# Clinical trial results:
# Multicenter, randomized, double-blind, parallel-group study of intra-erythrocyte dexamethasone versus placebo in patients with steroid-dependent Crohn's disease

## Summary

| | |
|---|---|
| EudraCT number | 2008-007329-38 |
| Trial protocol | IT ES |
| Global end of trial date | 30 December 2011 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 12 June 2022 |
| First version publication date | 12 June 2022 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CRODEX01 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01277289 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Erydel S.p.A. |
| Sponsor organisation address | Via Meucci, 3, Bresso (MI), Italy, 20091 |
| Public contact | Clinical Trial Transparency Manager, Erydel S.p.A., +39 0236504470, info@erydel.com |
| Scientific contact | Clinical Trial Transparency Manager, Erydel S.p.A., +39 0236504470, info@erydel.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 30 December 2011 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 December 2011 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 December 2011 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

Assessment of the efficacy of Ery-Dex vs placebo in maintaining patients with steroid-dependent Crohn's disease in clinical remission throughout 12 months without oral steroids.

Protection of trial subjects:

This study was conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 03 June 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 1 |
| Country: Number of subjects enrolled | Italy: 49 |
| Country: Number of subjects enrolled | Romania: 1 |
| Worldwide total number of subjects | 51 |
| EEA total number of subjects | 51 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 44 |
| From 65 to 84 years | 7 |

| | |
|---|---|
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

There were 63 patients enrolled into the screening phase at 10 sites; of these, 51 patients (representing the Safety population) were randomized at 9 sites.

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

This was a multicenter, randomized, double-blind, PLACEBO-controlled, parallel-group study comparing EryDex versus PLACEBO.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | EryDex |

Arm description:

EriDex (dexamethasone sodium phosphated administered as intra-erythrocyte drug at monthly intervals for 12 months).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | EriDex |
| Investigational medicinal product code | |
| Other name | dexamethasone sodium phosphate for encapsulation in human erythrocytes |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dexamethasone sodium phosphate encapsulated in human erythrocytes (EryDex): vials of 250 mg / 10 ml

Monthly administration of EryDex (500 mg / 2 vials) for 12 administrations (12 months).
50 ml of “encapsulated” erythrocytes (previously taken from the same patient) after conditioning with Dexamethasone Sodium Phosphate (500 mg in 20 ml).

| | |
|---|---|
| **Arm title** | Placebo comparator |

Arm description:

Placebo comparator (administered as intra-erythrocyte drug at monthly intervals for 12 months).

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Monthly administration of Placebo for 12 administrations (12 months).
Placebo (10 ml NaCl, 0.372%).

| **Number of subjects in period 1** | EryDex | Placebo comparator |
|---|---|---|
| Started | 28 | 23 |
| Completed | 5 | 2 |
| Not completed | 23 | 21 |
| Consent withdrawn by subject | 1 | 1 |
| Physician decision | 1 | - |
| Fragile vein | 1 | - |
| Adverse event, non-fatal | 2 | 1 |
| Violation | 1 | 1 |
| Premature closure of the study | 4 | 2 |
| Therapy failure and/or Crohn's surgery | 13 | 16 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | EryDex |
| Reporting group description: | |
| EriDex (dexamethasone sodium phosphated administered as intra-erythrocyte drug at monthly intervals for 12 months). | |
| Reporting group title | Placebo comparator |
| Reporting group description: | |
| Placebo comparator (administered as intra-erythrocyte drug at monthly intervals for 12 months). | |

| Reporting group values | EryDex | Placebo comparator | Total |
|---|---|---|---|
| Number of subjects | 28 | 23 | 51 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 47.3 | 43.4 | |
| standard deviation | ± 14.9 | ± 12.5 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 20 | 7 | 27 |
| Male | 8 | 16 | 24 |

## End points

### End points reporting groups

| Reporting group title | EryDex |
|---|---|
| Reporting group description: | |
| EriDex (dexamethasone sodium phosphated administered as intra-erythrocyte drug at monthly intervals for 12 months). | |
| Reporting group title | Placebo comparator |
| Reporting group description: | |
| Placebo comparator (administered as intra-erythrocyte drug at monthly intervals for 12 months). | |

### Primary: Proportion of patients maintaining steroid-free clinical remission (CDAI < 150) without surgery throughout 12 months

| End point title | Proportion of patients maintaining steroid-free clinical remission (CDAI < 150) without surgery throughout 12 months[1] |
|---|---|

End point description:

The primary efficacy end-point is the proportion of patients maintaining steroid-free clinical remission (CDAI < 150) without surgery.
The number of patients completing the 12 months of the study was low (n=51); therefore, only a descriptive
analysis was performed.
No statistical analyses were performed for the secondary end-points because of the early study termination.

| End point type | Primary |
|---|---|

End point timeframe:

12 months since the day of the first infusion.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The number of patients completing the 12 months of the study was low (n=51); therefore, only a descriptive analysis was performed.

| End point values | EryDex | Placebo comparator | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 23 | | |
| Units: percentage | | | | |
| number (not applicable) | 17.9 | 8.7 | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

At days 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360 (follow up), 420 (follow up) and 600 (follow up).

