Prospective rAndomized controlled tRial of Crohn's diseAse exclusion Diet vs corticosteroIds in patientS with activE Crohn's disease

PARADISE

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS NOT CONCERNING A HEALTH PRODUCT

Version no. 7.1 dated 09/07/2024

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SIGNATURE page for a research PROTOCOL

Title: Prospective rAndomized controlled tRial of Crohn's diseAse exclusion Diet vs corticosteroIds in adults and pediatric patientS with activE Crohn's disease / PARADISE STUDY

Version no. 7.1 dated: 09/07/2024

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
Anti-TNF	**Anti Tumor Necrosis Factor**
AR	**Adverse Reaction**
ASR	**Annual Safety Report**
CA	**Competent Authority**
CBC	**Complete Blood Count**
CD	**Crohn's Disease**
CDED	**Crohn's Disease Exclusion Diet**
CDAI	**Crohn's Disease Activity Index**
CDEIS	**Crohn's Disease Endoscopic Index of Severity**
CRA	**Clinical Research Associate**
CRP	**C-reactive protein**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EEN	**Exclusive Enteral Nutrition**
FCP	**Faecal Calprotectin**
GCP	**Good Clinical Practice**
HBI	**Harvey-Bradshaw Index**
IBD	**Inflammatory Bowel Disease**
IBDQ	**Inflammatory Bowel Disease Questionnaire**
ICF	**Informed Consent Form**
ITT	**Intent-to-treat principle**
PCC	**PillCam Crohn's Capsule**
PEN	**Partial Enteral Nutrition**
PIL	**Patient Information Letter**
(S)AE	**(Serious) Adverse Event**
SAP	**Statistical Analysis Plan**
SES-CD	**Simple Endoscopic Score for Crohn's Disease**
SF16	**Short Form 16**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
WPAI	**Work Productivity Index**

1 SUMMARY

Full title	**Prospective rAndomized controlled tRial of Crohn's diseAse exclusion Diet vs corticosteroIds in adults and pediatric patientS with activE Crohn's disease**
Acronym/reference	PARADISE
Coordinating investigator	Prof Franck Carbonnel APHP, CHU Kremlin-Bicêtre Service de gastro-entérologie Université Paris Saclay 78, rue du général Leclerc, 94275, Le Kremlin-Bicêtre Cedex France franck.carbonnel@aphp.fr
Sponsor	Assistance Publique – Hôpitaux de Paris
Main objective and primary endpoint	Main objective: to assess whether CDED is superior to corticosteroids, in terms of endoscopic response, in patients with mildly to moderately active, luminal, inflammatory CD. Primary endpoint: endoscopic response at week 16, without corticosteroids or further therapeutic intervention, assessed by a centralized, pseudonymized and blinded, double lecture panel of panenteric PillCam Crohn's Capsule (PCC). Endoscopic response is defined by a decrease of at least 50% in the Lewis score for patients with small bowel CD, decrease of SES-CD of at least 50% in patients with colonic CD and both of these in patients with small bowel and colonic CD, compared to baseline values.

Secondary objectives and endpoints	Compare between the 2 arms of the trial:
	- (Steroid-free) clinical remission (HBI <5) and response (a decrease of at least 3 points in HBI)
	- (Steroid-free) clinical remission (CDAI <150) and response (a decrease of at least 70 points in CDAI)
	- Need for further therapeutic intervention (i.e., steroids, immunosuppressants, new biologic or surgery)
	- Decrease of fecal calprotectin of at least 50% off steroids.
	- Fecal calprotectin of less than 250 µg/g, less than 100 µg/g and less than 50 µg/g
	- CRP serum level
	- Median HBI, CDAI, calprotectin and CRP
	- Endoscopic remission as defined as Lewis score <135 in the small bowel and/or SES-CD=0-2 in the colon, without further therapeutic intervention (surgery, biologics or dietary intervention)
	- Endoscopic response and remission graded by Eliakim scores
	- Segmental endoscopic response and remission
	- Gut microbiota composition (PCR 16s, PCR 18S for fungi and protists, metabolomics and shotgun metagenomics)
	- Compliance to corticosteroid treatment: Medication Adherence Report Scale
	- Compliance to CDED:
	  ○ Dietary habits questionnaires
	  ○ 72-H food diaries
	- Body weight, arterial pressure and fasting serum glucose
	- Safety will be assessed by the adverse events, either severe or not, and the SUSAR

	- Quality of life will be assessed by short IBDQ - Work productivity and activity will be assessed by the WPAI questionnaire
Design of the study	This is a multicentre, open-label, comparative, randomized, 2:1, controlled, single-blind, superiority
Population of study participants	Patients with active Crohn Disease
Inclusion criteria	− Patients aged 16 to 70 years, − With mild to moderate, luminal, active CD, defined by a HBI of 5 to 16, involving the small bowel, and/or the colon − Not treated with corticosteroids at baseline − Patients either naïve or previously exposed to a maximum of two classes of biologics or currently receiving a biologic therapy, and exposed to a maximum of two classes of biologic therapy, including the current one − Patent small bowel as assessed by the patency capsule − Active endoscopic lesions, as defined by Lewis score ≥ 225 in the small bowel and/or SES-CD≥ 4 in the colon. The eligibility of the patient will be determined by at least one central reader. − Informed consent to participate in this study. − In patients from France and Israel who are aged less than 18: parents' informed consent to participate in this study (parents' agreement is not required in patients aged 16 to 18 in the Netherlands) − Affiliation to social security or any health insurance
Exclusion criteria	− Inability to follow the CDED during 16 weeks. − Prior intolerance to corticosteroids. − Ongoing infections, evolving virus diseases. − Live vaccines. − Psychotic state not controlled by treatment. − Arthritis or uveitis as main presenting symptoms. − Patients with severe and/or predominant rectal or perianal disease. − Heavy smokers (more than 10 cigarettes per day). − Infliximab, adalimumab, vedolizumab, ustekinumab, rizankizumab, upadacitinib, methotrexate or azathioprine initiated less than 3 months before inclusion in this trial. − Change in methotrexate, azathioprine, infliximab, adalimumab, vedolizumab, upadactinib, risankizumab or ustekinumab dosage less than 2 months before inclusion. − Severe pubertal delay (Tanner 1 or Tanner 2) and/or height velocity z-score < 2.5 and/or bone mineral density z-score (hip or lumbar spine) <2.5 (if known). − Pregnant or lactating women. − Patients already included in a biomedical research other than an observational study (e.g. registry, cohort, biobank). Persons deprived of their liberty by a judicial or administrative decision, persons subject to psychiatric care under sections L.3212-1 and L.3213-1 and persons admitted to a health or social institution for purposes other than research (L.1121-6) in France − Present or past history of eating disorder including anorexia nervosa
Interventions or product under investigation	Crohn's Disease Exclusion Diet (CDED)

Comparator arm	Oral corticosteroids (prednisolone or budesonide)
Interventions added by the study	Two panenteric PCC CDED Biological collection: stool and serum collection Pregnancy tests
Expected benefits for the participants and for society	The potential benefit of the trial is that of an improvement of CD endoscopic lesions with dietary therapy that has no known side effects. Multiple studies have shown that healing of endoscopic lesions was associated with long-term beneficial outcomes.
Risks and burdens added by the study	So far, no risk associated with the exclusion diet, exclusive, partial enteral nutrition or CDED for Crohn's disease has been identified. Yet, CDED is burdensome because it consists in the avoidance of many food items. PCC carries the risk of intestinal obstruction or perforation if the capsule is blocked above an intestinal stricture. This risk can be avoided by the systematic use of the patency capsule prior to administration of the real capsule. Each of the two panenteric capsule endoscopies needs bowel preparation. However, patients whose endoscopic lesions are confined to the small bowel at the first PCC, will be prepared by only 1000 mL of PEG, 30 minutes after the second PCC. Moreover, PCC caries the risk of delayed or no excretion of the capsule and the risk of lesion or mucosal bleeding. ➔ The risk level of the study is B (= somewhat higher than the risk of standard medical care).
Practical implementation	See chart in 5.8
Number of participants included	80 randomized About 140 screened
Number of centres	17 in France, Israel and the Netherlands
Duration of the study	Inclusion period: 36 months Participation period (treatment + follow-up): 12 months Total duration : 48 months
Number of enrolments expected per site and per month	0.1
Statistical analysis	It will be based on the intent-to-treat principle (ITT). Based on the available literature, we hypothesize that 50 % of patients will reach the primary endpoint in the CDED arm *versus* 20% in the corticosteroid arm. We plan to screen 140 patients to include 80 patients. 54 will be randomized to CDED and 26 to corticosteroids.
Funding sources	PHRC, Nestlé, gift of a patient
Data Safety Monitoring Board	No, because there is no expected safety issue raised by CDED.

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Background

Current medical treatment of Crohn's disease (CD) consists of immunosuppressive drug therapy (corticosteroids, azathioprine, methotrexate, anti-TNF monoclonal antibodies). These agents control symptoms of CD in most patients but their withdrawal leads to disease relapse. They are also associated with serious adverse events, such as infections and lymphoma (1, 2). Future CD drugs are small molecules or biologics that antagonize pro-inflammatory cytokines or gut homing of lymphocytes. They have similar safety issues as the immunosuppressive agents currently in use.

Epidemiological and experimental studies have suggested that diet plays an important role in CD pathophysiology. The pathogenesis of CD appears to involve alteration of the microbiome as well as a breakdown in barrier function with defective bacterial clearance (3). Changes in dietary intake and industrialization may explain the rise in CD incidence over the past decades. These changes of food may induce alteration in the microbiome and impair the barrier function of the mucous layer and intestinal epithelium, which then allows adherence and immune triggering by the altered mucosal microbiome (3).

Exclusive enteral nutrition (EEN), consisting of a liquid formula diet while avoiding any other oral intake, has been used for decades to treat active CD in pediatric and adult patients. It improves symptoms and heals endoscopic lesions better than corticosteroids (4, 5, 6). EEN has no medical side effects, and is currently recommended as a first-line treatment in pediatric CD (8). However, long-term compliance of EEN is poor.

Crohn's Disease Exclusion Diet (CDED) is a new treatment of active CD. It is a whole-food diet coupled with Partial Enteral Nutrition (PEN). It is aimed to restore intestinal barrier and improve microbiota composition by exclusion of dietary components that contribute to its dysfunction (3). A recent randomized, controlled trial has shown that CDED was equally effective and better tolerated than exclusive enteral nutrition in pediatric CD patients (9). Importantly it was also highly effective for reduction in inflammation and partially corrected dysbiosis. This is the first demonstration of the efficacy of an exclusion diet in CD. Yet, there are several questions remaining:

- Does CDED have the same efficacy in adults?
- What is the effect on endoscopic lesions?
- What is the relative efficacy of CDED as compared with current treatment (10)?

Crohn's disease affects children but the majority of patients are adults. It is mandatory to ensure that CDED does not only relief symptoms, but also heals the mucosa.
In this randomized clinical trial, we aim to compare the tolerability and efficacy of CDED coupled with PEN with corticosteroids, in inducing endoscopic response.

2.2 Hypothesis for the study

The hypothesis of the present study is that CDED leads to a better endoscopic response than corticosteroids in adult and pediatric patients (16 to 70 years) with active CD. This hypothesis is based upon data showing better efficacy of EEN over corticosteroids on endoscopic lesions and equivalence between CDED and EEN on clinical response and calprotectin levels.

2.3 Description of knowledge relating to the condition in question

Crohn's disease (CD) is a chronic and disabling inflammatory bowel disease with increasing incidence worldwide. It is commonly accepted that environmental factors associated with western lifestyle play an important role in the rising incidence of CD. The pathogenesis of CD appears to involve alteration of the microbiome as well as a breakdown in barrier function with defective bacterial clearance (3). Changes in dietary intake and industrialization may explain the rise in CD incidence over the past decades. These changes

of food may induce alteration in the microbiome and impair the barrier function of the mucous layer and intestinal epithelium, which then allows adherence and immune triggering by the altered mucosal microbiome (3).

Yet, current medical treatment of CD consists of immunosuppressive drug therapy (corticosteroids, azathioprine, methotrexate, anti-TNF monoclonal antibodies). These agents control symptoms of CD in most patients but their withdrawal leads to disease relapse. They are also associated with serious adverse events, such as infections and lymphoma (1, 2). Newer and future CD drugs are small molecules or biologics that antagonize pro-inflammatory cytokines or gut homing of lymphocytes. They have similar safety issues as the immunosuppressive agents currently in use.

CD therapies targeting the microbiome or the intestinal barrier are timely and important but challenging. Dietary therapy is one of these.

2.4 Summary of relevant pre-clinical experiments and clinical trials

Exclusive enteral nutrition consists in a liquid formula diet and avoidance of any other oral intake; it has been used for decades to treat active CD in pediatric and adult patients. It improves symptoms and heals endoscopic lesions better than corticosteroids (4, 5, 6). EEN has no medical side effects, and is currently recommended as a first-line treatment in pediatric CD (8). However, long-term compliance of EEN is poor.

Crohn's Disease Exclusion Diet (CDED) is a new treatment of active CD. It is a whole-food diet coupled with Partial Enteral Nutrition (PEN). It is aimed to restore intestinal barrier and improve microbiota composition by exclusion of dietary components that contribute to its dysfunction (3). A recent randomized, controlled trial has shown that CDED was equally effective and better tolerated and accepted than exclusive enteral nutrition in pediatric CD patients (9). Importantly it was also effective for reduction in inflammation and partially corrected dysbiosis. After week 6, patients who were randomized to CDED had a stepdown version of the CDED + PEN (accounting for 25% of the energy intake), referred to as phase 2. Those who were randomized to EEN had a normal diet. Patients randomized in the CDED arm had better outcomes than those randomized to EEN, at week 12.

2.5 Description of the studied population and justification of main inclusion criteria

Patients included will be aged 16 to 70 years. They will have mildly to moderately active luminal CD. This choice is based on the fact that mild to moderate luminal disease is the primary indication for dietary therapy at the present time. Patients with active arthritis or uveitis, severe and/or predominant rectal or perianal disease, stricturing or penetrating phenotypes will be excluded because currently available experience suggests that CDED is less efficient in these categories of patients and because biologic therapy may be indicated, and we do not wish to cause harm. Patients who cannot tolerate Modulen even after addition of flavors will continue in the trial with only the CDED without Modulen and will be continue with the prescription of calcium supplement and vitamin D. Patient with small bowel CD will be assessed by the patency capsule before the first PCC. Patients will need to have significant, active endoscopic lesions in the small bowel and/or the colon, upon baseline panenteric capsule endoscopy, because the primary objective is to demonstrate that CDED improves endoscopic lesions of CD.

2.6 Brief description of the investigational product(s) or intervention(s)

The CDED is the investigational, dietary intervention; it will be tested in the experimental arm and compared to corticosteroids during the 16-week course of this randomized trial. During the first 6 weeks, patients will be prescribed the CDED and partial enteral nutrition (oral Modulen®, Nestlé Health Science, Vevey, Switzerland) with 1 liter of Modulen which will account for approximately 40% of energy intake. Between week 6 and 16, patients will be prescribed CDED and oral Modulen 500 mL®, as a supplement, which will account for 80% and 20% of the energy intake, respectively.

The principles underlying the CDED, the foods allowed and disallowed in the two phases (phase 1: week 0 to 6 and phase 2: week 6 to 16) for induction of remission have been published elsewhere (3, 8) and appear in section 18.1. The diet includes 5 mandatory foods to consume daily to provide specific fibers and starches as substrates for short chain fatty acids–producing taxa from Firmicutes, as well as sources of lean protein that are low in animal fat to decrease Proteobacteria and improve intestinal permeability. The CDED reduces exposure to animal and dairy fat, high fat from other sources, wheat, red or processed meat and protein sources rich in taurine, emulsifiers, artificial sweeteners, carrageenans and sulfites. During the phase 2, diet allows higher exposure to fruits, vegetables, and legumes along with some foods that are reintroduced to increase flexibility and reduce monotony. From week 16, patients will transit to the maintenance phase of the diet (phase 3) which does not induce remission but is designed to prevent rebound of dysbiosis and inflammation and maintain the effect of the first two stages. Vegetarians will receive a CDED without meat.

The patients randomized to receive CDED will receive education material, recipes and dietary instructions, by a CDED-trained registered clinical dietitian. Patients will be explained the CDED at baseline and week 6; they will also have telephone calls at weeks 1 and 9, to ensure compliance and understanding of the CDED. Prior to the start-up of individual centers, dietitians will be trained by dietitians from each country that had been already trained prior to the study. Patients and dietitians will also use USB keys and a smartphone application dedicated to the CDED. In France, a hotline managed by a research dietitian will be available for patients and dietitians for any questions regarding the diet. Diet implementation in France, the Netherlands and Israel will be performed using documents translated in the local language of patients.

Due to difficulties in implementing CDED in hospitals, hospitalized patients randomized in the CDED arm will continue to receive CDED during their hospital stay, if possible. If not, they will receive exclusive Modulen.

2.7 Summary of the known and foreseeable benefits and risks for the research participants

So far, no risk associated with the Crohn's Disease Exclusion Diet (CDED) or Partial Enteral Nutrition (PEN) for Crohn's disease has been identified. This diet is well balanced and provide adequate nutritional needs for patients. Yet, CDED is burdensome because it consists in the avoidance of many foods items.

PCC carries the risk of intestinal obstruction or perforation if the capsule is blocked above an intestinal stricture. This risk can be avoided by the systematic use of the patency capsule prior to administration of the real capsule. Each of the two PCC needs bowel preparation as detailed in Addenda 18.2 (adapted from Eliakim R, et al. Endosc Int Open. 2018;6:E1235). However, in patients with purely small bowel disease on the first PCC, the bowel preparation for the second videocapsule will consist in clear liquid diet at day-1 and 1 liter of PEG, 30 minutes after the ingestion of the PCC.

Moreover, PCC carries the risk of delayed or no excretion of the capsule and the risk of lesion or mucosal bleeding. The bowel preparation for PillCam Crohn's capsule is shown in Addenda 18.2.

The potential benefit of the trial is that of a better control of CD symptoms and endoscopic lesions with a therapy that has no medical complication. Multiple studies have shown that healing of endoscopic lesions was associated with long-term beneficial outcomes.

3 OBJECTIVES

3.1 Primary objective

The main objective is to assess whether CDED is superior to corticosteroids, in terms of endoscopic response, in patients with mildly to moderately active, luminal, inflammatory CD.

3.2 Secondary objectives

The secondary objectives are to compare in the two arms of the trial:

- Proportion of patients with endoscopic remission (at week 16 only);
- Fecal calprotectine and serum CRP;
- Clinical response and remission;
- Body weight, arterial pressure and fasting serum glucose
- Compliance;
- Safety;
- Patient satisfaction;
- Quality of life;
- Work productivity and activity

3.3 Objective of any potential ancillary study

The objectives of ancillary studies are to compare, at baseline, week 6, week 16, week 32 and week 48, in the two arms of the trial, gut microbiome composition (measured in feces) in terms of bacteria, protists, fungi, viruses and metabolomics.

4 STUDY DESIGN

4.1 Study endpoints

4.1.1 Primary endpoint

Endoscopic response at week 16, without corticosteroids or further therapeutic intervention (surgery, biologics or dietary intervention), assessed by a centralized, pseudonymized and blinded, double lecture panel of panenteric PillCam Crohn's Capsule (PCC).

Endoscopic response is defined by a decrease of at least 50% in the Lewis score for patients with small bowel CD, decrease of SES-CD of at least 50% in patients with colonic CD and both of these in patients with small bowel and colonic CD, compared to baseline values.

In patients with small bowel and colonic Crohn's disease and insufficient bowel preparation, precluding adequate assessment of a part of intestinal mucosa, endoscopic response will be assessed in the bowel part(s) adequately prepared at baseline and at week 16. For example, if a patient has an adequate preparation in the ileum and insufficient preparation in the colon, endoscopic lesions will be compared at baseline and week 16 in the ileum only.

4.1.2 Secondary endpoints

Compare in the 2 arms of the trial:

- (Steroid-free) clinical remission (HBI <5) and response (a decrease of at least 3 points in HBI) at baseline, week 6, 16, 32 and 48.
- (Steroid-free) clinical remission (CDAI <150) and response (a decrease of at least 70 points in CDAI) at baseline, week 6, 16, 32 and 48.
  CDAI will be measured by the investigator on the basis of prospective questionnaires filled in by patients during the week preceding each visit. *In patients between 16 and 18 years, the CDAI will also be used. Although the PCDAI is commonly used for pediatric case with the main difference between CDAI and pCDAI being evaluation of growth parameters, final stature will be achieved in most patients and therefore we chose to use the CDAI in all patients for consistency.*
- Need for further therapeutic intervention (i.e., steroids, immunosuppressants, new biologic or surgery) between baseline and 48.
- Decrease of fecal calprotectin of at least 50% compared to baseline, week 6, 16, 32 and 48, off steroids.
- Fecal calprotectin of less than 250 µg/g, less than 100 µg/g and less than 50 µg/g at week 16. Fecal calprotectin will be measured locally.
- CRP serum level <5 mg/L. CRP will be measured locally at baseline, week 6, 16, 32 and 48.
- Median HBI, CDAI, calprotectin and CRP at baseline, week 6, 16, 32 and 48.
- Endoscopic remission as defined as Lewis score <135 in the small bowel and/or SES-CD=0-2 in the colon, without further therapeutic intervention (surgery, biologics or dietary intervention), as compared to baseline, at week 16 (and week 32 for patients randomized in the control arm who have switched to CDED at week 16).
- Endoscopic response and remission graded by Eliakim score at week 16 (and week 32 for patients randomized in the control arm who have switched to CDED at week 16).
- Segmental endoscopic response and remission between baseline and week 16 (and week 32 for patients in the control arm who have switched to CDED at week 16).
- Gut microbiota composition (PCR 16s, PCR 18S for fungi and protists, metabolomics and shotgun metagenomics) at baseline, week 6, 16, 32 and 48.
- Compliance to corticosteroid treatment: Medication Adherence Report Scale at week 3, 6, 9 and 16.

- Compliance to CDED:
    - Dietary habits questionnaires at baseline, week 6 and 16 in the corticosteroid arm and at baseline, week 1, 3, 6, 9, 12 and 16, 32 and 48 in the CDED arm.
    - 72-H food diaries at baseline, week 6, 16 and 48 in the corticosteroid arm and at baseline, week 3, 6, 9, 16, 32 and 48 in the CDED arm.
- Body weight, arterial pressure and fasting serum glucose at baseline, week 3, 6, 16, 32 and 48.
- Safety will be assessed by the adverse events, either severe or not, and the SUSAR, after baseline.
- Quality of life will be assessed by short IBDQ at week 3, 6 and 16.
- Work productivity and activity will be assessed by the WPAI questionnaire at week 0, 6 and 16.

