



## Clinical trial results: Individualized Pneumoperitoneum Pressure in Colorectal laparoscopic surgery versus standard therapy (IPPCollapse II)

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2016-001693-15   |
| Trial protocol           | ES               |
| Global end of trial date | 19 November 2018 |

### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1 (current)   |
| This version publication date     | 05 February 2022   |
| First version publication date    | 05 February 2022   |
| Summary attachment (see zip file) | Results Article (Artículo resultados.pdf)<br>Protocol Article (Artículo protocolo.pdf) |

### Trial information

#### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | IPPCollapse-II |
|-----------------------|----------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Instituto de Investigación Sanitaria La Fe de Valencia   |
| Sponsor organisation address | Avenida Fernando Abril Martorell, Torre 106 A planta 7, Valencia, Spain, 46026   |
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| Scientific contact           | Jose María Millan Salvador, Instituto de Investigación Sanitaria La Fe, Instituto de Investigación Sanitaria La Fe de Valencia, 34 961246611, investigacion_clinica@iislafe.es |

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                       | 19 November 2018 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 19 November 2018 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To assess the post-operative recovery quality of the Individualized Pneumoperitoneum Pressure Therapy in Colorectal laparoscopic surgery versus standard therapy using a quality validated scale of postoperative recovery (PQRS- Postoperative Quality of Recovery Scale) within 15 minutes (T15) and 40 minutes (T40) of their stay in the Post-Anaesthesia Recovery Unit and the day 1 (POD1) and day 3 (POD3) of the postoperative (POD3 Postoperative Day).

Protection of trial subjects:

The reference study was conducted in Spain under the legal framework of Royal Decree 1090/2015. It has been performed in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996). In addition, the study has been conducted in accordance with the protocol, good clinical practice (GCP) in accordance with the guidelines of the international conference on harmonization (ICH) and regulatory requirements for participating institutions.

An appropriately performed informed consent has been used, in compliance with GCP according to ICH guidelines and approved by the CEIm of the Hospital Universitario y Politécnico La Fe. Prior to inclusion of subjects in the study, a copy of the CEIm-approved informed consent has been reviewed with the prospective participant, signed and dated. The investigator has provided a copy of each subject's signed informed consent form and has retained a copy in the subject's study file.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 February 2017 |
| 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: 166 |
| Worldwide total number of subjects   | 166        |
| EEA total number of subjects         | 166        |

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)                     | 166 |
| From 65 to 84 years                      | 0   |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The recruitment started on 01 February 2017, and ended on 16 November 2018. A number of 204 patients were included, 166 patients completed all the study procedures and 38 patients were excluded.

### Pre-assignment

Screening details:

Patients enrolled were more than 18 years old, whose surgery was classified in ASA-I-III following the American Society of Anesthesiologists classification, without cognitive deficit, and with previous informed consent signed.

### Pre-assignment period milestones

|                              |     |
|------------------------------|-----|
| Number of subjects started   | 166 |
| Number of subjects completed | 166 |

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Experimental procedure (overall period) |
| Is this the baseline period? | Yes                                     |
| Allocation method            | Randomised - controlled                 |
| Blinding used                | Double blind                            |
| Roles blinded                | Investigator, Subject                   |

### Arms

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

Arm description:

Patients allocated in Individualized Pneumoperitoneum

|  |                                 |
|--|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | Rocuronium                      |
| Investigational medicinal product code | 29349900                        |
| Other name                             | Rocuronium Bromide              |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Intravenous bolus use           |

Dosage and administration details:

Induction dose 0.6-1mg/kg and continuous perfusion 0.15-0.6,g/kg/h

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Bridion                |
| Investigational medicinal product code | 08466001               |
| Other name                             | Sugammadex             |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

4mg/kg

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | Standard Pneumoperitoneum |
|------------------|---------------------------|

Arm description:

Patients allocated in Standard Pneumoperitoneum

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |   |
|--|---|
| Investigational medicinal product name | Non-depolarizing neuromuscular blocking agent |
| Investigational medicinal product code |   |
| Other name                             | Rocuronium, cisatracurium, atracurium         |
| Pharmaceutical forms                   | Solution for injection                        |
| Routes of administration               | Intravenous bolus use                         |

Dosage and administration details:

Patients receive moderate neuromuscular blockade with rocuronium, cisatracurium or atracurium throughout surgery to maintain a train of four (TOF) between 2 and 4.

|  |                                 |
|--|---------------------------------|
| Investigational medicinal product name | Neostigmine                     |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Intravenous use                 |

Dosage and administration details:

2.5mg or 30–50 µg·kg<sup>–1</sup> according to usual care

| <b>Number of subjects in period 1</b> | Individualized<br>Pneumoperitoneum | Standard<br>Pneumoperitoneum |
|---------------------------------------|------------------------------------|------------------------------|
| Started                               | 85                                 | 81                           |
| Completed                             | 85                                 | 81                           |

## Baseline characteristics

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Individualized Pneumoperitoneum |
|-----------------------|---------------------------------|

