



## Clinical trial results:

### A Randomized Open Label Pilot Study to Compare Targinact vs. Oxycodone in Early Return of Gastrointestinal Function after Colorectal Surgery

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-005327-16 |
| Trial protocol           | GB             |
| Global end of trial date | 01 July 2016   |

#### Results information

|                                   |                                  |
|-----------------------------------|----------------------------------|
| Result version number             | v1 (current)                     |
| This version publication date     | 29 July 2020                     |
| First version publication date    | 29 July 2020                     |
| Summary attachment (see zip file) | Targinact (TACS Publication.pdf) |

#### Trial information

##### Trial identification

|                       |    |
|-----------------------|----|
| Sponsor protocol code | NA |
|-----------------------|----|

##### Additional study identifiers

|                                    |  |
|------------------------------------|--|
| ISRCTN number                      | -  |
| ClinicalTrials.gov id (NCT number) | NCT02109640  |
| WHO universal trial number (UTN)   | -  |
| Other trial identifiers            | Clintrials.gov Number: NCT02109640, REC Number: 14/ES/0016 |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | University of Edinburgh & NHS Lothian  |
| Sponsor organisation address | 47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ               |
| Public contact               | Hugh Paterson, University of Edinburgh, 07780 957402, hugh.paterson@ed.ac.uk |
| Scientific contact           | Hugh Paterson, University of Edinburgh, 07780 957402, hugh.paterson@ed.ac.uk |

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                       | 01 July 2016      |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 01 September 2015 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 01 July 2016      |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to compare Targinact (prolonged release naloxone + oxycodone) with current standard treatment (oxycodone alone) in post-operative return of normal gut function after elective colorectal resectional surgery.

Protection of trial subjects:

As with all opioid analgesics, there is a risk of side effects. Initial doses of the study drug were given in hospital under regular monitoring of observations as per normal practice in post-operative patients. Participants discharged on study drug were counselled on the risks of opioid analgesics as per normal practice and advised to discontinue use at the earliest opportunity.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 10 December 2014 |
| 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 | United Kingdom: 62 |
| Worldwide total number of subjects   | 62                 |
| EEA total number of subjects         | 62                 |

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)                      | 14 |
| From 65 to 84 years                       | 46 |
| 85 years and over                         | 2  |

## Subject disposition

### Recruitment

Recruitment details:

Patients scheduled for elective laparoscopic segmental colonic resection in a single colorectal surgery unit were recruited by study staff during scheduled preoperative visits.

### Pre-assignment

Screening details:

Patients scheduled for elective laparoscopic segmental colonic resection in a single colorectal surgery unit were screened for eligibility.

82 patients were assessed for eligibility. 20 of these were excluded: did not meet inclusion criteria n = 16; declined to participate n = 2; other reason n = 2. 62 patients were recruited.

### Period 1

|                              |                                     |
|------------------------------|-------------------------------------|
| Period 1 title               | Whole study period (overall period) |
| Is this the baseline period? | Yes                                 |
| Allocation method            | Randomised - controlled             |
| Blinding used                | Not blinded                         |

Blinding implementation details:

The statistician was blinded to which group was allocated to intervention and which to control.

### Arms

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| <b>Arm title</b>             | Oxycodone |

Arm description:

Post-op analgesia based on modified release oxycodone

|  |   |
|--|---|
| Arm type                               | Active comparator                       |
| Investigational medicinal product name | Oxycodone                               |
| Investigational medicinal product code | PL 16950/0097-0100,0123,0139-0141, 0150 |
| Other name                             |   |
| Pharmaceutical forms                   | Tablet                                  |
| Routes of administration               | Oral use                                |

Dosage and administration details:

5-20mgd bd

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Targinact |
|------------------|-----------|

Arm description:

Intervention arm

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Targinact    |
| Investigational medicinal product code | PRD506871    |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

5-20mg bd

| <b>Number of subjects in period 1</b> | Oxycodone | Targinact |
|---------------------------------------|-----------|-----------|
| Started                               | 30        | 32        |
| Completed                             | 23        | 27        |
| Not completed                         | 7         | 5         |
| Physician decision                    | 1         | 2         |
| Conversion to open surgery            | 2         | 1         |
| Ineligibility                         | 3         | 2         |
| Protocol deviation                    | 1         | -         |

## Baseline characteristics

### Reporting groups

|   |           |
|---|-----------|
| Reporting group title                                 | Oxycodone |
| Reporting group description:                          |           |
| Post-op analgesia based on modified release oxycodone |           |
| Reporting group title                                 | Targinact |
| Reporting group description:                          |           |
| Intervention arm                                      |           |

| Reporting group values  | Oxycodone | Targinact | Total |
|-------------------------|-----------|-----------|-------|
| Number of subjects      | 30        | 32        | 62    |
| Age categorical         |           |           |       |
| Units: Subjects         |           |           |       |
| Adults (18-64 years)    | 6         | 7         | 13    |
| From 65-84 years        | 16        | 19        | 35    |
| 85 years and over       | 1         | 1         | 2     |
| Excluded from analysis  | 7         | 5         | 12    |
| Age continuous          |           |           |       |
| Units: years            |           |           |       |
| median                  | 68        | 71        |       |
| full range (min-max)    | 50 to 87  | 30 to 83  | -     |
| Gender categorical      |           |           |       |
| Units: Subjects         |           |           |       |
| Female                  | 12        | 12        | 24    |
| Male                    | 11        | 15        | 26    |
| Not recorded            | 7         | 5         | 12    |
| Type of operation       |           |           |       |
| Right or left colectomy |           |           |       |
| Units: Subjects         |           |           |       |
| Right colectomy         | 10        | 14        | 24    |
| Left colectomy          | 13        | 13        | 26    |
| Excluded from analysis  | 7         | 5         | 12    |

### Subject analysis sets

|                            |   |
|----------------------------|---|
| Subject analysis set title | Subjects receiving the intervention/control |
| Subject analysis set type  | Per protocol                                |

Subject analysis set description:

Analyses of the data included Fisher's exact test for categorical data (owing to the small numbers in some of the cells), and Student's t test, with log transformation where appropriate. Estimates of differences in proportions and means were also calculated. The randomized groups were compared for a number of clinical measures, and in general a comment is made where there was little or no difference between the groups.