4.2 Description of research methodology

4.2.1 Design of the study

This is a multicentre, open-label, comparative, randomized, 2:1, controlled, single-blinded, superiority with two parallel arms:

- Experimental arm: 16-week course of CDED+Partial Enteral Nutrition.

During the first 6 weeks (phase 1 of CDED), patients will be prescribed the CDED and oral Modulen 1 liter (1000kcal) daily. Between week 6 and 16 (phase 2 of CDED), patients will be prescribed CDED and oral Modulen® (500 mL).

- Control arm: corticosteroids.

Patients will be prescribed either oral prednisolone or budesonide (for patients aged 18 years or more, with ileal or ileocaecal CD), with a fixed, tapering regimen such that patients should be off steroids by the last day of week 12. Increases in steroid dose during tapering of corticosteroids is allowed but if the patient receives steroids (other than hydrocortisone for adrenal insufficiency) after week 12, he/she is in ITT failure.

Oral prednisolone will be prescribed at an initial dose of 40 to 60 mg/day (or 1 mg/kg for those patients who weigh less than 40 kg).
The following tapering regimen will be applied:

- Prednisolone starting dose= 40 mg. This dose is maintained for 3 weeks followed by 1 week at a dose of 35 mg, 1 week at 30, 1 week at 25, 1 week at 20, 1 week at 15, 2 weeks at 10 and 2 weeks at 5 mg (prednisolone cumulative dose=1925 mg)
- Prednisolone starting dose= 50 mg. This dose is maintained for 2 weeks followed by 1 week at 45, 1 week at 40, 1 week at 35, 1 week at 30, 1 week at 25, 1 week at 20, 1 week at 15, 1 week at 10 and 1 week at 5 mg (prednisolone cumulative dose= 2275 mg)
- Prednisolone starting dose= 60 mg. This dose is maintained for 2 weeks followed by 1 week at 50, 1 week at 40, 1 week at 30, 1 week at 25, 1 week at 20, 1 week at 15, 1 week at 10 and 1 week at 5 mg (prednisolone cumulative dose= 2205 mg).

Budesonide will be prescribed at an initial dose of 9 mg/day for 8 weeks followed by 6 mg/day for 2 weeks and 3 mg/day for 2 weeks.

Long-term follow-up:

- Patients randomized to the experimental arm and who had responded will be asked to continue with the CDED during 48 weeks (phase 3 of CDED). Patients who will complete the CDED at week 48 will undergo an additional PCC, as in the current setting. These data will be collected.

- Patients randomized to the control arm will have the option to switch to CDED after week 16.
    - Patients who are not in clinical remission (HBI ≥ 5) AND/OR who have not reached endoscopic response will be proposed CDED phase 1 and 2, according to the same scheme as in the experimental arm for 16 weeks. A PCC will be proposed after 16 weeks of CDED (that is, week 32 after inclusion) while clinical and biological parameters will be collected similarly as in the controlled part of the trial. Subsequently, they will be proposed to enter into the phase 3 of CDED. This will be decided by the referral physician and will be conducted in the routine setting.
    - Patients in clinical remission (HBI less than 5) AND in endoscopic response (decrease of at least 50% in the Lewis score for patients with small bowel CD, decrease of SES-CD of at least 50% in patients with colonic CD and both of these in patients with small bowel and colonic CD, compared to baseline) will be proposed phase 3 of CDED, as a maintenance treatment.

4.2.2 Number of participating sites

This is a multicentre trial involving several participating centres in France, Israel and Netherlands.

Recruitment centres: Participants will be recruited in the following hospitals (centers expected):

FRANCE (9 centers)

- Adult centers (N=7)
    1. CHU du Kremlin Bicêtre, Prof Franck Carbonnel, Dr Antoine Meyer
    2. CHU de Reims, Prof Guillaume Cadiot
    3. CHU de Clermont Ferrand, Prof Anthony Buisson
    4. CHU de Nice Prof Xavier Hébuterne
    5. CHU de Lille, Dr Maria Nachury, Prof Pierre Desreumeaux
    6. CHU Saint Louis, Paris, Prof Matthieu Allez
    7. Hôpital Saint Antoine, Prof Philippe SEKSIK
- Pediatric centers (N=2)
    8. Hôpital Robert Debré, Paris, Prof Jean Pierre Hugot
    9. Hôpital Necker, Paris, Prof Frank Ruemmele

ISRAEL: country coordinator: Nitsan Maharshak

1. Adults : Department of Gastroenterology and Liver Diseases, Prof Nitsan Maharshak, Tel Aviv Medical Center,Israel
2. Adults: Emek Medical Center Afula, Dr Eran Zitan, Israel

Independent reader: Sheba Medical Center, Prof Rami Eliakim and Prof. Uri Kopilov, Tel Aviv, Israël (non-recruiting center, blinded lecture of PCC).

NETHERLANDS: country coordinator: Geert D'Haens

- Adult centers
    1. Amsterdam UMC, Prof. Geert d'Haens,
    2. University Medical Center Groningen (UMCG), Rinse Karel Weersma and and Gerard Dijkstra
    3. Onze Lieve Vrouwe Gasthuis (OLVG): Jeroen Jansen, Pieter Stokkers, Svend Rietdijk
    4. Leiden University Medical Center (LUMC): Andrea vd Meulen, Jeroen Maljaars
    5. RadboudUMC: Marjolijn Duijvestein

- Pediatric center
    6. Amsterdam UMC: Johan Van Limbergen

Independent reader: Dr. Mark Löwenberg, Amsterdam UMC (blinded lecture of PCC)

4.2.3 Identification of participants

The participants in this research will be identified as follows: Site number (3 digits) - Sequential enrolment number for the site (4 digits). This reference number is unique and will be used for the entire duration of the study. A randomisation number will also be assigned when the participant is randomised.

4.2.4 Randomisation

When selected, the patient eligibility will be evaluated from inclusion and non-inclusion criteria. Once the consent has been signed by the patient and investigator, the patient will be included and randomised by connecting the eCRF. The patient identification number will be allocated.

Randomization of patients will be centralized and carried out using a computerized system in the eCRF website (Cleanweb) according to a predefined randomization list. Distribution in the two groups will be made in a **2:1 ratio (54 in Experimental arm and 26 in the Control arm).**

The randomization list will be designed by the Sponsor and stratified by center. Each list will be based on permutation blocks, the size of which will be unknown to practitioners involved in patient accrual.

4.2.5 Blinding methods and measures put in place to protect blinding

Neither the patients nor the treating physician will be blinded during the trial. However, the PCC lecture will be centrally read by two independent readers in Tel Aviv and Amsterdam who will be blinded of the arm in which the patient will be randomized.

5 IMPLEMENTATION OF THE STUDY

5.1 Summary of biological materials collection

Stool collection:

At screening visit, as well as week 3, 6, 16 and 32, patients will be given two kits to collect stool specimens for calprotectin testing and microbiota analysis, before bowel preparation. These stool specimens will then be delivered at the next visits, i.e. baseline, week 6, 16, 32 and 48. Those who consent to participate will be asked to bring a stool specimen for the inclusion visit. For microbiome analyses, fecal sample will be self-collected (in tubes with incorporated 1g spoons) the day before the visit at the hospital and kept anaerobically at +4°C for 24 to 36 hours before being collected and frozen at -80°C at the hospital. This sampling process, without any preservative, is suitable for analyzing both the genomic material (from bacteria, fungi and viruses) and the metabolites (global metabolomics) within the samples. Briefly, the sampling kit contains 2 screw-cap tubes with incorporated 1g spoons. An anaerobic catalyzer within the provided bag will ensure anaerobic atmosphere in the sampling kit until -80°C freezing at the hospital. Batches of frozen samples will then be sent to the collection lab (INRA-Micalis) in dry ice and kept at -80°C before microbiome analyses.

Serum collection:

Two dry tubes of 5 ml of blood will be drawn by a nurse at day 0 (baseline) and week 16. They will be centrifuged and decanted into 4 alicots, stored frozen at -80°C, locally (in the CIC or within clinical units). Serum will be transferred to (along with th stools) and stored at the PhylHom laboratory from the INRA – Micalis Institute (INRAE – Micalis, Building 442, Domaine de Vilvert 78350 Jouy-en-Josas, France) under the supervision of Dr Patricia Lepage for a period of at least 5 years. All serum samples will be stored in duplicates in 2 different -80°C freezers (both equipped with security alarms) and located in 2 different buildings of the campus.

5.2 Screening visit

Before any examination or intervention related to the study may be carried out, the investigator must obtain the freely given, informed and written consent of the participant.

The screening visit will take place in outpatient consultation, between 21 days and no later than three days before the baseline visit. It will be conducted by the principal investigator or collaborating physician declared and trained in the study (gastroenterologist or paediatrician).

- The inclusion and exclusion criteria will be verified.
- Patients will be asked about their complete medical history and current symptoms according to a predefined form within the eCRF.
- The HBI and CDAI items will be collected and the HBI and CDAI will be calculated.
- A physical examination, including abdominal examination, blood pressure, cardiac and pulmonary examination will be conducted.
- The following laboratory tests will be prescribed for the next visit: CRP serum levels, albumin, CBC, serum creatinine and electrolyte levels, liver function tests, fasting serum glucose, serum vitamin D.
- A pregnancy test will be performed.
- The patients (or their legal representatives) will be informed of the study by the investigating physician. Their consent will be obtained after they have time (2 days or more) to consider their participation.

Patency Capsule and PCC:

Patients who consent to participate to the trial will be asked to ingest a patency capsule (PC). Written instructions will be given with the patency capsule for plain abdominal X-rays 30 hours after the patency capsule ingestion.

The criteria for small bowel patency are the following:

- Natural excretion of an intact PC (both plugs and body; see Addenda 3), ≤30 hours post-ingestion. Patients will be asked to take a picture of the patency capsule and to send it to the investigators. If the capsule is intact (Addenda 3), no plain abdominal X-rays will be performed;
- No visible PC on plain abdominal X-rays performed at 30 hours post ingestion
- Visible PC projection at 30 hours post-ingestion on abdominal X-ray, but an intact PC body excreted 30-36 hours post-ingestion
- No abdominal pain and/or obstructive symptoms during PC passage.

If the intestines are patent, the patients will be asked to ingest the real PCC after a bowel preparation, as detailed in addendum 18.2. PCC files will be read centrally.

- *Patients with significant lesions (Lewis score ≥ 225 in the small bowel and/or SES-CD≥ 4 in the colon) will be eligible for the study.*
- *Patients with patent small bowel but significant stenosis, as assessed by central readings of the PCC, will not be included in the trial; they will be proposed the CDED on an open label basis.*

In order to avoid an additional bowel preparation, patients who had undergone an ileocolonoscopy within 30 days prior to screening visit, and who had a video recording, and/or SES-CD scoring will have 1000 mL of PEG 1 hour after PCC, for small bowel videocapsule. At week 16, they will undergo a PCC with bowel preparation.

Summary of the patient's information:

Whose consent must be obtained	***Who informs the individuals and collects their consent***	***At what point the individuals are informed***	***At what point the consent is obtained***
The individual participating in the study *or holders of parental authority for minors*	The principal investigator or collaborating physician declared and trained in the study (gastroenterologist or paediatrician)	Screening visit; (standard of care visit)	After a reflection period of 2-5 days following the screening visit

5.3 Baseline visit / randomisation / inclusion visit

Reminder for French centers: before any examination or intervention related to the study may be carried out, the investigator must obtain the *freely given, informed and written consent of the participant, or of holders of parental authority* Individuals liable to participate in studies stipulated in line 1° of article L. 1121-1 of the *Code de la Santé Publique* (French Public Health Code) benefit from a preliminary medical examination adapted to the study.