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 12 |

### Reporting groups

| | |
|---|---|
| Reporting group title | EriDex - Safety set |
| Reporting group description: - | |
| Reporting group title | Placebo - Safety set |

Reporting group description: -

| Serious adverse events | EriDex - Safety set | Placebo - Safety set | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 28 (21.43%) | 4 / 23 (17.39%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Crohn's disease | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | 0 / 23 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 3 / 23 (13.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 1.5 %

| **Non-serious adverse events** | EriDex - Safety set | Placebo - Safety set | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 28 (60.71%) | 15 / 23 (65.22%) | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 6 / 28 (21.43%) | 4 / 23 (17.39%) | |
| occurrences (all) | 7 | 5 | |
| Hyperpyrexia | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | 0 / 23 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Irritability | | | |
| subjects affected / exposed | 5 / 28 (17.86%) | 2 / 23 (8.70%) | |
| occurrences (all) | 6 | 2 | |
| Oedema | | | |
| subjects affected / exposed | 3 / 28 (10.71%) | 0 / 23 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | 1 / 23 (4.35%) | |
| occurrences (all) | 2 | 1 | |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|---|---|---|---|
| disorders | | | |
| Influenza | | | |
| subjects affected / exposed | 4 / 28 (14.29%) | 4 / 23 (17.39%) | |
| occurrences (all) | 4 | 7 | |
| Pharyngolaryngeal pain | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |
| Affect lability | | | |
| subjects affected / exposed | 3 / 28 (10.71%) | 1 / 23 (4.35%) | |
| occurrences (all) | 3 | 1 | |
| Insomnia | | | |
| subjects affected / exposed | 4 / 28 (14.29%) | 3 / 23 (13.04%) | |
| occurrences (all) | 5 | 3 | |
| Investigations | | | |
| Blood iron decreased | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haematocrit decreased | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Red blood cell count decreased | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Weight increased | | | |
| subjects affected / exposed | 3 / 28 (10.71%) | 0 / 23 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Limb injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 3 / 23 (13.04%) | |
| occurrences (all) | 0 | 12 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | 0 / 23 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Anaemia macrocytic | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 3 / 23 (13.04%) | |
| occurrences (all) | 1 | 3 | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Neutrophilia | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Eye disorders | | | |
| Ocular hypertension | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | 1 / 23 (4.35%) | |
| occurrences (all) | 3 | 1 | |
| Acetonaemic vomiting | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | 1 / 23 (4.35%) | |
| occurrences (all) | 2 | 1 | |
| Anal fistula | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Crohn's disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 28 (7.14%) | 1 / 23 (4.35%) | |
| occurrences (all) | 2 | 1 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Faecal incontinence | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Faeces discoloured | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal reflux disease | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 10 | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |
| Nausea | | | |
| subjects affected / exposed | 3 / 28 (10.71%) | 2 / 23 (8.70%) | |
| occurrences (all) | 3 | 2 | |
| Rectal tenesmus | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Subileus | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 2 / 23 (8.70%) | |
| occurrences (all) | 1 | 2 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Dermatitis | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Erythema | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |
| Rash | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |
| Skin striae | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 1 / 23 (4.35%) | |
| occurrences (all) | 1 | 1 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 23 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |
| Endocrine disorders | | | |
| Cushingoid | | | |
| subjects affected / exposed | 5 / 28 (17.86%) | 0 / 23 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | 2 / 23 (8.70%) | |
| occurrences (all) | 2 | 2 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 1 / 23 (4.35%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|---|---|---|---|
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |
| Herpes zoster ophthalmicus | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 1 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 13 December 2008 | - change of exclusion criteria re: hemoglobin (Hb < 8 gr/dl, instead of Hb < 10 gr/dl) and liver enzymes (AST [GOT] ≥3x ULN and alkaline phosphatase ≥3x ULN, instead of ≥5x ULN for both parameters)<br>- washout from previous immunosuppressants reduced from 6 to 4 months<br>- the exclusion of subjects with prior therapy based on anti-TNF within 3 months of the enrolment was specified<br>- the "Clostridium difficilis" stool test was introduced at baseline<br>- antibiotics were permitted only if necessary because of infections and for not longer than 15 days. The use of antibiotics as specific therapy for Crohn's Disease was not allowed<br>- follow-up prolonged up to 6 months to check eventual relapse of disease in patients completing the study<br>- patient's diary completion extended from 7 days to the entire month between treatments<br>- SF 36 questionnaire on quality of life was added<br>- ICF was updated accordingly<br>- an additional ICF was introduced to collect long-term health-related information, in particular relapses, in patients withdrawing the consent to the general study |
| 20 July 2009 | - additional samples were requested for dexamethasone dosing in infusion bags from visit 4 to visit 11 to check stable dosing and correct encapsulation procedures in the long term; blood would be taken directly from the infusion bag; no additional venipuncture needed<br>- definition of resistance to AZT/6-MP/MTX corrected, because of a typing error, to stay in line with international guidelines (inability to suspend steroids after at least 4 months of AZT/6-MP/MTX treatment at appropriate dosage; instead of 6 months)<br>- other typing errors were corrected<br>- specifications added in the labeling of tubes for the plasma dexamethasone concentrations<br>- ICF was updated accordingly |
| 22 June 2010 | - change in the screening and identification of patients suitable for study (without changing the target patient population): allowed inclusion of subjects with at least one episode of relapse (CDAI > 150) in the last 12 months, in clinical remission (CDAI < 150) for at least four weeks, and on stable therapy with at least 10 mg of methylprednisolone (or equivalent) for at least 2 weeks<br>- ICF was updated accordingly<br>- reference to the already approved change of the Coordinating Investigator<br>- change in the name of the CRO following the study<br>- change in the number of participating sites (up to 15 in total)<br>- end of patients' enrolment: extended to December 2011<br>- minor, non substantial, changes to provide clarifications on issues that emerged and were discussed during the course of the study, without changes in the study conduct |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No limitations or caveats are applicable to this summary of results.

Notes: