany, a region of 3.7 million inhabitants in Italy. As advanced therapies, the following agents are addressed:

- Adalimumab
- Infliximab
- Golimumab
- Vedolizumab
- Tofacitinib

## 2. RESEARCH QUESTIONS AND OBJECTIVES

1. What was the history of utilization of drugs with possible use in UC (see table 2) in new users of any advanced treatments for UC in Tuscany between January 1st, 2015 to December 31st, 2019?
2. What is the utilization pattern of drugs for UC within one or two years in new users of any advanced treatment for UC in Tuscany between January 1st, 2015 to December 31st, 2019?
3. What was the pattern of Healthcare utilization (Emergency Department access, Hospitalization, access to specialist visits) within one or two years after initiating any advanced treatment for UC in Tuscany?
4. What was the estimated cost per patient/year within one or two years after initiating an advance treatment for UC in Tuscany?

## 3. RESEARCH METHODS

### 3.1 Study design

This is a descriptive, retrospective cohort study.

### 3.2 Data source

Data will be retrieved from administrative healthcare databases of Tuscany. Particularly, the study will use records of hospital discharge (cause of hospitalization [ICD-9 code], date of hospitalization and discharge, cost of hospitalization), of emergency department admission (cause of Ed admission [ICD-9 code], date of ED admission and discharge, cost of Ed admission), of drug dispensations (drugs [ATC codes], gender, birth date, dates of drug dispensation, drug doses, drug costs), and of specialist encounters (rheumatologic visits, date of rheumatologic visits, cost of visits) [Trifirò, 2018]. Data will be linked among the different databases using an anonymous unique patient code.

### 3.3 Cohorts definition

#### 3.3.1 Tofacitinib cohort

**Inclusion criteria**

Patients will be new users of tofacitinib between January 1st, 2015 and December 31st, 2019 AND with a diagnosis OR a co-payemnt exemption code for UC in the lookback period or in the follow up OR a visit in a gastroenterological ward (code: 058) in the year before the index date. Index date will be the date of the first supply. We define new users each subject without supply of tofacitinib in the look-back period (5 years before the index date). Patients will be followed up for one or two years after the index date.

**Censoring:** Death

**Follow-up:** from the index date to death or one/two years after the index date (last follow-up date is December 31st, 2020)

**Exclusion criteria**

a) Patients with less than 5 years of records in the look back period

b) Patients with less than 1 year of follow-up

c) Patients receiving more than one of the advanced therapy (table 1) at the index date

d) patients with a diagnosis or a co-payment exemption code for Crohn's disease, rheumatoid arthritis, psoriasis, multiple sclerosis (G35.-), axial spondyloarthritis and ankylosing spondylitis (M45.-), psoriatic arthritis (L40.-), hidradenitis suppurativa / acne inversa (L73.2), uveitis intermedia, uveitis posterior und panuveitis (H20.-, H30.-) at any time in the look-back period. This criterion will identify only patients with prompt record (clinically relevant conditions)

e) patients aged ≤ 18 at index date

f) patients with records of visits in rheumatology ward (071) or dermatology ward (052) in the 1 year before the index date

### 3.3.2 Adalimumab cohort

**Inclusion criteria**

Patients will be new users of an adalimumab between January 1st, 2015 and December 31st, 2019 AND with a diagnosis OR a co-payment exemption code for UC in the lookback period or in the follow up OR a visit in a gastroenterology ward (code: 058) in the year before the index date. Index date will be the date of the first supply. We define new users each subject without supply of adalimumab in the look-back period (5 years before the index date). Patients will be followed up for one or two years after the index date.

**Censoring:** Death

**Follow-up:** from the index date to death or one/two years after the index date (last follow-up date is December 31st, 2020)

**Exclusion criteria**

a) Patients with less than 5 years of records in the look back period

b) Patients with less than 1 year of follow-up

c) Patients receiving more than one of the advanced therapy (table 1) at the index date

d) patients with a diagnosis or a co-payment exemption code for Crohn's disease, rheumatoid arthritis, psoriasis, multiple sclerosis (G35.-), axial spondyloarthritis and ankylosing spondylitis (M45.-), psoriatic arthritis (L40.-), hidradenitis suppurativa / acne inversa (L73.2), uveitis intermedia, uveitis posterior und panuveitis (H20.-, H30.-) at any time during in the look-back period. This criterion will identify only patients with prompt record (clinically relevant conditions)

e) patients aged ≤ 18 at index date

f) patients with record of use of oral budesonide (box 1) in the 5 years before cohort entry

g) patients with records of visits in rheumatology ward (071) or dermatology ward (052) in the 1 years before cohort entry

### 3.3.3 Golimumab cohort

**Inclusion criteria**

Patients will be new users of an golimumab between January 1st, 2015 and December 31st, 2019 AND with a diagnosis OR a tax exemption code for UC in the lookback period or in the follow up OR a visit in a gastroenterology ward (code: 058) in the year before the index date. Index date will be the date of the first supply. We define new users each subject without supply of golimumab in the look-back period (5 years before the index date). Patients will be followed up for one or two years after the index date.