The baseline / randomization / inclusion visit will take place in in outpatient consultation.

- The inclusion and exclusion criteria will be verified.
- Patients will be asked about their symptoms according to a predefined form.
- The HBI and CDAI items will be collected and the HBI and CDAI will be calculated.

- Short IBDQ form will be filled in and collected.
- A 24-hour recall will be performed by a dietitian; energy, protein, fat, carbohydrate, fibre, calcium, zinc, iron, folates and vitamin B12 intakes wil be calculated.
- A 72-hour food diary will be filled in by the patient and reviewed by the dietitian.
- A dietary habits questionnaire will be filled in by the patient and reviewed by the dietitian.
- A physical examination, including abdominal examination, blood pressure, cardiac and pulmonary examination will be conducted.
- The results of the laboratory tests prescribed at the screening visit will be reviewed; their values and the expected laboratory standards will be filled in the eCRF.
- A randomization will be carried out using a computerized system in the eCRF website (Cleanweb).
- The patients randomized to receive CDED will be explained the CDED, they will receive education material, recipes and dietary instructions, they will be informed of the hotline and be invited to use the CDED-dedicated smartphone application, by a CDED-trained registered clinical dietitian.
- The patients randomized to receive corticosteroids will be prescribed oral corticosteroids (prednisolone or budesonide).
- All patients will be asked to fill the WPAI (Work Productivity and Activity Impairment) questionnaire.
- All patients will receive a prescription of 2000 IU (50 microgram) daily of vitamin D for the duration of study and 1000 mg of calcium.

Stool specimens:

Patients will deliver their stool specimens pot as asked by the physician at screening for calprotectin testing and microbiota analysis for fecal self-collection. Stool specimens will be sent for calprotectin testing and another specimen will be stored at -80°C for further microbiome analysis.

Serum collection:

Two dry tubes of 5 ml of blood will be drawn by a nurse at baseline. They will be centrifuged and decanted into 4 alicots, stored frozen at -80°C, locally (in the CIC or within clinical units). Serum will be transferred to (along with th stools) and stored at the PhylHom laboratory from the INRA – Micalis Institute (INRAE – Micalis, Building 442, Domaine de Vilvert 78350 Jouy-en-Josas, France) under the supervision of Dr Patricia Lepage for a period of at least 5 years. All serum samples will be stored in duplicates in 2 different -80°C freezers (both equipped with security alarms) and located in 2 different buildings of the campus.

5.4 Follow-up visits

5.4.1 Patients will be seen physically by the principal investigator or a collaborating physician declared and trained, at week 3, 6, 16 and 32 (±3 days for each).

The follow-up visits will take place in hospitalisation or, most often, in outpatient consultation.

- At each visit, patients will be asked about their symptoms according to a predefined form for calculation of HBI and CDAI.
- The HBI and CDAI items will be collected and the HBI and CDAI will be calculated.
- Compliance to corticosteroid treatment will be assessed by Medication Adherence Report Scale at week 3, 6, 9 and 16 (only in the control arm).
- Compliance to CDED will be assessed by:
    - Dietary habits questionnaires at week 16 in the corticosteroid arm and at week 3, 6, 16 and 32 in the CDED arm
    - 72 h food diaries at baseline, week 6, and 16 in the corticosteroid arm and at inclusion, week 3, 6, 16 and 32 in the CDED arm

- Adverse events, either severe or not, will be notified at each visit.
- Medications and their doses will be noted.
- A physical examination, including abdominal examination, blood pressure, cardiac and pulmonary examination will be conducted.
- The results of the blood tests prescribed at the previous visits will be reviewed (except week 3: no blood test will be prescribed at baseline); their values and the expected laboratory standards will be filled in the eCRF.
- Short IBDQ form will be filled in and collected at week 6 and 16.
- Bowel preparation will be prescribed at week 6 for PCC at week 16.
- Pregnancy test at week 6 and 16.
- Patients will be asked to fill the WPAI questionnaire at week 6 and 16.
- A 24-hour recall will be performed by a dietitian at week 6 and 16.
- Serum will be collected at week 16.

Stool specimens:

At week 3, 6 and 16, patients will be given a pot to collect a stool specimen for calprotectin testing and microbiota analysis for fecal self-collection 24 to 36h before visits at week 6, 16 and 32. Stool specimens will be sent for calprotectin testing and another specimen will be stored at -80°C for further microbiome analysis at week 6, 16 and 32.

Serum collection:

Two dry tubes of 5 ml of blood will be drawn by a nurse at week 16. They will be centrifuged and decanted into 4 alicots, stored frozen at -80°C, locally (in the CIC or within clinical units). Serum will be transferred to (along with th stools) and stored at the PhylHom laboratory from the INRA – Micalis Institute (INRAE – Micalis, Building 442, Domaine de Vilvert 78350 Jouy-en-Josas, France) under the supervision of Dr Patricia Lepage for a period of at least 5 years. All serum samples will be stored in duplicates in 2 different -80°C freezers (both equipped with security alarms) and located in 2 different buildings of the campus.

PCC at week 16:

Patients will undergo the PCC, after bowel preparation. A second patency capsule is not required before week 16 PCC, unless new symptoms, indicative of bowel obstruction appeared between baseline and week 16. Patients with endoscopic lesions confined to the small bowel will be prepared with 1000 mL of PEG for the second PCC.

PCC at week 32:

Patients that switch from the corticosteroid group to the CDED group at week 16 will be proposed a PCC at week 32.

All PCCs will be read centrally, in Amsterdam and Tel Aviv, in a blinded fashion.

5.4.2 All patients will have telephone calls with at weeks 1, 9 and 12 with the principal investigator or a collaborating physician. CDED patients will also have a telephone consultation at week 1, 9 and 12 with a CDED-trained dietitian.

In the CDED group, these visits will ensure compliance (using dietary habits questionnaire in all these visits and the 72h-diary at W9), understanding of the CDED, checking of adverse events and well-being.

In the control group, these visits will serve to check adverse events and well-being.

5.4.3 Decisions at week 16

5.4.3.1 Patients randomized to the CDED arm and who had responded clinically will be asked to continue with the phase 3 of the CDED diet until week 48, as in routine practice. Phase 3 of CDED includes Modulen IBD, which accounts for 25% of the energy intake.

5.4.3.2 Patients randomized to the control arm have the option to switch to CDED after week 16.

- Patients in clinical remission (HBI of less than 5) AND in endoscopic response (decrease of at least 50% in the Lewis score for patients with small bowel CD, decrease of SES-CD of at least 50% in patients with colonic CD and both of these in patients with small bowel and colonic CD, compared to baseline) will be proposed phase 3 of CDED, as a maintenance treatment.
- Patients who are not in clinical remission (HBI ≥ 5) AND/OR who have not reached endoscopic response will be proposed CDED phase 1 and 2, according to the same scheme and follow-up as in the experimental arm, for 16 weeks (this triggers additionnal visits for such patients at week 17, 19, 22, 25 and 28). A PCC will be proposed after 16 weeks of CDED (that is, week 32 after inclusion) while clinical and biological parameters will be collected similarly as in the randomized part of the trial. Subsequently, they will be proposed to enter into the phase 3 of CDED. This will be decided by the referral physician and will be conducted in the routine setting.

5.5 Last study visit

The last study visit will take place in hospitalisation or, most often, in outpatient consultation and will be performed at week 48 (no later than 52).

- Patients will be asked about their symptoms according to a predefined form.
- The HBI and CDAI items will be collected and the HBI and CDAI will be calculated.
- For patients randomized in the CDED arm, or who switched to CDED at week 16: food intake will be assessed by dietary habits questionnaire and 72-H food diaries.
- Adverse events either severe or not, will be notified.
- Medications and their doses will be noted.
- A short IBDQ form will be filled in and collected.
- A physical examination, including abdominal examination, blood pressure, cardiac and pulmonary examination will be conducted.
- The results of the laboratory tests prescribed at the previous visit will be reviewed; their values and the expected laboratory standards will be filled in the eCRF.
- Stool specimens will be sent for calprotectin testing and another specimen will be stored at -80°C for further microbiome analysis.
- Patients will be asked to fill the WPAI
- For patients randomized in the CDED arm, or who switched to CDED at week 16: a 24-hour recall will be performed by a dietitian

Stool specimens:

Patients will deliver their stool specimens pot as asked by the physician at week 32 for calprotectin testing and microbiota analysis for fecal self-collection. Stool specimens will be sent for calprotectin testing and another specimen will be stored at -80°C for further microbiome analysis.

5.6 Early termination visit

The early termination visit will take place in hospitalisation or in outpatient consultation. Early termination visit will be performed in patients who are dropped out of the trial. This visit will be similar to the last study visit. A follow-up until week 48 to 52 will be proposed to the patient.

5.7 Expected length of participation and description of the timeline and duration of the study

Duration of enrolment period	3 years
Length of participation for participants	1 year
Maximum period between screening and enrolment	21 days
Duration of interventions performed	16 weeks
Duration of follow-up period	9 months
Total study duration	4 years

5.8 Table summarising the chronology of the study

Actions	D-21 to D -3 (Screening) [d]	D0 (Baseline) [d]	W1 ± 3 days(d) [e]	W3 ± 3 d [d]	W6 ± 3 d [d]	W9 ± 3 d [e]	W12 ± 3 d [e]	W16 ± 3 d [d]	W32 ± 3 d [d]	W48 up to W52 ± 3 d [d]
Informed consent	Research									
Inclusion and exclusion criteria	Research	Research								
Medical history	Care									
Physical examination and symptoms	Care	Care		Care	Care			Care	Care	Care
Crohn's Disease Activity Index	Care	Care		Care	Care			Care	Care	Care
Harvey Bradshaw Index	Care	Care		Care	Care			Care	Care	Care
24-h recall [f]		Research			Research			Research		Research [b]
72-H Food diary [g]		Research		Research [b]	Research	Research [b]		Research	Research [b]	Research [b]
Randomization		Research								
Laboratory blood tests		Care			Care			Care	Care	Care
Pregnancy test	Care				Care			Care		
Fecal calprotectin and stool collection for microbiome analysis		Research (except calpro : Care)			Research (except calpro : Care)			Research (except calpro : Care)	Research (except calpro : Care)	Research (except calpro : Care)
Serum collection		Research						Research		
Patency capsule (X-ray after 30 hours[a])	Research									
PCC	Research							Research	Research [c]	
Adverse events			Research	Research	Research	Research	Research	Research	Research	Research
Medication Adherence Report Scale [h]				Research	Research	Research		Research		
Short IBDQ		Care			Care			Care		Care
WPAI		Research			Research			Research		Research
Dietary habits questionnaire (CDED group[b]) [g]		Research	Research	Research	Research	Research	Research	Research	Research	Research
Dietary habits questionnaire (control group[h]) [g]		Research						Research		
Consultation with a dietitian (CDED group[b])		Research	Research	Research	Research	Research	Research	Research	Research	Research
Consultation with a dietitian (control group[h])		Research			Research			Research		
Prescription of 2000 IU of vitamin D for the duration of study and 1000mg of calcium		Care								
Prescription of corticosteroids [h]		Care								

[a] X-ray only if patency capsule has not appeared in the stools. [b] For patients randomized to receive CDED (at weeks 32 and 48, also comprises patients initially randomized to receive corticosteroids, who then switched to CDED at week 16). [c] Patients randomized to the control arm will have the option to switch to CDED after week 16; active patients at W16 will be proposed a PCC after 16 weeks of CDED. [d] Physical visit. [e] Virtual or physical visit. [f] To be done by the dietitian. [g] Filled in by the patient assisted by the dietician. [h] For patients randomized to the corticosteroids arm.

