2. SYNOPSIS

Protocol code:	Cro.Co.Dex
Title:	Dexamethasone intra-erythrocyte therapy in patients with Crohn's Disease or Ulcerative Colitis
Test Product	Dexamethasone 21 Phosphate encapsulated in autologous erythrocytes
Methodology:	Single-site, open randomised, Placebo-controlled study
Clinical Phase:	II (explorative)
Trial period:	July, 22th 2003 – May, 15th 2007 (clinical phase)
Centers involved	1
Objectives and Criteria for evaluation:	The primary objective of this trial is to evaluate the patients response rate at the end of the study. Patients are considered responder if one of the following conditions occurs at the end of the study: disease remission (Powell Tuck ≤ 3 or CDAI < 150) and withdrawal of oral steroids therapy from at least the second treatment procedure or disease marked improvement versus basal conditions (at least 5 point decrease in Powell Tuck index or 150 point decrease in CDAI score) and withdrawal of oral steroids therapy from at least the second treatment procedure. The secondary objectives of the present study are to evaluate: • the endogenous cortisole production after the study treatment • the phlogosis indexes (ESR and CPR) after the study treatment • the safety of dexamethasone intra-erytrocyte therapy with particular attention to steroid-related adverse events • the endoscopic remission in patients suffering from mesalazine refractory UC.
Subjects Enrolment:	33 patients enrolled and treated.
Diagnosis and criteria for inclusion:	**Inclusion criteria:** – More than 18 years of age – Patient suffering from one of the following chronic inflammatory intestinal diseases:

- Steroid-dependent Crohn's Disease or Ulcerative Colitis following ECCO definition or
- Mild-moderate active UC (Powell-Tuck between 3 and 14 –an index of 14 is allowed; endoscopic Baron score >1) refractory to mesalazine

– Disease extension over the rectum (at least 15 cm) in patient suffering from ulcerative colitis
– Patient willing and able to give written informed consent.

Exclusion criteria:

- Intestinal sub-occlusion or a suspected abdomen abscess or a severe degree of the disease (CDAI > 450) in patient suffering from Crohn's Disease
- Patient affected by a sever Ulcerative Colitis (more than 6 evacuation of liquid, mucous-blooding stools combined to at least one systemic sign as body temperature > 37.8 °C, heart rate > 90 bpm, ESR > 30 mm/h or haemoglobin < 10.5 g/dL)
- Severe concurrent disease(s) as:
  - Medullar deficit: white blood cells < 3000/mm^3; platelets < 75000/mm^3; haemoglobin <10 g/dL;
  - Hepatic diseases presenting total bilirubin ≥ 3 mg/dL; AST (GOT) ≥ 5 UNL; alkaline phosphatase ≥ 5 UNL;
  - Renal failure with serum creatinine ≥ 3 mg/dL
  - Heart failure
  - Respiratory failure
  - Disabling neurological diseases
  - Neoplasia
  - Patient deemed candidate to surgery due to Crohn's Disease or Ulcerative Colitis
  - Chronic alcohol or drug abuse
  - Patient for whom the use of steroids is contraindicated (e.g. systemic infections)
- Treatment with Infliximab in the previous 4 months
- Pregnant woman or female for whom the conceiving could not be excluded during the study
- Non collaborating patient or subject unable to regularly undergo study procedure.

Treatment duration: Patients consenting to participate in this study were assigned to a treatment plan consisting in a treatment procedure every 15 or 30 days for a total of 3 or 6 procedures, respectively. The planned duration of individual patient participation in the study was a maximum of 6/28 weeks, depending from the assigned treatment plan.

Study populations: - Intention To Treat population (ITT): 33 subjects who underwent at least one treatment procedure;

- Per Protocol Population (PP): 29 subjects who underwent at least one treatment procedure without reporting any violation of inclusion criteria;
- Safety Population: all patient included in ITT population.

Statistical Methods:

In order to describe patients recruited in the study, descriptive statistics were reported as appropriate. Mean, median, standard deviation, minimum and maximum are reported for continuous variables, count and proportions are reported for discrete variables.

To asses primary objective patients percentage of responder patients at the end of the study were compared between treatments by a Chi-square test on the ITT and PP population and within each assigned treatment scheme (steroid-dependant IBD patients or active mesalazine refractory UC patients). Descriptive statistics on changes from baseline were produced on disease activity indeces, endogenous cortisol levels and inflammatory parameters.

Shift tables on score recorded at baseline and at the end of study within treatment group were used to describe changes in the Baron score of UC patients.