**Censoring:** Death

**Follow-up:** from the index date to death or one/two years after the index date (last follow-up date is December 31st, 2020)

**Exclusion criteria**

a) Patients with less than 5 years of records in the look back period

b) Patients with less than 1 year of follow-up

c) Patients receiving more than one of the advanced therapy (table 1) at the index date

d) patients with a diagnosis or a co-payment exemption code for Crohn's disease, rheumatoid arthritis, psoriasis, multiple sclerosis (G35.-), axial spondyloarthritis and ankylosing spondylitis (M45.-), psoriatic arthritis (L40.-), hidradenitis suppurativa / acne inversa (L73.2), uveitis intermedia, uveitis posterior und panuveitis (H20.-, H30.-) at any time during in the look-back period. This criterion will identify only patients with prompt record (clinically relevant conditions)

e) patients aged ≤ 18 at index date

f) patients with records of visits in rheumatology ward (071) or dermatology ward (052) in the 1 years before index date

### 3.3.4 Infliximab cohort

**Inclusion criteria**

Patients will be new users of an infliximab between January 1st, 2015 and December 31st, 2019 AND with a diagnosis OR a co-payment exemption code for UC in the lookback period or in the follow up OR a visit in a gastroenterology ward (code: 058) in the year before the index date.. Index date will be the date of the first supply. We define new users each subject without supply of infliximab in the look-back period (5 years before the index date). Patients will be followed up for one or two years after the index date.

**Censoring:** Death

**Follow-up:** from the index date to death or one/two years after the index date (last follow-up date is December 31st, 2020)

**Exclusion criteria**

a) Patients with less than 5 years of records in the look back period

b) Patients with less than 1 year of follow-up

c) Patients receiving more than one of the advanced therapy (table 1) at the index date

d) patients with a diagnosis or a co-payment exemption code for Crohn's disease, rheumatoid arthritis, psoriasis, multiple sclerosis (G35.-), axial spondyloarthritis and ankylosing spondylitis (M45.-), psoriatic arthritis (L40.-), hidradenitis suppurativa / acne inversa (L73.2), uveitis intermedia, uveitis posterior und panuveitis (H20.-, H30.-) at any time during in the look-back period. This criterion will identify only patients with prompt record (clinically relevant conditions)

e) patients aged ≤ 18 at index date

f) patients with record of use of oral budesonide (box 1) in the 5 years before cohort entry

g) patients with records of visits in rheumatology ward (071) or dermatology ward (052) in the 1 years before index date.

### 3.3.5 Vedolizumab cohort

**Inclusion criteria**

Patients will be new users of an vedolizumab between January 1st, 2015 and December 31st, 2019 AND with a diagnosis OR a tax exemption code for UC in the lookback period or in the follow up OR a visit in a gastroenterology ward (code: 058) in the year before the index date. Index date will

be the date of the first supply. We define new users each subject without supply of infliximab in the look-back period (5 years before the index date). Patients will be followed up for one or two years after the index date.

**Censoring:** Death

**Follow-up:** from the index date to death or one/two years after the index date (last follow-up date is December 31st, 2020)

**Exclusion criteria**

a) Patients with less than 5 years of records in the look back period

b) Patients with less than 1 year of follow-up

c) Patients receiving more than one of the advanced therapy (table 1) at the index date

d) patients with a diagnosis or a co-payment exemption code for Crohn's disease, rheumatoid arthritis, psoriasis, multiple sclerosis (G35.-), axial spondyloarthritis and ankylosing spondylitis (M45.-), psoriatic arthritis (L40.-), hidradenitis suppurativa / acne inversa (L73.2), uveitis intermedia, uveitis posterior und panuveitis (H20.-, H30.-) at any time during in the look-back period. This criterion will identify only patients with prompt record (clinically relevant conditions)

e) patients aged ≤ 18 at index date

f) patients with record of use of oral budesonide (box 1) in the 5 years before index date

**Box 1.** Budesonide italian authorization marketing codes of interest

| **BUDESONIDE A07EA06: AIC code (01/22/2020)** | | | | | | | |
|---|---|---|---|---|---|---|---|
| 700030505 | 700044896 | 033798024 | 033798012 | 043461019 | 043461021 | 043461033 | 043461045 |
| 034734020 | 034734018 | 036507022 | 036507034 | 036507059 | 036507046 | 036507010 | 036507073 |
| 044798027 | 044798039 | 044798041 | 044798054 | 045928052 | 045928013 | 045928025 | 045928037 |
| 043461058 | 043461060 | 036507085 | 044798015 | 045928049 | 036507061 | | |

Table 1 Advanced treatment for Ulcerative Colitis

| **Drug class** | **Drug name** | **ATC code** |
|---|---|---|
| JAKi | Tofacitinib | L04AA29 |
| anti-TNF | Adalimumab | L04AB04 |
| | Golimumab | L04AB06 |
| | Infliximab | L04AB02 |
| Anti-integrin | Vedolizumab | L04AA33 |

Table 2 Drugs of interest

| **Drug(s)** | **ATC code(s)** |
|---|---|
| **Advanced therapies*** | |
| Infliximab | L04AB02 |
| Adalimumab | L04AB04 |
| Golimumab | L04AB06 |
| Vedolizumab | L04AA33 |
| Tofacitinb | L04AA29 |
| **Other treatments of interests** | |
| Other biologic including Ustekinumab | L04AA* e L04AB* |
| Antibiotics | A07A* AND J01* |
| Salicilates | A07EC* |
| Mesalazine | A07EC02 |
| Azathioprine | L04AX01 |
| Methotrexate | L01BA01 and L04AX03 |
| Ciclosporin | L04AD01 |
| 6-mercaptopurine | L01BB02 |
| Corticosteroids for systemic use | H02* |
| Locally acting corticosteroids | A07EA* |
| Tacrolimus | L04AD02 |

*only when not index drug

### 3.4 Variables

For each subject in the cohort, the following variables will be computed:

- Use of any drug included in table 2 in the 5-year look back period (yes or no)
- Use of any drug included in table 2 in the 1 year-follow-up (yes or no)
- Use of any drug included in table 2 in the 2 year-follow-up (yes or no)
- Number of DDD of each drug included in table 2 in the 5-year look back period
- Number of DDD of each drug included in table 2 in the 1 year-follow-up
- Number of DDD of each drug included in table 2 in the 2 year-follow-up
- Number and causes of Emergency department admission in the year before cohort entry
- Number and causes of Emergency department admission the 1 year-follow-up
- Number and causes of Emergency department admission the 2 year-follow-up
- Number and causes of hospitalization in the year before cohort entry
- Number and causes of hospitalization in the 1 year-follow-up
- Number and causes of hospitalization in the 2 year-follow-up
- Number of gastroenterological specialist visits in the year before cohort entry
- Number of gastroenterological specialist visits in the 1 year-follow-up
- Number of gastroenterological specialist visits in the 2 year-follow-up
- Time from index date to the date of the first access to emergency department
- Time from index date to the date of the first hospitalization
- Cost of patient accesses to emergency department in 1 year-follow up
- Cost of patient accesses to emergency department in 2 year-follow up
- Cost of patient hospitalizations in the 1 year-follow-up
- Cost of patient hospitalizations in the 2 year-follow-up
- Cost of drugs included in table 2 dispensed to patient during the follow-up
- Cost of drugs other than those included in table 2 dispensed to patient in the 1 year-follow-up
- Cost of drugs other than those included in table 2 dispensed to patient in the 2 year-follow-up
- Cost of patient accesses to specialist visits in the 1 year-follow-up
- Cost of patient accesses to specialist visits in the 2 year-follow-up
- Unit costs of drug included in table 1

### 3.5 Covariates

The following covariates will be considered in the analysis:

- Age at index date
- Gender
- Calendar year of cohort entry

## 4. DATA ANALYSIS

### 4.1 Research question 1

1) Count of patients with at least one-year follow up receiving their first advanced therapy in the study period (overall and stratified by year, age, gender) (output table3)
2) Count of patients with at least one-year follow up with history of dispensation of drug of interest (table 2) before cohort entry (output table 4)
3) Count of DDD, mean DDD per patient, of each drug of interest before cohort entry (output table 5) (patients with at least one-year follow up)

| Output table 3 – Characteristics of new users of advanced therapy for UC in the year before index date | | | | | |
|---|---|---|---|---|---|
| | Tofacitinib | Adalimumab | Infliximab | Golimumab | Vedolizumab |
| Overall users | | | | | |
| Female n (%) | | | | | |
| Male n (%) | | | | | |
| Age (mean ± SD) | | | | | |
| Age (median ± IQR) | | | | | |
| Patients with no hospitalization n (%) | | | | | |
| Patients with at least one hospitalization n (%) | | | | | |
| Number of hospitalizations per patients (mean ± SD) | | | | | |
| Patients with no access to ED n (%) | | | | | |
| Patients with at least one access to ED n (%) | | | | | |
| Number of Ed accesses per patients (mean ± SD) | | | | | |
| Patients with no gastroenterological specialist visits (%) | | | | | |
| Patients with at least one gastroenterological specialist visit (%) | | | | | |
| Number of gastroenterological specialist visits per patients (mean ± SD) | | | | | |

SD: standard deviation; IQR: interquartile range, ED : emergency department

| Output table 4: History of use (5 years before index date) of drugs of interest in new users of tofacitinib for UC | | | | | |
|---|---|---|---|---|---|
| Advanced therapy | Tofacitinib | Adalimumab | Infliximab | Golimumab | Vedolizumab |
| Overall users | | | | | |
| No use (naive to advanced therapy) | | | | | |
| Any use of advanced therapy | | | | | |
| Tofacitinib | x | | | | |
| Adalimumab | | x | | | |
| Infliximab | | | x | | |
| Golimumab | | | | x | |
| Vedolizumab | | | | | x |
| Any combination of two advanced therapy | | | | | |
| Any combination of three advanced therapy | | | | | |
| All advanced therapy | | | | | |
| Other biologic including Ustekinumab | | | | | |
| Antibiotics | | | | | |
| Salicilates | | | | | |
| Mesalazine | | | | | |
| Azathioprine | | | | | |
| Methotrexate | | | | | |
| Ciclosporin | | | | | |
| 6-mercaptopurine | | | | | |
| Corticosteroids for systemic use | | | | | |
| Locally acting corticosteroids | | | | | |
| Tacrolimus | | | | | |
| No use of both advanced therapies or other drugs of interests | | | | | |
| Any other drug of interest but not any advanced therapy | | | | | |
| Both advanced therapy and other drugs of interest | | | | | |