Research means procedures that are part of the research protocol / Care means procedures that are part of the routine care for patients.

Patients randomized in the control arm who then switch to CDED at week 16 will have visits at weeks 17, 19, 22, 25, 28 and 32 in the same way patients randomized to receive CDED will have visits between baseline and week 16.

5.9 Distinction between standard care and study

The interventions specific for the study are the CDED, the two PCCs endoscopies (including bowel preparation) and the stool collection for microbiota.

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Interventions, procedures and treatments carried out for research purposes	*Interventions, procedures and treatments associated with standard care*	*Interventions, procedures and treatments added for research purposes*
Visits	All visits with physicians	Informed consent Inclusion/non inclusion criteria Randomisation Adverse events Patient diary Consultations with dietitians at baseline, week 3, 6, 16, 32, 48; telephone calls at week 1, 9, 12
Laboratory tests	All of them except serum and stool collections for microbiota. Pregnancy test at baseline, W6 and W16.	Stool collection for microbiota at baseline, W6, W16, W32, W48. Serum collection at baseline and week 16.
Imaging		Patency and PCC at baseline and week 16. And at w32 (for patients who switch to CDED after steroid failure)
Product under investigation	Corticosteroids and tapering regimen Modulen	Crohn's disease exclusion diet (CDED)

5.10 Biological samples collection

Stool samples taken as part of the study will be stored in a biological sample collection.

During the study the fecal sample collection will be stored at the PhylHom laboratory from the INRA – Micalis Institute (INRAE – Micalis, Building 442, Domaine de Vilvert 78350 Jouy-en-Josas, France) under the supervision of Dr Patricia Lepage for a period of at least 5 years. All fecal samples will be stored in duplicates in 2 different -80°C freezers (both equipped with security alarms) and located in 2 different buildings of the campus.

Blood samples: 2 dry tubes of 5 ml of blood to be centrifuged and decanted into 4 alicots, stored frozen at -80°C at baseline and 16 weeks. Serum will be transferred to (along with th stools) and stored at the PhylHom laboratory from the INRA – Micalis Institute (INRAE – Micalis, Building 442, Domaine de Vilvert 78350 Jouy-en-Josas, France) under the supervision of Dr Patricia Lepage for a period of at least 5 years. All serum samples will be stored in duplicates in 2 different -80°C freezers (both equipped with security alarms) and located in 2 different buildings of the campus.

At the end of the study, the samples may be used for further analysis not described in the initial protocol but which may be useful for investigation of the condition in light of advances in scientific knowledge, provided the participant is informed and does not oppose this, as stated in the information note/consent form. In case patients do not consent for their samples to be used for further analyses, the samples will be destroyed 2 years after the end of the study.

If the samples are kept at the end of the study, the sample collection will be declared to the ministry of research [and to the director of the competent regional healthcare authority - if the entity is a health establishment] (Article L. 1243-3 of the *Code de la Santé Publique* [French Public Health Code]).

Type of sample	Quantity	Storage location (name and entity)	Supervisor of the sample collection (name and entity)	Purpose of the sample collection	Storage duration	End use/Future (destruction, etc.)
Fecal samples	**300 samples (in duplicates)**	**INRAE - Micalis**	**Patricia LEPAGE INRAE Micalis Institute**	**Microbiome analyses**	**>5 years**	**If agreed by the patient, samples could be kept 2 years more for further studies. Otherwise, samples will be destroyed 2 years after the end of the study**
Serum samples	**10 mL**	**INRAE - Micalis**	**Patricia LEPAGE INRAE Micalis Institute**	**Proteomic analyses**	**>5 years**	**If agreed by the patient, samples could be kept 2 years more for further studies. Otherwise, samples will be destroyed 2 years after the end of the study**

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Patients aged 16 to 70 years
- With mild to moderate, luminal, active CD, defined by a HBI of 5 to 16, involving the small bowel, and/or the colon.
- Not treated with corticosteroids at baseline
- Patients either naïve or previously exposed to a maximum of two classes of biologics or currently receiving a biologic therapy, and exposed to a maximum of two classes of biologic therapy, including the current one
- Patent small bowel as assessed by the patency capsule
- Active endoscopic lesions, as defined by Lewis ≥ 225 in the small bowel and/or SES-CD≥ 4 in the colon. The eligibility of the patient will be determined by at least one central reader.
- Informed consent to participate in this study
- In patients from France and Israel who are aged less than 18: parents' informed consent to participate in this study (parents' agreement is not required in patients aged 16 to 18 in the Netherlands)
- Affiliation to social security or any health insurance

6.2 Exclusion criteria

- Inability to follow the CDED during 16 weeks.
- Prior intolerance to corticosteroids.
- Ongoing infections, evolving virus diseases.
- Live vaccines.
- Psychotic state not controlled by treatment.
- Arthritis or uveitis as main presenting symptoms.
- Patients with severe and/or predominant rectal or perianal disease.
- Heavy smokers (more than 10 cigarettes per day).
- Infliximab, adalimumab, upadacitinib, vedolizumab, ustekinumab, risankizumab, methotrexate or azathioprine initiated less than 3 months before inclusion in this trial.
- Change in infliximab, adalimumab, upadacitinib, vedolizumab, ustekinumab, risankizumab, methotrexate or azathioprine methotrexate, azathioprine, infliximab, adalimumab, vedolizumab or ustekinumab dosage less than 2 months before inclusion.
- Severe pubertal delay (Tanner 1 or Tanner 2) and/or height velocity z-score < 2.5 and/or Bone mineral density z-score (hip or lumbar spine) <2.5 (if known).
- Pregnant or lactating women.
- Patients already included in a biomedical research other than an observational study (e.g. registry, cohort, biobank).
- Persons deprived of their liberty by a judicial or administrative decision, persons subject to psychiatric care under sections L.3212-1 and L.3213-1 and persons admitted to a health or social institution for purposes other than research (L.1121-6) in France.
- Present or past history of eating disorder including anorexia nervosa.

6.3 Recruitment procedure

Patients will be recruited by hospital physicians, either paediatricians or adult gastroenterologists, mostly in outpatient consultations, less likely in hospitalizations.

	Number of participants
Total number of participants to be screened	About 140
Total number of participants to be randomised	80
Number of centres	17
Enrolment period (months)	36
Number of participants/centre	5
Number of participants/centre/month	0.1

6.4 Termination rules

6.4.1 Criteria and methods for premature discontinuation of study-related interventions/procedures/strategies or product administration

Several situations are possible

- Temporary suspension of CDED or corticosteroids, the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
- Premature discontinuation of CDED or corticosteroids, but the participant remains enrolled in the study until the end of her/his participation
- Premature discontinuation of CDED or corticosteroids, and withdrawal from the study

The investigator must:

- Document the reason(s)
- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant for 12 months following the premature discontinuation of study-related interventions or of the product. Notification of a serious adverse event must be sent to the C.R.O. in charge of research vigilance by email. The serious adverse event will be monitored until it is resolved.

6.4.1.1. Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- If, during the course of his/her participation in the study, the participant presents one exclusion criteria, then the study must be discontinued but the participant will continue to be monitored for the study.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead.

If a patient exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment) (NB: this must be stated in the information and consent form)
- Premature exit from the study will not affect the participant's subsequent care which will be decided by the referring physician.
- In case of serious adverse events, see the corresponding section on vigilance

The case report form must list the various reasons why the participant has discontinued the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

6.4.1.2. Follow-up of participants following premature withdrawal from the study

If a participant discontinues the study, this will in no way affect their usual care for their condition.
In the event of serious adverse events following premature discontinuation of study-related interventions/procedures/strategies or of the product used and participation of the patient in the study; see section 6.4.1.

6.4.1.3. Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the study arms or if there is a discrepancy in the serious adverse reactions between the study arms, requiring a reassessment of the benefit-risk ratio for the study.
Similarly, AP-HP as the sponsor or the Competent Authority (ANSM) may decide to prematurely discontinue the study due to unforeseen issues or new information about CDED in light of which the objectives of the study or clinical programme are unlikely to be achieved.

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

In all cases in which a study is discontinued, the care options must be specified for participants currently enrolled in the study. Notably, it must be specified if the participants included in the study must be monitored until the end of their participation, as set forth in the protocol.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) within a period of 15 days.

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 Experimental arm: CDED

The CDED will be prescribed to patients randomized in the experimental arm, along with calcium and vitam D. It is described above, in section 2.6.

7.2 Control arm: corticosteroids (standard care)

Oral prednisolone or budesonide will be prescribed to patients randomized in the control arm at an initial dose of prednisolone of 40 to 60 mg/day (or 1 mg/kg for those patients who weigh less than 40 kg) or budesonide (for patients aged 18 years or more; initial dose of 9 mg/day), both for 12 weeks, with a fixed, tapering regimen such that patients should be off steroids by the last day of week 12. Calcium, vitamin D and, if needed, potassium, will be prescribed orally.

Increases in steroid dose during tapering of corticosteroids is allowed but if the patient receives steroids (other than hydrocortisone for adrenal insufficiency) after week 12, he/she is in ITT failure. However, patients who received corticosteroids after week 12 will have a PCC at week 16 and will be analyzed separately.

7.3 Authorised and prohibited treatments, including rescue medications

Patients will be allowed to receive a stable dose of immunomodulator or start thiopurines or methotrexate at or after week 12, because the latency of these drugs is unlikely to affect the week 16 endpoint. Patients could receive antibiotics for intercurrent infections, with the exception of quinolones and metronidazole which might have an effect in CD.

8 EFFICACY ASSESSMENT

Panenteric capsule (PillCam Crohn's capsule (PCC); Medtronic) can visualize mucosa of the small bowel and colon. It avoids general anesthesia and is better tolerated by patients than colonoscopy (D'Haens G, et al. Clinical Gastroenterol Hepatol 2015;13:1480). Bowel preparation for PCC is excellent or good in 76 to 84% of patients (D'Haens G, et al. Clinical Gastroenterol Hepatol 2015;13:1480 and Eliakim R et al. Endoscopy International Open; 2018:6:e1235). PCC agrees with colonoscopy for the measurement of SES-CD and SES-CD (intraclass correlation coefficients 0.65 (0.43–0.80) and 0.66 (0.32–0.85) (D'Haens G, et al. Clinical Gastroenterol Hepatol 2015;13:1480).
Endoscopic activity within the small bowel will be measured by the Lewis score. Endoscopic activity within the colon will be measured by the SES-CD.
Patients with a Lewis score ≥ 225 in the small bowel and/or SES≥4 in the colon will be eligible for the trial.

The primary endpoint is the endoscopic response at week 16, assessed by a centralized lecture panel of PCC using centralized, pseudonymized and blinded reading of PCC. For this, in each investigator centre, after pseudonymized, PCC files will be stored locally and uploaded on the eCRF. Video recordings of the PCC will be read centrally in Amsterdam UMC (Mark Lowenberg) and Sheba Medical Center in Tel Aviv (Uri Kopylov). Dr Lowenberg will determine the SES CD and Dr Kopylov will determine the Lewis score. Their access to the eCRF has been configured so that central readers can upload and watch patients' video recordings of PCC while they have no access to clinical data.
Endoscopic response is defined by a 50% drop in the Lewis score in the small bowel and/or a 50% drop of the SES CD in the colon.