Reporting group description:

Patients allocated in Individualized Pneumoperitoneum

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Standard Pneumoperitoneum |
|-----------------------|---------------------------|

Reporting group description:

Patients allocated in Standard Pneumoperitoneum

| Reporting group values                | Individualized<br>Pneumoperitoneum | Standard<br>Pneumoperitoneum | Total |
|---------------------------------------|------------------------------------|------------------------------|-------|
| Number of subjects                    | 85                                 | 81                           | 166   |
| Age categorical<br>Units: Subjects    |                                    |                              |       |
| Adults from 58-74 years               | 68                                 | 0                            | 68    |
| Adults from 59-77 years               | 0                                  | 67                           | 67    |
| Adults from 18-58 years               | 17                                 | 14                           | 31    |
| Gender categorical<br>Units: Subjects |                                    |                              |       |
| Female                                | 27                                 | 36                           | 63    |
| Male                                  | 58                                 | 45                           | 103   |

## End points

### End points reporting groups

|   |                                 |
|---|---------------------------------|
| Reporting group title                                 | Individualized Pneumoperitoneum |
| Reporting group description:                          |                                 |
| Patients allocated in Individualized Pneumoperitoneum |                                 |
| Reporting group title                                 | Standard Pneumoperitoneum       |
| Reporting group description:                          |                                 |
| Patients allocated in Standard Pneumoperitoneum       |                                 |

### Primary: Physiological Postoperative Quality of Recovery (PQRS)

|  |  |
|--|--|
| End point title  | Physiological Postoperative Quality of Recovery (PQRS) |
| End point description:   |  |
| <p>The Postoperative Quality of Recovery Scale (PQRS), used to assess the primary endpoint, is a verbal survey tool that assesses recovery in five domains: physiological, nociceptive, emotional, functional and cognitive; it also collects data on overall patient perspective<sup>15</sup>. Each of these domains is assessed by means of multiple items on an ordinal scale and compared with baseline to evaluate recovery. A baseline PQRS score was obtained before surgery. After surgery, the PQRS score was obtained at 15 and 40 min after arrival in the postanesthesia care unit, and in the ward during the morning of postoperative day (POD) 1 and POD 3. It was anticipated that patients would stay in the hospital of surgery for at least 3 days, based on local experience. If the patient was discharged before day 3, it was planned to censor data from the point of last follow-up within the hospital of surgery.</p> |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| At 15 and 40 min after arrival in the postanesthesia care unit and in the ward during the morning of postoperative day 1 (POD1) and POD3   |  |

| End point values               | Individualized Pneumoperitoneum | Standard Pneumoperitoneum |  |  |
|--------------------------------|---------------------------------|---------------------------|--|--|
| Subject group type             | Reporting group                 | Reporting group           |  |  |
| Number of subjects analysed    | 85                              | 81                        |  |  |
| Units: % of patients recovered |                                 |                           |  |  |
| 15 min                         | 38                              | 24                        |  |  |
| 40 min                         | 73                              | 50                        |  |  |
| Day 1                          | 75                              | 73                        |  |  |
| Day 3                          | 73                              | 75                        |  |  |

### Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Two tailed T Test                          |
| Statistical analysis description:  |  |
| <p>All analyses were undertaken using R software version 3.5.2. Two-tailed P &lt;0.050 was considered statistically significant and no correction for multiple comparisons was preplanned.</p> |  |
| Comparison groups  | Individualized Pneumoperitoneum v Standard |

|   |                            |
|---|----------------------------|
|   | Pneumoperitoneum           |
| Number of subjects included in analysis | 166                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.05                     |
| Method                                  | t-test, 2-sided            |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 2.77                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 1.19                       |
| upper limit                             | 6.4                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 1.82                       |

### Secondary: Nociceptive Postoperative Quality of Recovery (PQRS)

|                        |   |
|------------------------|---|
| End point title        | Nociceptive Postoperative Quality of Recovery (PQRS)            |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   | 15, 40 minutes after surgery, and at postoperative day 1 and 3. |

| End point values            | Individualized<br>Pneumoperiton<br>eum | Standard<br>Pneumoperiton<br>eum |  |  |
|-----------------------------|--|----------------------------------|--|--|
| Subject group type          | Reporting group                        | Reporting group                  |  |  |
| Number of subjects analysed | 85                                     | 81                               |  |  |
| Units: % Patients recovered |  |                                  |  |  |
| 15 min                      | 60                                     | 49                               |  |  |
| 40 min                      | 73                                     | 47                               |  |  |
| Day 1                       | 37                                     | 35                               |  |  |
| Day 3                       | 58                                     | 37                               |  |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Two tailed T Test   |
| Comparison groups          | Standard Pneumoperitoneum v Individualized Pneumoperitoneum |



|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 166                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.05 <sup>[1]</sup>      |
| Method                                  | t-test, 2-sided            |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 0.47                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.22                       |
| upper limit                             | 0.99                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.29                       |

Notes:

[1] - All analyses were undertaken using R software version 3.5.2. Two-tailed P <0050 was considered statistically significant and no correction for multiple comparisons was preplanned.