Output table 5: Dispensation of Drugs of interest (5 years before cohort entry) in patients receiving Tofacitinib for UC

| | Tofacitinib | | Adalimumab | | Infliximab | | Golimumab | | Vedolizumab | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Drugs** | **Overall Number of ddd (n)** | **mean number of DDD per patients (± SD)** | **Overall Number of ddd (n)** | **mean number of DDD per patients (± SD)** | **Overall Number of ddd (n)** | **mean number of DDD per patients (± SD)** | **Overall Number of ddd (n)** | **mean number of DDD per patients (± SD)** | **Overall Number of ddd (n)** | **mean number of DDD per patients (± SD)** |
| **Advanced therapy** | | | | | | | | | | |
| Adalimumab | | | | | | | | | | |
| Golimumab | | | | | | | | | | |
| Infliximab | | | | | | | | | | |
| Vedolizumab | | | | | | | | | | |
| **Other drugs** | | | | | | | | | | |
| Mesalazine | | | | | | | | | | |
| Azathioprine | | | | | | | | | | |
| Methotrexate | | | | | | | | | | |
| Ciclosporin | | | | | | | | | | |
| 6-mercaptopurine | | | | | | | | | | |
| Corticosteroids for systemic use | | | | | | | | | | |
| Locally acting corticosteroids | | | | | | | | | | |
| Tacrolimus | | | | | | | | | | |
| Other biologics | | | | | | | | | | |
| Antibiotics | | | | | | | | | | |
| Salicilates | | | | | | | | | | |
| | | | | | | | | | | |

## 4.2 Research question 2

In each of the 5 cohorts of users (index drugs: tofacitinib, adalimumab, infliximab, golimumab, vedolizumab):

1) Number of DDD of the index drug in the one-year and two-year follow up periods, overall and stratified by calendar year of cohort entry (Output table 8 and 9)

2) Percentage of day covered by the index drugs during the one-year and two-years follow-up periods (output table 8-9)

3) Count of patients with at least one prescription of an advanced therapy other than the index drug in the one-year and in the two-years follow-up periods and stratification based on the different advanced therapies supplied (1, 2, 3, 4) (output table 8-9)

4) Time free from and advanced therapy different from any index drug (survival analysis) in the one-year and the two-year follow-up periods (Kaplan-Mayer)

5) Count of patients with at least one prescription of a drug of interest (table 2) in the one-year and two-years follow-up periods (output table 11 and 12)

6) Number of DDD received for any advanced therapy other than the index drug in the one-year and two-years follow-up periods, overall and stratified by calendar year of cohort entry (output table 13 and 14)

7) Number of DDD received for any drug of interest (table 2) in the one-year and two-years follow-up period, overall and stratified by calendar year of cohort entry (output tables 15 and 16)

| Output table 8 – DDD of advanced therapies supplied in the **one year follow-up** and % day covered, overall and stratified by year of cohort entry | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug | Overall | Mean % day covered (±SD) | 2015 | | | 2016 | | | 2017 | | | 2018 | | | 2019 | | |
| | | | Patients (n) | Number DDD | Mean % day covered (±SD) | Patients (n) | Number DDD | Mean % day covered (±SD) | Patients (n) | Number DDD | Mean % day covered (±SD) | Patients (n) | Number DDD | Mean % day covered (±SD) | Patients (n) | Number DDD | Mean % day covered (±SD) |
| Tofacitinib | | | | | | | | | | | | | | | | | |
| Adalimumab | | | | | | | | | | | | | | | | | |
| Infliximab | | | | | | | | | | | | | | | | | |
| Golimumab | | | | | | | | | | | | | | | | | |
| Vedolizumab | | | | | | | | | | | | | | | | | |

| Output table 9– DDD of advanced therapies supplied in the **two years follow-up** and % day covered, overall and stratified by year of cohort entry | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug | Overall | Mean % day covered (±SD) | 2015 | | | 2016 | | | 2017 | | | 2018 | | |
| | | | Patients (n) | Number DDD | Mean % day covered (±SD) | Patients (n) | Number DDD | Mean % day covered (±SD) | Patients (n) | Number DDD | Mean % day covered (±SD) | Patients (n) | Number DDD | Mean % day covered (±SD) |
| Tofacitinib | | | | | | | | | | | | | | |
| Adalimumab | | | | | | | | | | | | | | |
| Infliximab | | | | | | | | | | | | | | |
| Golimumab | | | | | | | | | | | | | | |
| Vedolizumab | | | | | | | | | | | | | | |

| Output table 10 – patients receiving advanced therapies other than the index drug in **the one year follow-up** period | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Drug | At least 1 adavnced therapy other than index drug | Only 1 index drug | Any combination of 2 index drugs | Any combination of three index drugs | 4 index drugs | Tofacitinib | adalimumab | infliximab | Golimumab | Vedolizumab |
| Tofacitinib | | | | | | **X** | | | | |
| Adalimumab | | | | | | | **X** | | | |
| Infliximab | | | | | | | | **X** | | |
| Golimumab | | | | | | | | | **X** | |
| Vedolizumab | | | | | | | | | | **X** |

| Output table 10 – patients receiving advanced therapies other than the index drug in the **two years follow-up** period | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Drug | At least 1 index drug | Only 1 index drug | Any combination of 2 index drugs | Any combination of three index drugs | 4 index drugs | Tofacitinib | adalimumab | infliximab | Golimumab | Vedolizumab |
| Tofacitinib | | | | | | **X** | | | | |
| Adalimumab | | | | | | | **X** | | | |
| Infliximab | | | | | | | | **X** | | |
| Golimumab | | | | | | | | | **X** | |
| Vedolizumab | | | | | | | | | | **X** |

| Output table 11 – Patients receiving at least one supply of each drug included in table 2 the index drug in **the one year follow-up** period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug | Other biologics | antibiotics | salicilates | mesalazine | azathioprine | methotrexate | ciclosporin | 6-MP | Corticosteroids (systemic) | Corticosteroids (local) | Tacrolimus |
| Tofacitinib | | | | | | | | | | | |
| Adalimumab | | | | | | | | | | | |
| Infliximab | | | | | | | | | | | |
| Golimumab | | | | | | | | | | | |
| Vedolizumab | | | | | | | | | | | |

| Output table 12 – Patients receiving at least one supply of each drug included in table 2 the index drug in **the two years follow-up** period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug | Other biologics | antibiotics | salicilates | mesalazine | azathioprine | methotrexate | ciclosporin | 6-MP | Corticosteroids (systemic) | Corticosteroids (local) | Tacrolimus |
| Tofacitinib | | | | | | | | | | | |
| Adalimumab | | | | | | | | | | | |
| Infliximab | | | | | | | | | | | |
| Golimumab | | | | | | | | | | | |
| Vedolizumab | | | | | | | | | | | |

| Output table 13 – DDD of advanced therapies other than the index drug supplied in the **one year follow-up**, overall and stratified by year of cohort entry | | | | | | |
|---|---|---|---|---|---|---|
| Drug | Overall DDD | 2015 | 2016 | 2017 | 2018 | 2019 |
| **TOFACITINIB** | | | | | | |
| Adalimumab | | | | | | |
| Infliximab | | | | | | |
| Golimumab | | | | | | |
| Vedolizumab | | | | | | |
| **ADALIMUMAB** | | | | | | |
| Tofacitininb | | | | | | |
| infliximab | | | | | | |
| Golimumab | | | | | | |
| Vedolizumab | | | | | | |
| **INFLIXIMAB** | | | | | | |
| Tofacitininb | | | | | | |
| adalimumab | | | | | | |
| Golimumab | | | | | | |
| Vedolizumab | | | | | | |
| **GOLIMUMAB** | | | | | | |
| Tofacitininb | | | | | | |
| adalimumab | | | | | | |
| Infliximab | | | | | | |
| Vedolizumab | | | | | | |
| **VEDOLIZUMAB** | | | | | | |
| Tofacitininb | | | | | | |
| adalimumab | | | | | | |
| Infliximab | | | | | | |
| Golimumab | | | | | | |

| Output table 14 – DDD of advanced therapies other than the index drug supplied in the **two years follow-up**, overall and stratified by year of cohort entry | | | | | |
|---|---|---|---|---|---|
| Drug | Overall DDD | 2015 | 2016 | 2017 | 2018 |
| **TOFACITINIB** | | | | | |
| Adalimumab | | | | | |
| Infliximab | | | | | |
| Golimumab | | | | | |
| Vedolizumab | | | | | |
| **ADALIMUMAB** | | | | | |
| Tofacitininb | | | | | |
| infliximab | | | | | |
| Golimumab | | | | | |
| Vedolizumab | | | | | |
| **INFLIXIMAB** | | | | | |
| Tofacitininb | | | | | |
| adalimumab | | | | | |
| Golimumab | | | | | |
| Vedolizumab | | | | | |
| **GOLIMUMAB** | | | | | |
| Tofacitininb | | | | | |
| adalimumab | | | | | |
| Infliximab | | | | | |
| Vedolizumab | | | | | |
| **VEDOLIZUMAB** | | | | | |
| Tofacitininb | | | | | |
| adalimumab | | | | | |
| Infliximab | | | | | |
| Golimumab | | | | | |

| Output table 15 – DDD of other drugs of interest (table 2) supplied in the **one year follow-up**, overall and stratified by year of cohort entry | | | | | | |
|---|---|---|---|---|---|---|
| Drug | Overall | 2015 | 2016 | 2017 | 2018 | 2019 |
| **TOFACITINIB** | | | | | | |
| Other biologics | | | | | | |
| Antibiotics | | | | | | |
| Salicilates | | | | | | |
| Mesalazine | | | | | | |
| azathioprine | | | | | | |
| methotrexate | | | | | | |
| Cyclosporin | | | | | | |
| 6-MP | | | | | | |
| Corticosteroids (systemic) | | | | | | |
| Crticosteroids (local) | | | | | | |
| Tacrolimus | | | | | | |
| **ADALIMUMAB** | | | | | | |
| Other biologics | | | | | | |
| Antibiotics | | | | | | |
| Salicilates | | | | | | |
| Mesalazine | | | | | | |
| azathioprine | | | | | | |
| methotrexate | | | | | | |
| Cyclosporin | | | | | | |
| 6-MP | | | | | | |
| Corticosteroids (systemic) | | | | | | |
| Crticosteroids (local) | | | | | | |
| Tacrolimus | | | | | | |
| **INFLIXIMAB** | | | | | | |
| Other biologics | | | | | | |
| Antibiotics | | | | | | |
| Salicilates | | | | | | |
| Mesalazine | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| azathioprine | | | | | | |
| methotrexate | | | | | | |
| Cyclosporin | | | | | | |
| 6-MP | | | | | | |
| Corticosteroids (systemic) | | | | | | |
| Crticosteroids (local) | | | | | | |
| Tacrolimus | | | | | | |
| **GOLIMUMAB** | | | | | | |
| Other biologics | | | | | | |
| Antibiotics | | | | | | |
| Salicilates | | | | | | |
| Mesalazine | | | | | | |
| azathioprine | | | | | | |
| methotrexate | | | | | | |
| Cyclosporin | | | | | | |
| 6-MP | | | | | | |
| Corticosteroids (systemic) | | | | | | |
| Crticosteroids (local) | | | | | | |
| Tacrolimus | | | | | | |
| **VEDOLIZUMAB** | | | | | | |
| Other biologics | | | | | | |
| Antibiotics | | | | | | |
| Salicilates | | | | | | |
| Mesalazine | | | | | | |
| azathioprine | | | | | | |
| methotrexate | | | | | | |
| Cyclosporin | | | | | | |
| 6-MP | | | | | | |
| Corticosteroids (systemic) | | | | | | |
| Crticosteroids (local) | | | | | | |
| Tacrolimus | | | | | | |

