Protocol : GT-2021-02

GETAID-2021-02

CLINICAL STUDY SYNOPSIS

A 24-month real life PErsistence efficacy and safety study in IBD patients in REMission switched from intravenous infliximab to subcutaneous infliximab CT-P13 Remsima®

PEREM STUDY

A 24-month French multicenter, observational, retroprospective and prospective cohort study

Version N°1- Date: 12/02/2021

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SPONSOR	GETAIDGroupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif

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LIST OF ABREVIATIONS

µg	microgramme
5ASA	5-aminosalicylic acid
6-MP	Mercaptopurine
ANA	antinuclear antibody
ANGH	Association Nationales, Hépato-Gastroentérologues
BMQ	Beliefs about Medicines Questionnaire
CD	Crohn Disease
COVID-19	Covid-19 disease
CR	Clinical Remission
CREGG	Club de Réflexion des Cabinets et Groupes d'Hépato-Gastroentérologie
CRP	C-Reactive Proteins
CT-P13	
ECCO	European Crohn´s and Colitis Organisation
FC	Faecal Calprotectin
GETAID	Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestive
GETAID	gramme
HAS	Haute Autorité de Santé
HBI	Harvey Bradshaw Index
Hep B	Hepatitis B
Hep C	Hepatitis C
HIV	human immunodeficiency virus
IBD	Inflammatory Bowel Disease
IFX	Infliximab
IOBD	International Organization for the Study of Inflammatory Bowel Diseases
IV	Intra veinous
JAK	Janus kinase inhibitor
kg	Kilogramme
mg	Milligramme
MPR	Medication Possession Ratio
PMS	Partial Mayo Score
PRO2	Patient Reported outcomes
S1P	Sphingosine 1-phosphate
SATMED-Q	Treatment Satisfaction With Medicines Questionnaire
SC	Sub Cutaneous
UC	Ulcerative Colitis

PROTOCOL SYNOPSIS

TITLE	A 24-month real life **PE**rsistence efficacy and safety study in IBD patients in **REM**ission switched from intravenous infliximab to subcutaneous infliximab CT-P13 Remsima®
SHORT TITLE	PEREM STUDY
PRINCIPAL INVESTIGATOR	MATHIEU Nicolas MD
SPONSOR	GETAID
STUDY RATIONAL	Biosimilars represent great potential in cost saving and re-investment opportunities in healthcare. Biosimilars of infliximab appear to be clinically equivalent to the reference product in patients with rheumatoid arthritis and psoriasis and IBD. However, infliximab SC (Remsima® SC) is not considered as infliximab IV biosimilar by HAS, as it is the first infliximab SC formulation, therefore, real-life data are needed for long-term, efficacy maintenance/ persistency, safety and pharmacokinetics reasons and giving the risk of nocebo effect in patients receiving longstanding maintenance IV infliximab therapy.
METHODOLOGY	24-months multicentre, observational, retro/prospective cohort GETAID study will be performed in clinical remission IBD outpatients. Patients under stable clinical and biological remission will be proposed to switch from intravenous originator Remicade or one of its biosimilars® to subcutaneous infliximab (Remsima® SC) as part of routine care.
PRIMARY OBJECTIVE	To describe subcutaneous infliximab persistence after the switch from IV infliximab originator Remicade® or one of its biosimilars to SC infliximab (Remsima® SC) at week 48.
PRIMARY ENDPOINT	Persistence of subcutaneous infliximab at 48 weeks after switching from IV infliximab to SC infliximab Remsima®.
SECONDARY OBJECTIVES	• Steroid-free clinical remission at 24 months after switching. • To investigate factors associated with SC infliximab Remsima® persistence at week-48. • To observe the long-term safety of subcutaneous infliximab Remsima® SC during a 96-week period after switching from intravenous infliximab originator or one of its biosimilars in IBD patients in clinical remission.
SECONDARY ENDPOINTS	• Percentage of patients on steroid free clinical remission at week 24- after switch. → Steroid-free Clinical Remission (CR) is defined as a Harvey Bradshaw Index (HBI) score≤4 for CD patients and a Partial Mayo Score (PMS) ≤2 with each sub-score of 1 or less for UC.