9 SPECIFIC STUDY COMMITTEES

9.1 Steering Committee

Composition: coordinating investigator, one or several other investigators, biostatistician, sponsor representatives appointed for this study.

Members of the committee:

- Pr Franck Carbonnel,
- Pr Matthieu Resche-Rigon,
- Thibaut Vanrietvelde,
- Lakhdar Mameri

Role:

- Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the study.
- Propose procedures to be followed during the study. The DRCI sponsor retains decision-making authority.

9.2 Endpoint Adjudication Committee

- Made up of experts in charge of uniformly approving, while blinded to research procedures, the primary endpoint of the trial. The members of this committee are not necessarily independent from the study (they may be investigators) but they will work blinded to the study.

10 SAFETY ASSESSMENT - RISKS AND BURDENS ADDED BY THE STUDY

10.1 Definitions

According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

10.1.1. Adverse event

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

10.1.2. Adverse reaction

Adverse event occurring in a person enrolled in a study involving human participants, when this event is related to the study or to the product being studied.

10.1.3. Serious adverse event or reaction

Any adverse event or reaction that results in death, threatens the life of the research participant, requires hospitalisation or prolongs hospitalisation, causes a serious or long-term disability or handicap, or results in a congenital abnormality or deformity.

10.1.4. Unexpected adverse reaction

Any adverse reaction for which the nature, severity or progression are not consistent with information pertaining to the products, acts practiced and methods used during the study.

Pursuant to article R. 1123-46 of the Code de la Santé Publique and the opinion of the clinical trial sponsor not relating to a health product (ANSM):

10.1.5. Emerging safety issue

Any new information that may lead to a reassessment of the risk/benefit ratio of the study or the product under investigation, modifications to the use of the product, the conduct of the clinical trial, or the clinical trial documents, or to a suspension, interruption or modification of the clinical trial or of similar studies.

For example, this concerns:

- any clinically significant increase in the frequency of an expected serious adverse reaction;

- early termination or a temporary halt for safety reasons for a trial carried out in another country with the same product (act or method) as the one being studied in France;
- recommendations from the Data Monitoring Committee, if applicable, if they are relevant to the safety of the participants;
- suspected unexpected serious adverse reactions in participants who have terminated the trial and of which the sponsor has been notified by the investigator, in addition to any possible follow-up reports.

10.2 The role of the investigator

For each adverse event, the investigator must assess its severity and report all serious and non-serious adverse events in the case report form (e-CRF).

The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events by using general terms:

- *Mild: tolerated by the patient, does not interfere with daily activities*
- *Moderate: sufficiently uncomfortable to affect daily activities*
- *Serious: prevents daily activities*

Note: the degree of severity should not be confused with seriousness.

The investigator must **assess the causal relationship between** a serious adverse events and interventions/procedures added by the study. The method used by the investigator is based on the WHO Uppsala Monitoring Centre Method), and uses the following 4 causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not excluded)

Their definition is presented in the following table (excerpt from WHO-UMC causality categories, version dated 17/04/2012).

Table: WHO-UMC: causality categories (excerpt)

Causality term	Assessment criteria*
Certain to occur	· Event or laboratory test abnormality, with plausible time relationship to drug intake** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable/Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with

**Or study procedures

10.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

As per Article R.1123-49 of the *Code de la Santé Publique* (French Public Health Code), the investigator informs the sponsor without delay on the day he/she becomes aware of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the *Code de la Santé Publique*. A serious adverse event is any untoward medical occurrence that:

1- results in death 2- is life-threatening to the participant enrolled in the study 3- requires hospitalisation or prolongation of existing hospitalisation 4- results in persistent or significant disability/incapacity 5- is a congenital anomaly/birth defect

10.2.2 Specific features of the protocol

Other events that require the investigator to notify the sponsor without delay.

- Adverse events deemed "medically significant"

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above). These are adverse events can be attributable to corticosteroids (hypertension, infection, weight gain, sleep or mood disorders, et.c…) or PCC (intestinal obstruction, capsule retention).

- *In utero* exposure

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.

- *Exposure while breastfeeding*

Exposure while breastfeeding occurs when an infant or child may have been exposed during breastfeeding by a mother who has undergone an intervention/procedure added by the study.
Even if it is not associated with an adverse event, the investigator must notify the sponsor immediately upon learning about the exposure while breastfeeding.

10.2.3 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the case report forms. A data retrieval of the case report forms will be implemented for serious adverse events every year by the URC and transmitted to safety department of CRO.

Examples:

- planned hospitalisation for monitoring the condition under investigation [no deterioration in the participant's condition compared to baseline];
- hospitalisation for routine treatment or for monitoring of the condition under investigation, not associated with a deterioration in the participant's condition;
- emergency hospitalisation at inclusion or prolonged hospitalisation after inclusion to monitor the studied condition in the context of the study.

- *Special circumstances*

- Hospitalisation for a pre-existing illness or condition
- Hospitalisation for a medical or surgical treatment scheduled prior to the study
- Admission for social or administrative reasons

- *Adverse events potentially related to treatments prescribed as part of the care provided during the study follow-up*

For France, the investigator must report these adverse events to the relevant regional pharmacovigilance centre, Centre Régional de Pharmacovigilance (CRPV).

10.2.4 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:

- from the inclusion visit
- throughout the whole follow-up period required for the trial

- Indefinitely, if the SAE is likely to be due to interventions/procedures/examinations performed/added by the study.

10.2.5 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym and number of participant .

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the C.R.O. in charge of research vigilance by email according to the instructions noted in the eCRF. It should be noted that it is possible to send SAE reports to the C.R.O. by fax only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication) (instruction on the SAE form).

This study will use e-CRFs:
- the investigator will complete the SAE notification form in the e-CRF, then he will validate, print, and sign the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the C.R.O. in charge of research vigilance can be reached via email.
For cases of *in utero* exposure, the investigator will complete the "report and follow-up form for pregnancy during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.

10.3 Role of the sponsor

The sponsor, represented by its Safety Department, continuously, throughout the trial, assesses participant safety throughout the study.

10.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all the adverse events reported
- the **causal relationship** with each specific intervention/procedure/examination added by the study,
  All serious adverse events that the investigator and/or the sponsor believe could have a causal relationship with the CDED or corticosteroids that could reasonably be considered as having suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction is considered to be unexpected when the nature, severity or progression are not consistent with information pertaining to the CDED or corticosteroids.
  The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

Serious adverse events (except death) likely to be related to PCC and considered as expected are as follows:

- intestinal obstruction or perforation if the capsule is blocked above an intestinal stricture, delayed or no excretion of the capsule, lesion or mucosal bleeding.

Serious adverse events (except death) likely to be related to biological collection and considered as expected are as follows:

- hematoma, malaise, bleeding.

Serious adverse events (except death) likely to be related to withdrawal of corticosteroids at W12 and considered as expected are as follows:

- relapse or flare of Crohn's disease.

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency):

- The sponsor must send the initial report immediately upon learning of the unexpected serious adverse reaction if is fatal or life-threatening, or otherwise within 15 days from learning of any other type of unexpected serious adverse reaction;
- All additional, relevant information must be declared by the sponsor in the form of monitoring reports within a period of 8 calendar days starting from when the sponsor had this information.

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

10.3.2 Analysis and declaration of other safety data

Pursuant to article 1123-46 of the Code de la Santé Publique, a new development is defined by any new data that may lead to a reassessment of the study's risk-benefits ratio or studied product, to modifications in the use of this product, in the conduct of the study, or documents pertaining to the study, or to suspend or halt or modify the study protocol or similar studies.

The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issues and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issues, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 7 days from learning of the information.

10.3.3 Annual safety report

Serious adverse reactions that occurred in France in the concerned study during the period covered by the report. Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report (ASR or annual safety report), which includes, in particular:
- a safety analysis for the research participants,
- a list of all the suspected and unexpected serious adverse events,
- summary tables including all of the SAEs that have occurred since the start of the study.

The annual safety report must be sent no later than 60 days after the anniversary of the date on which the first participant was included in the study.

10.4 Data Safety Monitoring Board

There is no need to establish a DSMB for this trial, because there is no medical complication related to CDED and partial enteral nutrition. Corticosteroids are prescribed in IBD for 50 years and their toxicity profile is very well known.

11 DATA MANAGEMENT

11.1 Data access

In accordance with GCPs:

- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

11.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé Publique* [French Public Health Code]) will take all necessary precautions to ensure the confidentiality of information relating to the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non identifying.
Under no circumstances shall the names and addresses of the participants involved be shown.
Only the encoded number specific to the study indicating the order of enrolment of the participant will be recorded,
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.4 Data processing and storage of research documents and data

11.4.1 Identification of the data processing manager and location(s)

The patients' data will be entered via a web browser into the eCRF, which is managed by the clinical research unit in St Louis Hospital, Paris, under the responsibility of Prof. Sylvie Chevret. She will be responsible for data storage, statistical analysis, tables and figures for the study report. The eCRF allows the safe storage of patients' data as well as the coding of their identifying data. Therefore, Prof. Sylvie Chevret will not have access to the core personal data of Dutch patients, such as their name, age or location. Data will be stored during 2 years after the final report of the study is written and will then be archived St Louis Hospital clinical research unit's servers for 15 years.

The videos of the PillCam Crohn's Capsule (PCC) have to be reviewed because the protocol only foresees the participation of patients whose active endoscopic lesions are defined by Lewis score as ≥ 225 in the small bowel and/or SES-CD≥ 4 in the colon. This reviewing of the videos will be made by at least one of the following two experts, who is then going to decide whether the patient is eligible to randomisation:

1. Pr. Mark Lowenberg, gastroenterology endocrinology metabolism medical specialist, Amsterdam UMC (Netherlands)
2. Pr. Uri Kopylov, inflammatory bowel disease physician, Sheba Medical Center, Tel Hashomer (Israel)

The reviewing and grading of active endoscopic lesions in the small bowel and the colon is a rare and difficult expertise, which is why this task is delegated to two remote experts. With each of these two institutions, AP-HP has signed a contract, reviewed by the data protection officers (DPO) of each institution to ensure GDPR provisions are enforced. The European Commission has adopted a GDPR adequacy decision regarding Israel's data protection law, and Tel Aviv's institutions will abide by the same data processing rules as the Amsterdam center.

In detail, the reviewers will have access to coded PCC video through the eCRF. Each of the two institutions guaranteed it had sufficient safety measures to ensure the data is secure from unauthorised use as prescribed by the GDPR, and that patients can exercise their rights. Other than for the reviewing of the PCC videos, no data is going to be transferred outside the EU in this study. Except for the videos, AP-HP will be the sole data processor.

11.4.2 Data entry

Pseudonymised data will be entered electronically via a web browser.

11.5 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 Description of statistical methods to be used

The analysis of the trial will be based on the intent-to-treat principle, meaning that each randomized patient will be analysed in the group allocated by randomization, whatever the treatment actually received.
Complementary analyses will exclude patients withdrawn within the first 48 hours due to unwillingness to comply with the protocol or to hospitalization or worsening of disease, in a modified intent-to-treat analysis.
Treatment effect on primary and secondary outcome measures will be estimated with point estimates and 95% confidence interval.
A subgroup analysis on primary and secondary outcome measures be performed within the group of patients under 18 years of age (Age < 18 years). Moreover, a qualitative and/or quantitative interaction between the treatment effect and the age under 18 on the primary outcome will be assessed using Gail and Simon test.