| Output table 16 – DDD of other drugs of interest (table 2) supplied in the **two years follow-up**, overall and stratified by year of cohort entry | | | | | |
|---|---|---|---|---|---|
| Drug | Overall | 2015 | 2016 | 2017 | 2018 |
| **TOFACITINIB** | | | | | |
| Other biologics | | | | | |
| Antibiotics | | | | | |
| Salicilates | | | | | |
| Mesalazine | | | | | |
| azathioprine | | | | | |
| methotrexate | | | | | |
| Cyclosporin | | | | | |
| 6-MP | | | | | |
| Corticosteroids (systemic) | | | | | |
| Crticosteroids (local) | | | | | |
| Tacrolimus | | | | | |
| **ADALIMUMAB** | | | | | |
| Other biologics | | | | | |
| Antibiotics | | | | | |
| Salicilates | | | | | |
| Mesalazine | | | | | |
| azathioprine | | | | | |
| methotrexate | | | | | |
| Cyclosporin | | | | | |
| 6-MP | | | | | |
| Corticosteroids (systemic) | | | | | |
| Crticosteroids (local) | | | | | |
| Tacrolimus | | | | | |
| **INFLIXIMAB** | | | | | |
| Other biologics | | | | | |
| Antibiotics | | | | | |
| Salicilates | | | | | |
| Mesalazine | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| azathioprine | | | | | |
| methotrexate | | | | | |
| Cyclosporin | | | | | |
| 6-MP | | | | | |
| Corticosteroids (systemic) | | | | | |
| Crticosteroids (local) | | | | | |
| Tacrolimus | | | | | |
| **GOLIMUMAB** | | | | | |
| Other biologics | | | | | |
| Antibiotics | | | | | |
| Salicilates | | | | | |
| Mesalazine | | | | | |
| azathioprine | | | | | |
| methotrexate | | | | | |
| Cyclosporin | | | | | |
| 6-MP | | | | | |
| Corticosteroids (systemic) | | | | | |
| Crticosteroids (local) | | | | | |
| Tacrolimus | | | | | |
| **VEDOLIZUMAB** | | | | | |
| Other biologics | | | | | |
| Antibiotics | | | | | |
| Salicilates | | | | | |
| Mesalazine | | | | | |
| azathioprine | | | | | |
| methotrexate | | | | | |
| Cyclosporin | | | | | |
| 6-MP | | | | | |
| Corticosteroids (systemic) | | | | | |
| Crticosteroids (local) | | | | | |
| Tacrolimus | | | | | |

### 4.3 Research question 3

1) Count of number of access to Emergency department for any cause during the one year-year and the two-year follow up for each advanced therapy (output table 17)
2) Count of number of hospitalizations for any cause during the one year and the two-year follow up for each advanced therapy (output table 17)
3) Count of number of gastroenterological specialist visits during the one year and the two-years follow up for each advanced therapy (output table 17)
4) Count of patients with at least one access to Emergency Department during the one year and the two-year follow up for each advanced therapy, overall and stratified by gender, age group, and calendar year of cohort entry (output table 18-19)
5) Count of patients with at least one hospitalization during the one year and the two-year follow up for each advanced therapy (output table 18-19)
6) Count of patients with at least one gastroenterological visit during the one year and the two-year follow up for each advanced therapy (output table 18-19)
7) In patients with at least one access in emergency department during the follow up, median and mean time to the first emergency department access (output table 18-19)
8) In patients with at least one hospitalization during the follow up, median and mean time to the first hospitalization (output table 18-19)
9) In patients with at least one rheumatologic visits during the follow up, median and mean time to the first gastroenterological visits (output table 18-19)
10) Count and percentage of causes of emergency department admission during the follow up (output table 20a-e)
11) Count and percentage of causes of hospitalization during the follow up (21a-e)

| Output table 17: Number of Emergency department (ED) admissions, hospitalizations, specialist visits (gastroeneterological) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Drug | Overall patients (n) | | ED admissions (n) | | Hospitalizations (n) | | Gastroenterological visits (n) | |
| | 1-year | 2-years | 1-year | 2-years | 1-year | 2-years | 1 year | 2-year |
| Tofacitinib | | | | | | | | |
| Adalimumab | | | | | | | | |
| Infliximab | | | | | | | | |
| Golimumab | | | | | | | | |
| Vedolizumab | | | | | | | | |

| Output table 18: Number of patients with at least 1 Emergency department (ED) admission, hospitalization, and specialist visit (gastroenterological) in **the one-year follow-up**, and mean time too first event overall and stratified by gender | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ED admissions (n) | | | | Hospitalizations (n) | | | | Gastroenterological visits (n) | | | |
| | Overall<br>N (%) | Mean time (days) to first event (±SD)<br>Median (±IQ) | M<br>N (%) | F<br>N (%) | Overall<br>N (%) | Mean time (days) to first event (±SD)<br>Median (±IQ) | M<br>N (%) | F<br>N (%) | Overall<br>N (%) | Mean time (days) to first event (±SD)<br>Median (±IQ) | M<br>N (%) | F<br>N(%) |
| Tofacitinib<br>(n = ) | | | | | | | | | | | | |
| Adalimumab<br>(n = ) | | | | | | | | | | | | |
| Infliximab<br>(n = ) | | | | | | | | | | | | |
| Golimumab<br>(n = ) | | | | | | | | | | | | |
| Vedolizumab<br>(n = ) | | | | | | | | | | | | |