	→ When HBI scoring will not be feasible (stoma, pouch), evaluation of clinical remission will be estimated by physician global assessment. → Patients having discontinued subcutaneous infliximab therapy whatever the reason during the 48 months of follow-up as well as patients referred to disease-related surgery and patients lost to follow-up before week 96 will be considered as failure to subcutaneous infliximab Remsima® SC therapy (intention to treat analysis) and will be classified in the group of patients having failed to maintain steroid free clinical remission under subcutaneous infliximab Remsima® SC during the whole study period. • Percentage of patients who switch back to originator previous therapy IV infliximab at 48 weeks after switching from IV infliximab to SC infliximab Remsima® SC in IBD patient. • Percentage of PRO2 response and remission at week 48. • Percentage of biological remission rates (FC <250 µg/g, CRP <5 mg/L) at week 48. • Percentage of clinical relapse free rates at week 48. • Percentage of loss of response rates at week 48. • Percentage of clinical response and remission at week 12. • Mean change from baseline in HBI or PMS, and mean change from baseline in CRP and fecal calprotectin. • Proportion of patients with positive antibodies (IFX, ANA) comparing therapy with original and biosimilar infliximab. • Adherence to biosimilar switch during the follow-up: MPR ratios. *Safety Endpoints of interest: • Twelve-month cumulative surgery rates. • Hospitalization rate at week 48 and 96. • Cumulative infection rate at week 48 and 96. • Cumulative injection reactions at week 48 and 96. • Discontinuation of biosimilar infliximab therapy cumulative rates at week 48 and 96. • Incidence of specific anti-drug antibodies detected during the study. *Explanatory factors behind a nocebo effect during the follow-up: BMQ, SATMED-Q, and the IBD Disk at week 12, 24, 48 and 96.
INCLUSION CRITERIA	• Male or female subjects who are more than 18 years of age, on the day of signing informed consent. • Documented diagnosis of CD or UC established based on standard clinical, endoscopic and histological criteria. • CD or UC remission defined per clinical assessment as a Harvey Bradshaw Index (HBI) score ≤4 for CD patients and a Partial Mayo Score (PMS) ≤2 with each sub-score of 1 or less for UC and/or according to ECCO classification within previous 6 months.

	• Currently treated with IV infliximab: originator or biosimilars. • Patients agreeing to switch from IV to SC formulation. • Receiving or not the concomitant following drugs (but must remain on stable dose for 12 weeks): → Oral 5-aminosalicylates (5ASA) compounds or rectal formulations of 5ASA provided the dose to be stable at least 4 weeks before switching. → Azathioprine, 6-MP or methotrexate provided the dose has been stable for 4 weeks prior to inclusion (dose must remain stable for 10 weeks after switching). • Each patient is required to provide written informed consent to be included in the study.
EXCLUSION CRITERIA	• Current use of vedolizumab or ustekinumab • Current use of JAK inhibitors or S1P modulators • Treatment with any investigational agent in the past 30 days or five half-lives prior to the screening visit • Current CD abscess • Active clinically significant infection or HIV, Hep B, Hep C, untreated tuberculosis
STUDY DESIGN	A 24-month multicentre, observational, retro prospective cohort study. Patients under stable clinical and biological remission will be proposed to switch from the intravenous originator Remicade® or one of its biosimilars to the subcutaneous infliximab Remsima® SC as part of routine care. All consecutive patients in IBD centers participating in the study will be proposed to participate in the study during their regular outpatients' visits. Patients will first be asked to read an information letter on biosimilars, the physician will also give to the patient a thorough explanation on the nocebo effect and its risks with a written patient information brochure on the biosimilar concept and on the switch modalities. After these 2 steps, patients will be switched from IV infliximab into SC biosimilar Remsima®. Patients fill in 2 self-administered questionnaires: BMQ (screening, week 48 and 96), SATMED-Q (weeks 12, 24, 48 and 96), and the IBD Disk (each visit). Blood and faecal samples (for monitoring faecal calprotectin, serum CRP and infliximab specific antibodies) will be collected at inclusion, week 12, 24, and 48. As IBD patients are in stable steroid free clinical and biological remission, SC infliximab doses are those expected under infliximab maintenance treatment, according to daily practice guidelines and bodyweight (SC CT-P13 120 mg if bodyweight <80 kg or 240 mg if bodyweight >8o kg every 2 weeks). Immunosuppressive drugs into two groups will stratify IBD patients: mono and combotherapy with SC infliximab and by optimal dose or interval between IV infliximab injections. According to GETAID recommendations, SC infliximab non-responders IBD patients will be offered the 240 mg every 2 weeks regimen with the possibility to switch back to IV infliximab after 3 SC injections.