12.2 Calculation of the number of participants required and the result

There have been four randomized trials of EEN versus conventional corticosteroids that assessed the endoscopic lesions of CD; all were performed in pediatric patients. If we pool the results of these trials, 58/76 (76%) of children randomized in the EEN arm reached endoscopic remission as compared to 17/65 (26%) of those randomized within the corticosteroid arm (4, 5, 6). Endoscopic remission rates in patients treated with budesonide are within this range (7). In the CDED trial there was no endoscopic evaluation (9) but among patients in remission at week 12, 48% of patients in the CDED arm reduced their calprotectin by at least 50% or had a fecal calprotectine lower than 200 mg/g (Arie Levine, personal communication). A recent trial has shown that CDED with partial enteral nutrition (Modulen) leads to endoscopic remission in 42% of patients at week 24 (11).

Hypotheses: In the present trial, we hypothesize that 50 % of patients will reach the primary endpoint in the CDED arm versus 20% in the corticosteroid arm. We plan to screen 140 patients to include 80 patients.

Sample size computation used the PASS software.

Group sample sizes of 50 in group 1 and 25 in group 2 achieve 80.228% power to detect a difference between the group proportions of 0,3000. The proportion in group 1 (the treatment group) is assumed to be 0.2000 under the null hypothesis and 0.5000 under the alternative hypothesis. The proportion in group 2 (the control group) is 0.2000. The statistic test used is the two-sided Z-Test with unpooled variance. The significance level of the test is 0.0500. Power was computed using the normal approximation method.

Thus, a total sample size of 75 patients will be recruited. The sample size will be increased to 80 patients, to take into account patients lost to follow-up, including those withdrawing in the first days of the trial due to unwillingness to comply with the protocol or to hospitalization or worsening of disease. Therefore, 54 patients will be randomized to CDED and 26 patients wil be randomized to corticosteroids.

Reference

Ryan, Thomas P. 2013. Sample Size Determination and Power. John Wiley & Sons. Hoboken, New Jersey[UMO1] .

12.3 Anticipated level of statistical significance

All statistical tests will be two-sided, with p-values of 0.05 or less denoting statistical significance.

12.4 Method for taking into account missing, unused or invalid data

Patients who dropped out before the evaluation of the main endpoint on week 16, will be considered as failures.

Multiple imputation techniques will be used in case of missing covariates, though all effort will be made to avoid such missingness.

12.5 Management of modifications made to the analysis plan for the initial strategy.

All modifications of the statistical analysis plan (SAP) will be submitted to the ethics committee of the trial.

12.6 Choice of individuals to be included in the analyses

Primary analysis will be based on intent-to-treat principle.

A modified ITT will be performed as an exploratory analysis (see section 12.1).

13 QUALITY CONTROL AND ASSURANCE

Every research project involving human participants managed by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored interventional research involving human participants.

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

Monitoring will be performed by CRAs from each coordonnating center in each country (France, Israel and Netherlands).

13.2 Strategy for centre opening

The strategy for opening the centres established for this study is determined using the appropriate monitoring plan.

13.3 Scope of centre monitoring

In the case of this risk study, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: level B.

13.4 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the

Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the products used.

13.5 Case report forms

This study will use electronic CRF:
All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.

Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.

When the investigators complete the CRF via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.

A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

13.6 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor. These non-compliances will be managed in accordance with the sponsor's procedures.

13.7 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

13.8 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals or BIG registration (In the Netherlands). The CV must include any previous involvement in clinical research and related training.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing research participants and obtaining their consent

- ***Who is informed?*** *the participant*
- ***Who is providing consent?*** *The participant*
- ***When?*** *Before the person is screened*
- ***How?*** *information note given to the participant and oral explanation*
- ***Who informs the patients?*** *The treating physician will provide the information and request patient permission to be contacted by the investigator or his/her representative*
- ***Who obtains the consent?*** *The investigator, or his/her representative.*

For the Netherlands:

The informed consent form and subject information sheet describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet contains:

• a statement that the study involves research
• a full and fair explanation of the procedures to be followed
• a full explanation of the nature expected duration and objectives of the study
• a description of any reasonably foreseeable risks or discomfort to the patient
• a description of any benefits which may reasonably be expected
• a statement that patient data will be handled with care and confidentially
• a statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits, in which case the patient will receive standard treatment with same degree of care the date informed consent is given.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form and subject information sheet (if applicable) must be approved by both the IRB and the sponsor prior to use. The informed consent form and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. (3) Have an opportunity to consider or reconsider participation of a maximum of 7 days before onset of the individual study procedures. If the subject determines he or she will participate in the study, then the informed consent form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form and subject information sheet will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, and subject information sheet (if applicable) shall be given to the subject. All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

For France: French public health code provisions

In accordance with Article L1122-1-1 of the *Code de la Santé Publique* (French Public Health Code), no interventional research involving human participants can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.
A reflection period of **48 hours** is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

14.2 France only: information of the holders of parental authority and their consent in the case of a study protocol involving a minor

In accordance with Article L.1122-2 of the Code de la santé publique (French Public Health Code), when an interventional study involving human participants is conducted on a non-emancipated minor, consent must be given by the holders of parental authority.

The freely-given, written, informed consent of the holders of parental authority is obtained by the investigator, or by a physician representing the investigator, before definitive inclusion of the minor in the study.

14.3 France only: information for minors participating in the research

Minors receive the information specified in Article L. 1122-1 of the *Code de la Santé Publique* (French Public Health Code), appropriate to their level of understanding, both from the investigator and from the holders of parental authority.
Minor's personal endorsement is sought regarding their participation in the study involving human participants. In any cases, the investigator cannot override their refusal or the revocation of their acceptance.

One copy of the signed and dated consent form is given to the holders of parental authority. The principal investigator or the physician representing him/her will keep one copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

14.4 France only : information recorded in the minor's medical file

The investigator will record the minor's participation in the clinical study in the minor's medical file, along with the procedure for informing and obtaining consent from the holders of parental authority as well as the procedure for informing the minor and a record of the minor's non-rejection to take part.

Minors who reach the age of majority during their participation in the study will be given new, relevant information at that time. After they have been given this information, they will be asked to confirm their consent.

Minors who reach the age of majority during their participation in the research will be given new, relevant information at that time. After they have been given the information, they will be asked to confirm their consent.

14.5 Prohibition from participating in another clinical study or exclusion period set after the study

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study. The participants can however participate in other non-interventional studies

14.6 Legal obligations

14.6.1 Role of the sponsor

Assistance Publique Hôpitaux de Paris (AP-HP) is the sponsor of this study and by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the *Code de la Santé Publique* (French Public Health Code). Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.6.2 Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants not concerning a health product mentioned in Article L5311-1, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory provisions in force.

14.6.3 Request for authorisation from ANSM

Proit to starting the study, AP-HP, as sponsor, must obtain authorisation from the ANSM (French Health Products Safety Agency) for the interventional study involving human participants not concerning a health product,, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

14.6.4 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

This research is governed by the CNIL (French Data Protection Agency) "Reference Methodology for processing personal data used within the scope of health research" (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this "Reference Methodology"

Data transfers outside the French territory and to a third country:

The primary endpoint is the endoscopic response at week 16, assessed by a centralized lecture panel of PCC using centralized, pseudonymized and blinded reading of PCC.
For this, in each investigator centre, after pseudonymized, a copy of PCC files will be sent to Amsterdam UMC (NETHERLANDS) and Sheba Medical Center in Tel Aviv (ISRAEL) for blinding reading. According CNIL website:

- In Netherlands, data protection is protected by GDPR. This country is an EDPB member.
- Israel insures an adequate level of data protection recognizes by EU.

14.6.5 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the CPP (Research Ethics Committee) and authorisation from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
In the Netherlands any modification to the protocol by the coordinating investigator must be sent to the METCAmsterdam for approval.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.6.6 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

14.6.7 Archiving

Specific documents for an interventional study involving human participants not concerning a health *product will be archived by the investigator and the sponsor for 15 years after the end of the research.*
This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the investigator and the sponsor, including (non-exhaustive list):
  - the successive versions of the protocol (identified by the version number and its date), and any appendices
  - the ANSM authorisations and CPP (Research Ethics Committee) decisions
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - final study report
- the data collection documents

15 FUNDING AND INSURANCE

15.1 Funding source

This study will receive funds from different sources:
- The PHRC (Hospital Funding for Clinical Research) if the study is accepted
- 100000 euros from Nestlé
- 300000 euros from a patient's gift

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique - Hôpitaux de Paris (AP-HP) has taken out insurance with HDI - GLOBAL SE through BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the Code de la Santé Publique (French Public Health Code).

16 PUBLICATION RULES

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France

16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

- "The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l'Innovation)"

16.3 Mention of the financial backer in the acknowledgements of the text

- The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 20XX (French Ministry of Health)

This study has been registered on the website http://clinicaltrials.gov/ under the NCT05284136

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18 LIST OF ADDENDA

18.1 CDED dietary instructions

(From supplementary Table 3 of Levine A, et al. Gastroenterology. 2019;157:440)

Supplementary Table 3. CDED Dietary Instructions

Stage 1 (first 6 weeks) Mandatory or allowed foods coupled with Modulen The diet should be administered by a trained dietitian or physician	Stage 2 (second 6 weeks) Mandatory or allowed foods coupled with Modulen The diet should be administered by a trained dietitian or physician
Mandatory Daily Foods and Quantities	**Mandatory Daily Foods and Quantities**
Fresh Chicken breast 150-200 g/d	Fresh Chicken breast 150-200 g/d
2 Eggs/d	2 Eggs/d
2 Bananas/d	2 Bananas/d
1 Fresh Apple/ d	1 Fresh Apple/d
2 Potatoes/d Potatoes must be cooked and refrigerated before use	2 Potatoes/d (or ½ sweet potato and 1 potato) Potatoes must be cooked and refrigerated before use
Allowed Foods Daily	**Allowed Foods Daily**
Fresh Strawberries	Fresh Strawberries
Fresh Melon (1 slice)	Fresh Melon (1 slice)
Rice flour	Rice flour
White rice and rice noodles (unlimited)	White rice and rice noodles(unlimited)
2 Tomatoes (additional allowed for cooking)	2 Tomatoes(additional allowed for cooking)
2 Cucumbers (medium size)	2 Cucumbers (2 medium size)
2 Avocado halves	2 Avocado halves
1 Carrot	1 Carrot
Spinach 1 cup uncooked leaves	Spinach 1 cup uncooked leaves
Lettuce (3 leaves)	Lettuce (3 leaves)
Onion	Onion
Fresh green herbs (eg, basil, parsley, coriander, rosemary, thyme, mint , dill)	Fresh green herbs (eg, basil, parsley, coriander, rosemary, thyme, mint, dill)
I glass freshly squeezed orange juice from fresh oranges (not from cartons or bottles)	I glass freshly squeezed orange juice from fresh oranges (not from cartons or bottles)
Water, sparkling water	Water, sparkling water
Salt, pepper, paprika, cinnamon, cumin, turmeric	Salt, pepper, paprika, cinnamon, cumin, turmeric
3 tablespoons honey	3 tablespoons honey
4 teaspoons sugar	4 teaspoons sugar
Fresh ginger and garlic cloves, lemons and limes	Fresh ginger and garlic cloves
**********	One slice whole grain bread daily
**********	Quinoa
**********	3 Tablespoons cooked lentils or peas
**********	6 almonds or walnut halves (unprocessed)
**********	Baking soda