| Output table 19: Number of patients with at least 1 Emergency department (ED) admission, hospitalization, and specialist visit (gastroenterological) in **the two-years follow-up**, and mean time to first event, overall and stratified by gender | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ED admissions (n) | | | | Hospitalizations (n) | | | | Gastroenterological visits (n) | | | |
| | Overall n | Mean time (days) to first event (±SD) | M N (%) | F N (%) | Overall n | Mean time (days) to first event (±SD) | M N (%) | F N (%) | Overall | Mean time (days) to first event (±SD) | M N (%) | F N(%) |
| Tofacitinib (n = ) | | | | | | | | | | | | |
| Adalimumab (n = ) | | | | | | | | | | | | |
| Infliximab (n = ) | | | | | | | | | | | | |
| Golimumab (n = ) | | | | | | | | | | | | |
| Vedolizumab (n = ) | | | | | | | | | | | | |

| Output Table 20a: Causes of access to Emergency department (tofacitinib) | |
|---|---|
| Description (ICD-9) | Number of cases (%) |
| Overall | |
| | |
| | |

| Output Table 20b: Causes of access to Emergency department (adalimumab) | |
|---|---|
| Description (ICD-9) | Number of cases (%) |
| Overall | |
| | |
| | |

| Output Table 20c: Causes of access to Emergency department (infliximab) | |
|---|---|
| Description (ICD-9) | Number of cases (%) |
| Overall | |
| | |
| | |

| Output Table 20d: Causes of access to Emergency department (golimumab) | |
|---|---|
| Description (ICD-9) | Number of cases (%) |
| Overall | |
| | |
| | |

| Output Table 20e: Causes of access to Emergency department (vedolizumab) | |
|---|---|
| Description (ICD-9) | Number of cases (%) |
| Overall | |
| | |
| | |

| Output Table 21a: Causes of access to Hospitalization (tofacitinib) | |
|---|---|
| Description (ICD-9) | Number of cases (%) |
| Overall | |
| | |
| | |

| Output Table 21b: Causes of access to Hospitalization (adalimumab) | |
|---|---|
| Description (ICD-9) | Number of cases (%) |
| Overall | |
| | |
| | |

| Output Table 21c: Causes of access to Hospitalization (infliximab) | |
|---|---|
| Description (ICD-9) | Number of cases (%) |
| Overall | |
| | |
| | |

| Output Table 21d: Causes of access to Hospitalization (golimumab) | |
|---|---|
| Description (ICD-9) | Number of cases (%) |
| Overall | |
| | |
| | |

| Output Table 21e: Causes of access to Hospitalization (vedolizumab) | |
|---|---|
| Description (ICD-9) | Number of cases (%) |
| Overall | |
| | |
| | |

### 4.4 Research question 4

1) Direct health cost of the population of new users of each advanced therapy (5 cohorts) for UC in the one-year and the two-years follow-up, overall and stratified by type of cost, including cost of dispensed drugs (other advanced therapies plus other drugs of interest included in table 2 and additional treatments), cost of emergency department admission, cost of hospitalization, cost of specialist visits (gastroenterological) (output table 22-23)
2) Mean and median cost per patient for each advanced therapy for UC in the one-year and the two-years follow-up, overall and stratified by year of cohort entry (output table 24-25)

| Output Table 22 – Direct Costs in the **one-year** follow up | | | | | |
|---|---|---|---|---|---|
| | Cost (€) | | | | |
| | Tofacitinib | Adalimumab | Infliximab | Golimumab | Vedolizumab |
| Total cost | | | | | |
| Drugs | | | | | |
| Emergency department access | | | | | |
| Hospitalization | | | | | |
| Specialist visits (gastroenterological) | | | | | |
| Median cost per patient | | | | | |
| Drugs | | | | | |
| Emergency department access | | | | | |
| Hospitalization | | | | | |
| Specialist visits (gastroenterological) | | | | | |

| Output Table 23 – Direct Costs in the **two-years** follow up | | | | | |
|---|---|---|---|---|---|
| | Cost (€) | | | | |
| | Tofacitinib | Adalimumab | Infliximab | Golimumab | Vedolizumab |
| Total cost | | | | | |
| Drugs | | | | | |
| Emergency department access | | | | | |
| Hospitalization | | | | | |
| Specialist visits (gastroenterological) | | | | | |
| Median cost per patient | | | | | |
| Drugs | | | | | |
| Emergency department access | | | | | |
| Hospitalization | | | | | |
| Specialist visits (gastroenterological) | | | | | |

| Output Table 24 – Direct Costs in the **one-year** follow up, stratified by calendar years of cohort entry | | | | | |
|---|---|---|---|---|---|
| | Cost (€) | | | | |
| | 2015 | 2016 | 2017 | 2018 | 2019 |
| **Tofacitinib** | | | | | |
| Total cost | | | | | |
| Mean/Median cost per patient | | | | | |
| Drugs | | | | | |
| Advanced therapy | | | | | |
| Other UC treatments | | | | | |
| Other non UC treatments | | | | | |
| Emergency department access | | | | | |
| Hospitalization | | | | | |
| Specialist visits (gastro) | | | | | |
| **Adalimumab** | | | | | |
| Total cost | | | | | |
| Mean/Median cost per patient | | | | | |
| Drugs | | | | | |
| Advanced therapy | | | | | |
| Other UC treatments | | | | | |
| Other non UC treatments | | | | | |
| Emergency department access | | | | | |
| Hospitalization | | | | | |
| Specialist visits (gastro) | | | | | |
| **Infliximab** | | | | | |
| Total cost | | | | | |
| Mean/Median cost per patient | | | | | |
| Drugs | | | | | |
| Advanced therapy | | | | | |
| Other UC treatments | | | | | |
| Other non UC treatments | | | | | |
| Emergency department access | | | | | |
| Hospitalization | | | | | |
| Specialist visits (gastro) | | | | | |
| **Golimumab** | | | | | |
| Total cost | | | | | |
| Mean/Median cost per patient | | | | | |
| Drugs | | | | | |
| Advanced therapy | | | | | |
| Other UC treatments | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Other non UC treatments | | | | | |
| Emergency department access | | | | | |
| Hospitalization | | | | | |
| Specialist visits (gastro) | | | | | |
| **Vedolizumab** | | | | | |
| Total costs | | | | | |
| Mean/Median cost per patient | | | | | |
| Drugs | | | | | |
| Advanced therapy | | | | | |
| Other UC treatments | | | | | |
| Other non UC treatments | | | | | |
| Emergency department access | | | | | |
| Hospitalization | | | | | |
| Specialist visits (gastro) | | | | | |

| Output Table 25 – Direct Costs in the **two-year** follow up, stratified by calendar years of cohort entry | | | | |
|---|---|---|---|---|
| | Cost (€) | | | |
| | 2015 | 2016 | 2017 | 2018 |
| **Tofacitinib** | | | | |
| Total cost | | | | |
| Mean/Median cost per patient | | | | |
| Drugs | | | | |
| Advanced therapy | | | | |
| Other UC treatments | | | | |
| Other non UC treatments | | | | |
| Emergency department access | | | | |
| Hospitalization | | | | |
| Specialist visits (gastro) | | | | |
| **Adalimumab** | | | | |
| Total cost | | | | |
| Mean/Median cost per patient | | | | |
| Drugs | | | | |
| Advanced therapy | | | | |
| Other UC treatments | | | | |
| Other non UC treatments | | | | |
| Emergency department access | | | | |
| Hospitalization | | | | |
| Specialist visits (gastro) | | | | |
| **Infliximab** | | | | |
| Total cost | | | | |
| Mean/Median cost per patient | | | | |
| Drugs | | | | |
| Advanced therapy | | | | |
| Other UC treatments | | | | |
| Other non UC treatments | | | | |
| Emergency department access | | | | |
| Hospitalization | | | | |
| Specialist visits (gastro) | | | | |
| **Golimumab** | | | | |
| Total cost | | | | |
| Mean/Median cost per patient | | | | |
| Drugs | | | | |
| Advanced therapy | | | | |
| Other UC treatments | | | | |

| | | | | |
|---|---|---|---|---|
| Other non UC treatments | | | | |
| Emergency department access | | | | |
| Hospitalization | | | | |
| Specialist visits (gastro) | | | | |
| **Vedolizumab** | | | | |
| Total costs | | | | |
| Mean/Median cost per patient | | | | |
| Drugs | | | | |
| Advanced therapy | | | | |
| Other UC treatments | | | | |
| Other non UC treatments | | | | |
| Emergency department access | | | | |
| Hospitalization | | | | |
| Specialist visits (gastro) | | | | |

## 5. QUALITY CONTROL

All data will be managed according to the Good Clinical Practice and the Good Pharmacovigilance Practice referred to the observational studies.

*https://www.ich.org/products/guidelines/efficacy/efficacy-single/article/integrated-addendum-good-clinical-practice.html)*

*https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices*

## 6. PROTECTION OF HUMAN SUBJECT

This will be a retrospective study; consequently, all treatments have been performed according to the EULAR guidelines and the University Hospital procedures. Any insurance will not be needed.

All data will be managed according with EU data protection directive (95/46/EC), ePrivacy directive (2002/58/EC) and its revision (2009/136/EC) and the General data protection regulations (May 2018). The personnel of the Unit of Rheumatology of Pisa University Hospital involved in the study will manage clinical data according with the privacy protection. To ensure pseudo-anonymization of sensitive data we will use 3 K-anonymity, which are: 1) the unique ID code for patient, 2) the truncated ZIP code (dropped to the first 3 numbers, e.g. 561XX instead of 56126), 3) age as a range of 5 years (e.g. 50-55 years old instead of 53 aged).

Only personnel normally allowed to access patients' sensitive data (clinicians managing patients' care) will be involved in the process of pseudo-anonymization. The other persons involved in the present study will never have access to patients' individual sensitive data.

The agreement between Tuscan Region and ARS, based on the new EU data protection regulations will protect the decrypt process from patient sensitive data to anonymous ID code and vice versa.

## 7. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Due to the retrospective design of this study, the notification of adverse events detected during the study to the competent authority is not required.

## 8. DATA HOLDING

Data will be collect in excel file and the promoter and the Principal Investigator will store all documents related to Michelangelo study for at least seven years as electronic and/or paper folders.

## 9. AMENDMENTS AND DEVIATIONS

This is the original version of the protocol. No amendments or deviations reported.

## 10. PLAN FOR COMMUNICATION OF STUDY RESULT

Study results will be included in the report on drug use in Tuscany 2021 and presented in the related meeting scheduled for December 2021 in Florence. The study results will be published in a peer review journal and presented in national and international conferences.

## 11. REFERENCES


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