All of the analyses are descriptive, no adjustment was made for multiple comparisons.

A two-sided 5 per cent significance level was applied throughout.

Participant data was anonymised prior to analysis and the analysis was conducted by an independent statistician who was blinded to the treatment.

| <b>Reporting group values</b>                                    | Subjects receiving the intervention/control |  |  |
|--|---|--|--|
| Number of subjects   | 50  |  |  |
| Age categorical<br>Units: Subjects                               |   |  |  |
| Adults (18-64 years)   | 13  |  |  |
| From 65-84 years   | 35  |  |  |
| 85 years and over  | 2   |  |  |
| Excluded from analysis   | 12  |  |  |
| Age continuous<br>Units: years<br>median<br>full range (min-max) |   |  |  |
| Gender categorical<br>Units: Subjects                            |   |  |  |
| Female   | 24  |  |  |
| Male   | 26  |  |  |
| Not recorded   | 12  |  |  |
| Type of operation  |   |  |  |
| Right or left colectomy<br>Units: Subjects                       |   |  |  |
| Right colectomy  | 24  |  |  |
| Left colectomy   | 26  |  |  |
| Excluded from analysis   | 12  |  |  |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title                                 | Oxycodone                                   |
| Reporting group description:                          |   |
| Post-op analgesia based on modified release oxycodone |   |
| Reporting group title                                 | Targinact                                   |
| Reporting group description:                          |   |
| Intervention arm                                      |   |
| Subject analysis set title                            | Subjects receiving the intervention/control |
| Subject analysis set type                             | Per protocol                                |

Subject analysis set description:

Analyses of the data included Fisher's exact test for categorical data (owing to the small numbers in some of the cells), and Student's t test, with log transformation where appropriate. Estimates of differences in proportions and means were also calculated. The randomized groups were compared for a number of clinical measures, and in general a comment is made where there was little or no difference between the groups.

All of the analyses are descriptive, no adjustment was made for multiple comparisons.

A two-sided 5 per cent significance level was applied throughout.

Participant data was anonymised prior to analysis and the analysis was conducted by an independent statistician who was blinded to the treatment.

### Primary: Return of postoperative gut function

|   |                                      |
|---|--------------------------------------|
| End point title   | Return of postoperative gut function |
| End point description:  |                                      |
| Post-operative at which composite of the following achieved: tolerating oral diet; passage of flatus/faeces/minimal nausea and vomiting |                                      |
| End point type  | Primary                              |
| End point timeframe:  |                                      |
| Assessed on postoperative day 3   |                                      |

| End point values            | Oxycodone       | Targinact       |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 23              | 27              |  |  |
| Units: number               |                 |                 |  |  |
| number (not applicable)     |                 |                 |  |  |
| Day 3                       | 15              | 13              |  |  |
| Day 4                       | 17              | 23              |  |  |

|                                   |   |
|-----------------------------------|---|
| <b>Attachments (see zip file)</b> | Postoperative day of return of gut function/Targinact.pdf |
|-----------------------------------|---|

### Statistical analyses

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | Return of gut function day 3 |
| Comparison groups                       | Oxycodone v Targinact        |
| Number of subjects included in analysis | 50                           |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.264 <sup>[1]</sup>       |
| Method                                  | Fisher exact                 |
| Parameter estimate                      | Absolute % difference        |
| Point estimate                          | 17.1                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | -10                          |
| upper limit                             | 40.7                         |

Notes:

[1] - unadjusted

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

30 days after operation

Adverse event reporting additional description:

Normal postoperative events such as mild nausea, pain etc excluded a priori

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Complications |
|-----------------------|---------------|

Reporting group description:

There were two major complications in the intervention arm of the study: one intra-abdominal collection was drained percutaneously and one (day 4) anastomotic dehiscence required reoperation, repair and proximal diversion. There were no major complications in the control arm.

| Serious adverse events                            | Complications  |  |  |
|---|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 2 / 3 (66.67%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |
| Surgical and medical procedures                   |                |  |  |
| Intra-abdominal fluid collection                  |                |  |  |
| subjects affected / exposed                       | 1 / 3 (33.33%) |  |  |
| occurrences causally related to treatment / all   | 1 / 1          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |
| Anastomotic complication                          |                |  |  |
| subjects affected / exposed                       | 1 / 3 (33.33%) |  |  |
| occurrences causally related to treatment / all   | 1 / 1          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events                            | Complications  |  |  |
|---|----------------|--|--|
| Total subjects affected by non-serious adverse events |                |  |  |
| subjects affected / exposed                           | 1 / 3 (33.33%) |  |  |

|                                 |                |  |  |
|---------------------------------|----------------|--|--|
| Surgical and medical procedures |                |  |  |
| Hospitalisation                 |                |  |  |
| subjects affected / exposed     | 1 / 3 (33.33%) |  |  |
| occurrences (all)               | 1              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment   |
|--------------|---|
| 05 June 2014 | Change of study design from double-blinded to open label blinded design.<br>Addition of a novel method of documenting nutritional intake (Digital Photography of Food Method).<br>Addition of postoperative in-patient activity monitoring. |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

---

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27762434>