Foods allowed only once a week	**Foods allowed only once a week**
Fresh lean fish (not deep fried, dietitian guidance required)	Fresh lean fish (not deep fried, dietitian guidance required)
**********	200 gr Sirloin or fillet steak (Maximum)
**********	1 slice whole grain bread (Maximum)
**********	1 can tuna (in olive or canola oil) **drained**
**********	½ cup oatmeal or cut oats
**********	**Additional daily foods from week 7**
**********	Broccoli, Cauliflower 2 florets daily
**********	4 fresh mushrooms (not canned)
**********	½ red bell pepper
**********	1 zucchini or slice squash
**********	1 pear **or** kiwi **or** ripe nectarine
**********	**Additional daily foods from week 10**
**********	Most vegetables (restricted amounts with dietitian guidance)
**********	Most fruits (restricted amounts with dietitian guidance)
**********	Quinoa
**********	3-4 Tablespoons cooked lentils or peas
Stage 1 Disallowed Foods Partial List	**Stage 2 Disallowed Foods Partial List (unless allowed above)**
Dairy	Dairy
Animal fat	Animal fat
Wheat	Wheat
Emulsifiers	Emulsifiers
Artificial Sweeteners	Artificial Sweeteners
Other cuts or parts of chicken	Other cuts or parts of chicken
Other sources animal or soy protein	Other sources animal or soy protein
Carrageenans	Carrageenans
Maltodextrins(and sucralose)	Maltodextrins (and sucralose)
Sulfite containing foods	Sulfite containing foods
Xanthan gum	Xanthan gum
Packaged, canned or frozen precooked foods, doughs, baked goods	Packaged, canned or frozen precooked foods, doughs, baked goods
Frozen , canned fruits and vegetables	Frozen , canned fruits and vegetables
Oral Iron supplements	Oral Iron supplements
Soy or Gluten-free products	Soy or Gluten-free products
Ready to use sauces, syrups, spreads, dressings, margarine, butter	Ready to use sauces, syrups, spreads dressings, margarine, butter
Vinegar, soy sauce, ketchup, mayonnaise	Vinegar, soy sauce, ketchup, mayonnaise
Alcoholic beverages, soft drinks, juices	Alcoholic beverages, soft drinks, juices
Deep-fried or oily foods	Deep-fried or oily foods

Explanations: The induction phase of the CDED is comprised of two 6-week phases. Stage 1 is critical for remission. It contains 5 mandatory foods to be consumed every day: chicken breast, 2 eggs, 2 bananas, 1 apple, and 2 medium-sized potatoes (that have been cooked [eg, baked, boiled, broiled] and refrigerated before use, as this changes the composition of the starch). The diet should not be altered. The most important aspect of the diet is EXCLUSION of products that are not in the allowed or mandatory list, therefore the excluded products are more important than the added products, substitutes are not allowed. Many of the ingredients that are excluded may not appear in the labels. It is important at the present time to avoid all dairy, wheat, or products containing animal fats and additives. Products that are substitutes for gluten and labeled as gluten-free may actually contain additives that need to be excluded. If foods were not on the allowed list, study participants were asked to consider them as disallowed. Coffee and alcohol were disallowed. Herbal tea such as Chamomile tea was allowed.
When quantities appear as uncooked portion, the food may be cooked, the amount specified is of the precooked ingredient. Deep-fried foods are not allowed in stage 1.

Patients should consult a dietitian before using the diet, as patients with strictures or dietary restrictions will need guidance. Patients who refuse to consume meat may consume more formula. Patients who refuse formula should receive a calcium supplement. The first stage of the diet is coupled with 50% of caloric needs with a polymeric formula. Health professionals may obtain the recipe books and recommended explanations as to why each food is added or excluded via the mymodulife.com site**.**

In the second phase, deep-fried foods such as French fries are allowed only once a week. The second stage is divided in to two 3-week periods(week 7–9, and week 10–12), such that by week 10 of the diet almost all fruits and vegetables are allowed if strictures and abdominal pain are not present. Fruits and vegetables should not be consumed in a large quantity all at once. Daily allowances of fruits and vegetables should be divided throughout the day (some at breakfast, some at lunch some at dinner or for snacks) to prevent obstruction if luminal narrowing is still present.

18.2 Bowel preparation for Pillcam Crohn's capsules

Bowel Prep for PCC

Days before PCC	PCC day
10 days before : stop oral iron if any **Get** ❑ PEG for colonoscopy 3 liters (MOVIPREP® optional) ❑ IZINOVA® or PICOPREP® (or their equivalent in Netherlands): 1 box ❑ Metoclopramide 10mg : 1 tablet ❑ Bisacodyl 10mg : 1 suppository **Two days before PCC** : low residue diet **The day before the PCC** : Collect morning stool with the stool kit and stock it in the fridge at 4°C Clear liquid diet (water, tea, clear stock), no solid food, fruit, legume, vegetables, whole grain cereals, fruit juices with pulp, fiber-containing drink **Between 7:00 and 9:00 PM** : Drink 1,5 to 2 L of PEG (35mL/kg for children with small body weight). Or MOVIPREP® 1L (Optional) **After midnight** : no smoke, drink or food, except for medicines with a sip of water	**1) 07:00 to 08:00 AM :** Drink 1,5L of PEG (35mL/kg for small children) Or MOVIPREP® 1L (Optional) **2) 9:00 : Swallowing of PCC** **3) 10:00 AM : Alarm N°1.** - If it displays 0 : 1 tablet of metoclopramide and wait for display of number 1 If the alarm does not display 1, refer to the doctor for erythromycine prescription - When it displays 1: PCC has reached the small bowel. 1st booster. ✓ IZINOVA : (half a sachet (88mL) in 240mL of water **Or** ✓ PICOPREP one sachet in 150mL of water. ✓ **Then** drink 1L of water gradually ✓ Walking recommended **4) 1:00 PM : Alarm N°2. 2nd booster (same as 1st booster)** **5) 3:00 PM : Alarm N°3. Light meal** **6) 3:00 to 5:00PM** : Alarm N° 4: Bisacodyl suppository if PCC is not in stools

18.3 Images showing intact and disintegrated patency capsules

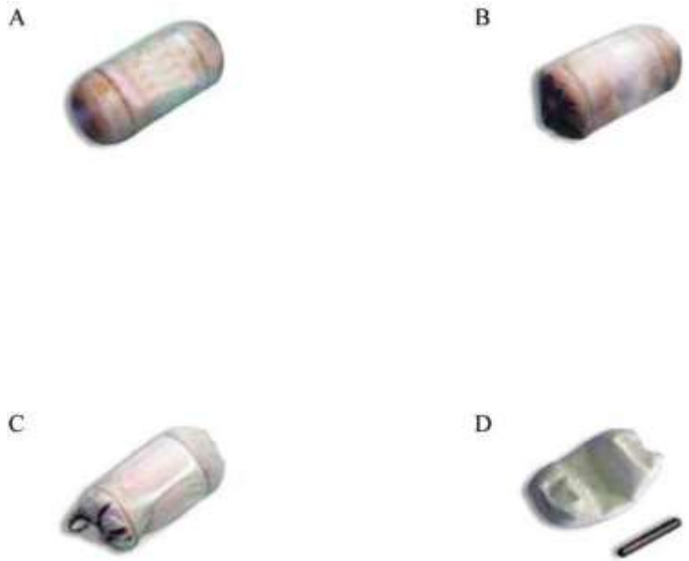
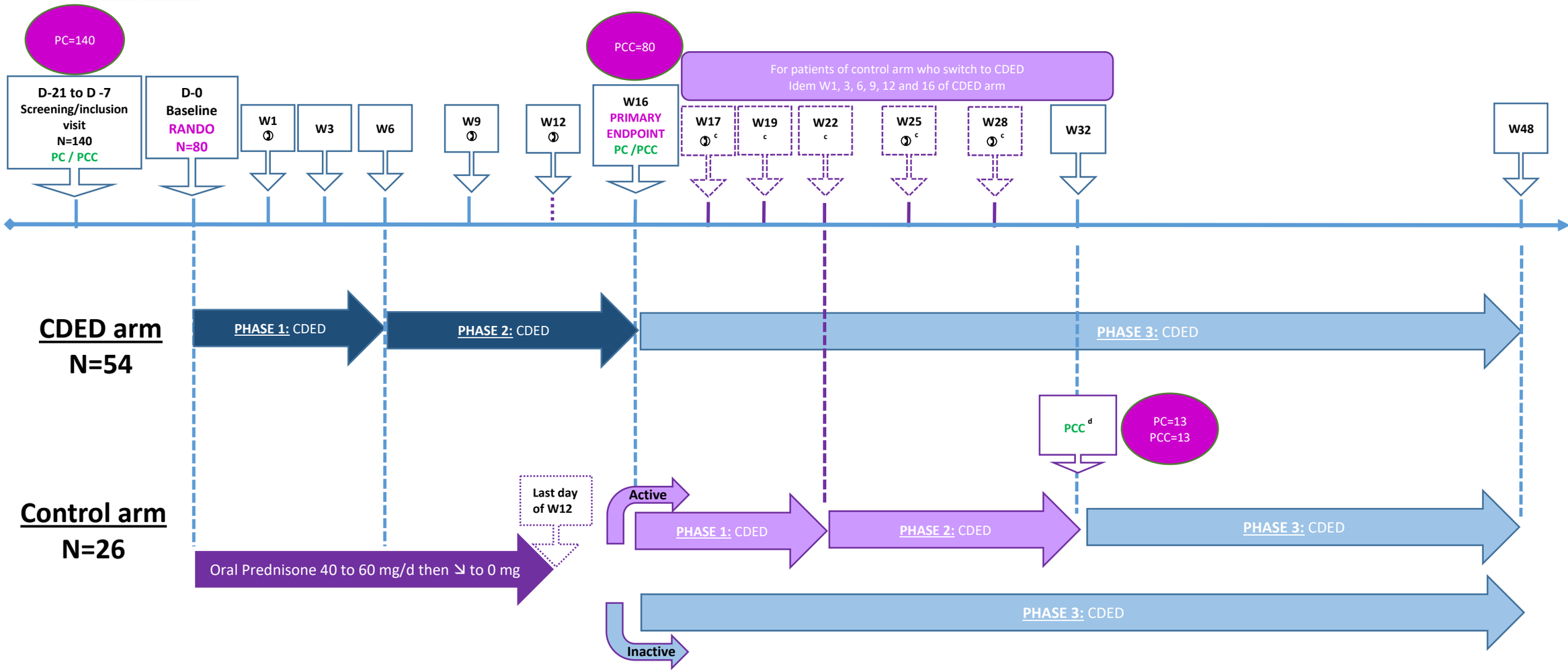


FIGURE 3. Images demonstrating intact and disintegrated PC. Images A and B demonstrate a PC with intact body and/or intact plugs. In these cases, proceeding with wireless capsule is considered safe. Images C and D demonstrate a disintegrated PC. In these cases, proceeding with wireless capsule is not recommended. A, An intact PC body with intact plugs. B, An intact PC body with eroded plugs. C, Disintegrating PC body. D, Empty PC shell and RFID tag. Images taken from Medtronic's brochure catalog for PILLCAM PATENCY CAPSULE (16-emea-pillcam-patency-brochure-1104873). PC indicates patency capsule; RFID, Radio Frequency Identification.

18.4 Study scheme



c Patients randomized to the control arm will have the option to switch to CDED after W16. A PCC will be proposed after 16 weeks of CDED
d Physical visit
❍ Virtual or physical visit
PC = Patency Capsule
PCC = PillCam Capsule
D = STUDY DISPENSATION of MODULEN
Patients randomized in the control arm who then switch to CDED at week 16 will have visit at weeks 17,19,22,25,28 (these visits correspond to respective W1,W3,W6,W9 and w12) and W32 in the same way patients randomized to receive CDED will have visits between baseline and week 16.