Adverse Events were presented as per MedDra SOC and a list of steroid related adverse reactions reported at the end of the study was produced.

Results:

Efficacy

Efficacy results of this study, 71% and 72% of responder patient in ITT and PP population respectively, support the efficacy of Dex 21-P encapsulated autologous erythrocytes in inducing or maintaining remission in IBD patients ($p<0.001$ when compared to placebo).

In the ITT population the percentage of responder patients in Dex 21-P group is 71% against the 8% registered in the Placebo group. However, the solely responder and placebo treated patient is a subject presenting P [redacted] at study inclusion and therefore excluded form the PP population.

When considering the response rates with respect to treatment scheme, the efficacy of Dex 21-P encapsulated autologous erythrocytes is confirmed in the group of steroid-dependent patients (one treatment procedure every 30 days): 69% of responder patients in Dex 21-P group against 0% of responder patients in Placebo group ($p<0.05$).

Secondary objective results pertaining to laboratory measurements or activity indices should be considered only as indicative due to the bias introduced by the use of concomitant steroid treatments by some patients (29% and 83% of pts in the Dex 21-P and Placebo group, respectively).

Differently, results referring to the changes in Baron score in the two treatment groups could provide more reliable information: none of the 3 patients (pt ID PP [redacted]) reporting an improvement in the score and treated with Dex 21-P encapsulated erythrocytes were assuming concomitant oral/i.m. steroids while 4 out of 5 patients with a better final

score in placebo group were receiving assuming concomitant oral/i.m. steroids (pt ID PP) and the solely remaining pt is the pt ID PPD at baseline.

Safety

More then half of the treated patients (58%) reported at least one
adverse event: 53% and 67% in the Dex 21-P and Placebo group respectively. However, the majority of these events are related to the underling IBD or related treatment. It could not be excluded a relationship with the PPD e occurred to the placebo treated patient (pt ID P) and the treatment procedure itself (re-infusion of autologous erythrocytes) but that isolated event was considered of light intensity by the investigator and did not prevent the patient from concluding all the planned procedures. Furthermore, the serious adverse event occurred, PPD , was considered a side effect to the previously assumed azathioprine.
The percentages of patients reporting steroid related adverse events at the end of the study are higher in the Placebo group (25%) then in the Dex 21-P group (14%) and this comes along with the facts that all patients complaining steroid related adverse events were assuming oral/i.m. steroids.
Contrarily, the 3 pts reporting steroid adverse events at the end of the treatment were all oral/i.m. steroid free but the PPD P experienced by the pt ID P was still present at the baseline visit and the PPD y occurred in a subject with history of PPD n a .
In conclusion, the solely Dex 21-P related reaction reported in all the 21 treated pts appears to be the decrease in blood calcium levels observed in the pt ID PP

Conclusions:

Results presented in this CSR refers to 33 pts suffering from CD or
UC requiring corticosteroids and treated with Dex 21-P encapsultated erythrocytes. From a previous experience on IBD patients (12) emerged that, after three encapsulation procedures at 30 day intervals, patients assumed a total of 16 mg of Dex 21-P and the mean dose of Dex 21-P loaded in the erythrocytes was 5.5 ± 2.4 mg. The response rates, 71% in Dex 21-P treated patients against 8.3% observed in the Placebo group, support the efficacy of this therapeutic approach in IBD patients. Furthermore, the observed adverse events do not provide evidence for unknown risks associated with the treatment procedure, while new steroid related adverse events were complained only by 2 out of 21 pts of the Dex 21-P group.
From a procedural point of view some considerations need to be outlined: this study was conducted from 2003 to 2006, but monitoring, data collection and reporting activities were performed on 2010 when EryDel entered Dideco as study sponsor, besides the study population includes 33 evaluable pts that could be grouped by many different criteria: disease (CD OR UC), therapeutic history (steroid dependent or

mesalazine refractory pts), treatment scheme (3 or 6 procedures) and treatment received (Dex 21-P or Placebo).
With these premises, the observed response rate at the given dose of Dex 21-P, although far to be conclusive, are promising: steroid-dependant IBD patients are generally exposed to high dose of steroids for periods that should be interrupted due to the related adverse events and mesalazine refractory patients are treated, as per ECCO indication [13], with an initial dose of 40 mg/day of oral steroid that is reduced to 5 mg/day to maintain the remission.
Further studies, more strictly controlled during the clinical phase and involving more than one site, could provide stronger evidence of this bright therapeutic approach.