SUBJECTS NUMBER	400 patients
STUDY CENTERS	A 24-month French multicentre, observational, prospective cohort GETAID study. Study Centers: Around 40 centers will be selected among GETAID, CREGG & ANGH centers.
STUDY DURATION	Study Duration: 24 months Inclusion period: 12 months Duration of treatment: 12 months Follow-up: 12 months Statistical analysis and manuscript writing: 12 months
STATISTICAL CONSIDERATIONS	For comparison of disease activity, the score at the switch time-point will be compared to the average score after switching to subcutaneous infliximab therapy. This will be done using the Wilcoxon Mann-Whitney Test. P< .05 will be considered as statistically significant..
EXPECTED BENEFITS	The PEREM study will provide real life data according to the switch from IV infliximab to SC infliximab and inserts for prevention and management of the nocebo effect in those biosimilar-treated IBD patients. The study will allow identifying the high-risk patients for the switch back to further prevent it. Patients' education may help minimize misconceptions about therapy changes and prevent or reduce nocebo effect. Patients participating in the study will receive infliximab through a more comfortable delivery mode while avoiding hospital visits for scheduled infusions. In the current setting of COVID-19 pandemic, S/C biosimilar strategies are eagerly awaited, as proposed by the International Organization for the study of IBD (IOBD) and other societies suggested considering switching to or starting SC treatments. Health-care systems could benefit from the introduction of CT-P13 SC for different reasons on top of direct drug costs. In fact, ready-to-use medication can reduce handling burden on hospital staff, costs and risks of organizing infusion visits, and drug waste through different packaging and more flexible formulation. A more practical route of administration could also improve patients' acceptance of non-medical switch to a biosimilar and thus reduce the nocebo effect.

QUESTIONNAIRE DU SATMED-Q®

Nous souhaiterions connaître votre degré de satisfaction quant au traitement médicamenteux que vous prenez actuellement.

Ce questionnaire comprend 2 pages. Pour chaque question, cochez le numéro qui reflète le mieux votre opinion, sachant qu'il n'y a pas de bonnes ou mauvaises réponses. Si vous hésitez concernant l'une des réponses, sélectionnez celle qui vous semble la mieux adaptée à votre cas.

- Avez-vous ressenti un quelconque effet indésirable lié au traitement médicamenteux ?

☐Non, aucun ☐Oui, au moins un

Lequel/Lesquels :

_____
_____

_____
_____

_____
_____

_____
_____

- Les questions suivantes portent sur les effets indésirables liés au traitement médicamenteux :

	Non, pas du tout	Un peu	Modérément	Assez	Oui, beaucoup
1. Les effets indésirables du traitement ont un impact sur mes capacités physiques	0	1	2	3	4
2. Les effets indésirables du traitement ont un impact sur mes activités de loisir et de temps libre	0	1	2	3	4
3. Les effets indésirables du traitement ont un impact sur mes tâches quotidienne	0	1	2	3	4

- Les questions suivantes portent sur l'efficacité du traitement médicamenteux, c'est-à-dire sa capacité à traiter votre maladie et à soulager vos symptômes :