## Secondary: Emotionall Postoperative Quality of Recovery (PQRS)

|                 |   |
|-----------------|---|
| End point title | Emotionall Postoperative Quality of Recovery (PQRS) |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

PQRS score was obtained at 15 and 40 min after arrival in the postanaesthesia care unit, and in the ward during the morning of postoperative day (POD) 1 and POD 3

| End point values                | Individualized Pneumoperiton eum | Standard Pneumoperiton eum |  |  |
|---------------------------------|----------------------------------|----------------------------|--|--|
| Subject group type              | Reporting group                  | Reporting group            |  |  |
| Number of subjects analysed     | 85                               | 81                         |  |  |
| Units: %o of Patients recovered |                                  |                            |  |  |
| 15 min                          | 88                               | 75                         |  |  |
| 40 min                          | 85                               | 75                         |  |  |
| Day 1                           | 80                               | 75                         |  |  |
| Day 3                           | 77                               | 73                         |  |  |

## Statistical analyses

|                            |                   |
|----------------------------|-------------------|
| Statistical analysis title | Two tailed T Test |
|----------------------------|-------------------|

Statistical analysis description:

All analyses were undertaken using R software version 3.5.2. Two-tailed P <0050 was considered statistically significant and no correction for multiple comparisons was preplanned.

|                   |   |
|-------------------|---|
| Comparison groups | Standard Pneumoperitoneum v Individualized Pneumoperitoneum |
|-------------------|---|

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 166                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.05                     |
| Method                                  | t-test, 2-sided            |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 4.59                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 1.37                       |
| upper limit                             | 15.29                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 1.18                       |

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

All events that meet the definition of an AE and occur within the period from the time the patient signs the informed consent form until 28 days after the end of treatment should be recorded.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 24.1   |

### Reporting groups

|                                |                        |
|--------------------------------|------------------------|
| Reporting group title          | Experimental treatment |
| Reporting group description: - |                        |
| Reporting group title          | Control treatment      |
| Reporting group description: - |                        |

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No data indicated in final report

| Serious adverse events                               | Experimental treatment | Control treatment |  |
|--|------------------------|-------------------|--|
| Total subjects affected by serious adverse events    |                        |                   |  |
| subjects affected / exposed                          | 5 / 85 (5.88%)         | 8 / 81 (9.88%)    |  |
| number of deaths (all causes)                        | 1                      | 1                 |  |
| number of deaths resulting from adverse events       | 1                      | 1                 |  |
| Surgical and medical procedures                      |                        |                   |  |
| Anastomotik leak                                     |                        |                   |  |
| subjects affected / exposed                          | 1 / 85 (1.18%)         | 3 / 81 (3.70%)    |  |
| occurrences causally related to treatment / all      | 0 / 1                  | 0 / 3             |  |
| deaths causally related to treatment / all           | 0 / 0                  | 0 / 0             |  |
| Cardiac disorders                                    |                        |                   |  |
| Recurrent cardiac decompensation                     |                        |                   |  |
| subjects affected / exposed                          | 0 / 85 (0.00%)         | 1 / 81 (1.23%)    |  |
| occurrences causally related to treatment / all      | 0 / 0                  | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0                  | 0 / 0             |  |
| General disorders and administration site conditions |                        |                   |  |
| Wound abscess  |                        |                   |  |
| subjects affected / exposed                          | 1 / 85 (1.18%)         | 0 / 81 (0.00%)    |  |
| occurrences causally related to treatment / all      | 0 / 1                  | 0 / 0             |  |
| deaths causally related to treatment / all           | 0 / 0                  | 0 / 0             |  |
| Incarcerated inguinal wound                          |                        |                   |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed                            | 0 / 85 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all             | 0 / 0          | 1 / 1          |  |
| <b>Gastrointestinal disorders</b>                      |                |                |  |
| Paralytic ileus  |                |                |  |
| subjects affected / exposed                            | 1 / 85 (1.18%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| Perianal Pain  |                |                |  |
| subjects affected / exposed                            | 1 / 85 (1.18%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| Hemoperitoneum   |                |                |  |
| subjects affected / exposed                            | 0 / 85 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                |                |  |
| Pneumonia  |                |                |  |
| subjects affected / exposed                            | 0 / 85 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 1          |  |
| <b>Infections and infestations</b>                     |                |                |  |
| Septic shock   |                |                |  |
| subjects affected / exposed                            | 1 / 85 (1.18%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 1          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Experimental treatment | Control treatment |  |
|---|------------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                        |                   |  |
| subjects affected / exposed                           | 0 / 85 (0.00%)         | 0 / 81 (0.00%)    |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                     |
|------------------|-------------------------------|
| 28 December 2016 | Not specified in Final report |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32506481>

<http://www.ncbi.nlm.nih.gov/pubmed/30944044>