	Non, pas du tout	Un peu	Modérément	Assez	Oui, beaucoup
4. Le traitement que je prends actuellement soulage mes symptômes	0	1	2	3	4
5. Le traitement commence à faire effet après une durée que j'estime satisfaisante	0	1	2	3	4
6. Je me sens mieux maintenant qu'avant de commencer le traitement	0	1	2	3	4

- Les questions suivantes sur les aspects pratiques du traitement médicamenteux et sur sa facilité d'administration :

	Non, pas du tout	Un peu	Modérément	Assez	Oui, beaucoup
7. Mon traitement est pratique à prendre	0	1	2	3	4
8. Mon traitement est dans l'ensemble facile à prendre / utiliser sous sa forme actuelle (goût, taille, etc.)	0	1	2	3	4
9. Les horaires de prise sont pratiques	0	1	2	3	4

- Les questions suivantes portent sur les effets du traitement médicamenteux sur votre quotidien :

	Non, pas du tout	Un peu	Modérément	Assez	Oui, beaucoup
10. Le traitement que je prends actuellement facilite mes activités de loisir et de temps libre	0	1	2	3	4
11. Mon traitement facilite ma toilette	0	1	2	3	4
12. Mon traitement facilité mes tâches quotidiennes	0	1	2	3	4

- Les questions suivantes concernent le suivi médical de votre maladie :

	Non, pas du tout	Un peu	Modérément	Assez	Oui, beaucoup
13. Mon médecin (ou autre professionnel de santé) m'a fourni des informations détaillées sur ma maladie	0	1	2	3	4
14. Mon médecin (ou autre professionnel de santé) m'a expliqué comment traiter correctement ma maladie	0	1	2	3	4

- Pour finir, voici quelques questions concernant votre opinion générale sur ce traitement médicamenteux et sur votre état de santé :

	Non, pas du tout	Un peu	Modérément	Assez	Oui, beaucoup
15. J'ai l'intention de poursuivre ce traitement	0	1	2	3	4
16. Je me sens bien avec ce traitement	0	1	2	3	4
17. Je suis globalement satisfait€ de ce traitement	0	1	2	3	4

<u>Nous vous remercions de votre collaboration</u>

QUESTIONNAIRE DU BMQ®

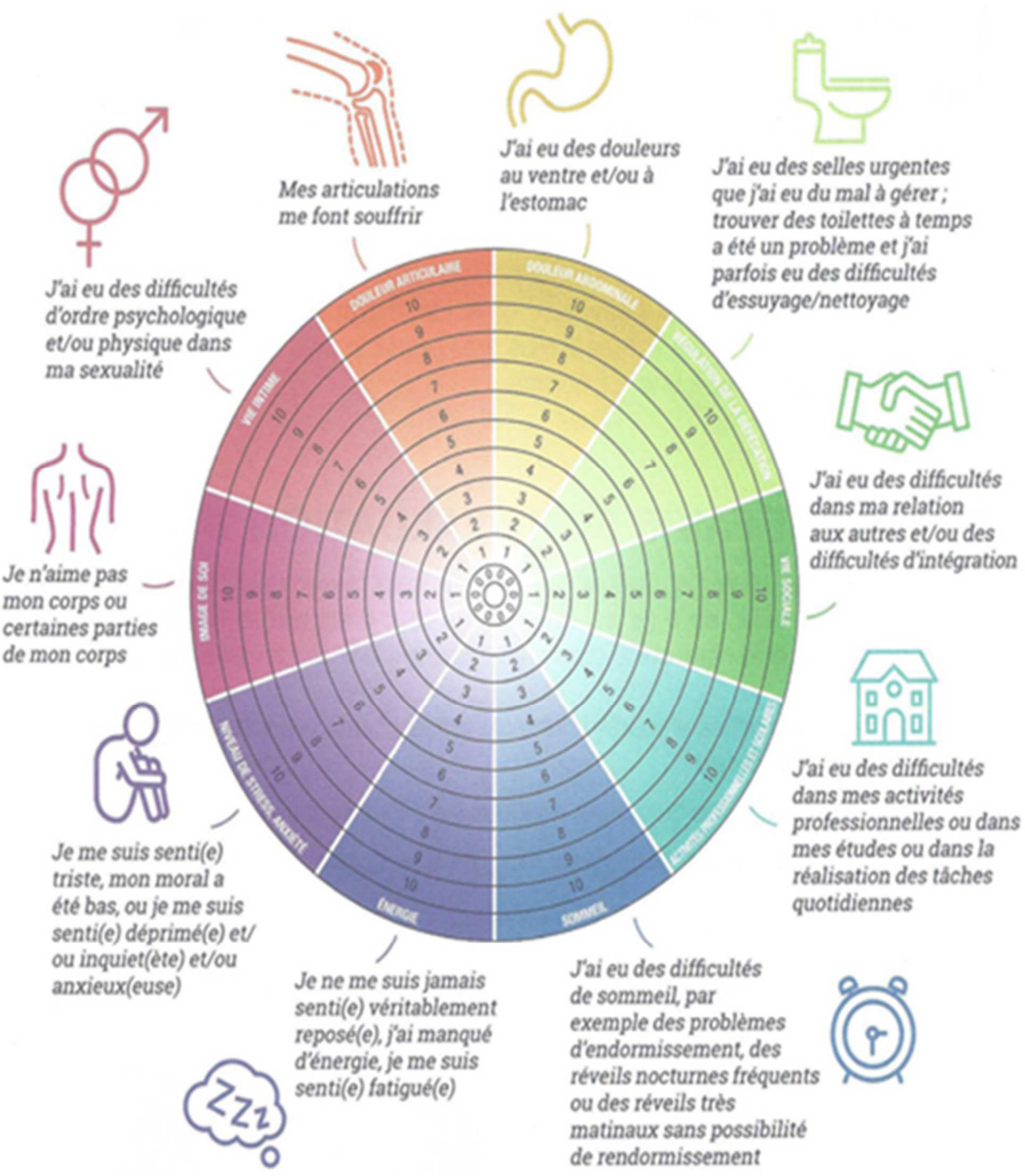
Ce questionnaire consiste en un certain nombre d'appréciations personnelles à propos des médicaments que vous prenez. Veuillez s'il vous plait indiquer votre avis en cochant la case correspondante (Pas du tout d'accord, plutôt pas d'accord, Ni en désaccord, ni d'accord, plutôt d'accord, tout à fait d'accord). Il n'y a ni de bonnes, ni de mauvaises réponses. Vos réponses seront toujours bonnes si vous dites vraiment ce que vous pensez.

	Pas du tout d'accord	Plutôt pas d'accord	Ni en désaccord ni d'accord	Plutôt d'accord	Tout à fait d'accord
1. Mes médicaments me permettent de ne pas aller plus mal					
2. Tout de suite, ma santé dépend de mes médicaments					
3. Dans l'avenir, ma santé dépend de mes médicaments					
4. Sans mes médicaments, je serai très malade					
5. Ma vie serait impossible sans mes médicaments					
6. Je m'inquiète quelques fois des effets à long terme de mes médicaments					
7. Mes médicaments sont un mystère pour moi					
8. Je m'inquiète quelques fois d'être devenu trop dépendant à mes médicaments					
9. Je m'inquiète d'avoir à prendre des médicaments					
10. Mes médicaments perturbent ma vie					
11. Les docteurs utilisent trop de médicaments					
12. Si les docteurs passaient plus de temps avec les patients, ils prescriraient moins de médicaments					
13. Les docteurs placent trop de confiance dans les médicaments					
14. Les remèdes naturels sont plus sûrs que les médicaments					
15. La plupart des médicaments sont addictifs					
16. Les personnes qui prennent des médicaments devraient arrêter leur traitement de temps en temps					
17. Les médicaments font plus de mal que de bien					
18. Tous les médicaments sont des poisons					

Nous vous remercions de votre collaboration

BMQ questionnaire

A remplir lors du switch et à un an (w48) de celui-ci



IBD Disk (Ghosh 2017)

A remplir lors du switch, 3 mois, 6 mois et 1 an du switch