



Clinical trial results:

Etude ESPER : Epargne Sanguine au cours de la pose d'une Prothèse de hanche totale grâce à l'Exacyl chez le patient traité par Rivaroxaban
Essai multicentrique thérapeutique contrôlé randomisé en double aveugle évaluant l'efficacité de l'acide tranéxamique versus placebo sur les pertes sanguines péri-opératoire selon deux modes d'administration (standard et prolongé) lors de la réalisation d'une arthroplastie totale de hanche chez des patients bénéficiant d'une prophylaxie anti-thrombotique par un nouvel anti-coagulant oral d'action rapide : le rivaroxaban

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-000107-94 |
| Trial protocol | FR |
| Global end of trial date | 29 August 2017 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 06 May 2021 |
| First version publication date | 06 May 2021 |
| Summary attachment (see zip file) | Résumé du rapport final (Résumé du rapport final ESPER.pdf) |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | 29BRC15.0005 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02403596 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | CHRU de Brest |
| Sponsor organisation address | 2 avenue Foch, Brest, France, |
| Public contact | Arnaud CLAVE, CHRU de Brest, Arnaud CLAVE, CHRU de Brest, aclave06@me.com |
| Scientific contact | Arnaud CLAVE, CHRU de Brest, Arnaud CLAVE, CHRU de Brest, aclave06@me.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 | No |

| | |
|--------------------------------|--|
| 1901/2006 apply to this trial? | |
|--------------------------------|--|

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 06 July 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 August 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 August 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

L'objectif principal de l'étude est l'évaluation de l'impact de l'utilisation en post-opératoire de l'acide tranéxamique selon deux modes d'administration (standard ou prolongé) versus placebo sur les pertes sanguines dans la chirurgie prothétique de la hanche.

Protection of trial subjects:

not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 04 May 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | France: 227 |
| Worldwide total number of subjects | 227 |
| EEA total number of subjects | 227 |

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) | 94 |
| From 65 to 84 years | 126 |

| | |
|-------------------|---|
| 85 years and over | 7 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

Les inclusions ont débuté en octobre 2015 et se sont achevées en janvier 2017, les chirurgies se sont déroulées entre novembre 2015 et mai 2017, la dernière visite à 3 mois à eu lieu le 29 août 2017. Les patients ont été inclus dans 4 centres de la région Finistère (département 29)

Pre-assignment

Screening details:

Critères d'inclusion:

Patients :

- De plus de 18 ans,
- Opérés pour une arthroplastie totale de hanche, de première intention, non traumatique, programmée
- Acceptant de participer à l'étude
- Affiliés à un régime de protection sociale

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 229 ^[1] |
| Number of subjects completed | 227 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 2 |
|----------------------------|---------------------------------|

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: two patient withdraw their consent and asked to not keep data.

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 |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

placebo d'Exacyl® selon le schéma suivant : 1g de placebo d'Exacyl® en IVL à H0 (moment de l'incision) puis 1g de placebo d'Exacyl® à H+3 puis 1g de placebo d'Exacyl® à H+7 et H+11

| | |
|--|---------------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placbo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1g de placebo d'Exacyl® en IVL à H0 (moment de l'incision) puis 1g de placebo d'Exacyl® à H+3 puis 1g de placebo d'Exacyl® à H+7 et H+11

| | |
|-----------|--------------|
| Arm title | Exacyl court |
|-----------|--------------|

Arm description:

1 g d'Exacyl® en IVL à H0 (moment de l'incision) puis 1g d'Exacyl® à H+3 puis 1g de placebo d'Exacyl® à H+7 et H+11

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

1 g d'Exacyl® à H0 (moment de l'incision)

1g d'Exacyl® à H+3 (3 heures après l'incision)

| | |
|------------------|-------------|
| Arm title | Exacyl Long |
|------------------|-------------|

Arm description:

1 g d'Exacyl® en IVL H0 (moment de l'incision) puis 1g d'Exacyl® à H+3 puis 1g d'Exacyl® à H+7 et H+11

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Exacyl |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

1 g d'Exacyl® à H0 (moment de l'incision)

1g d'Exacyl® à H+3 (3 heures après l'incision)

1g d'Exacyl® à H+7 (7 heures après l'incision)

1g d'Exacyl® à H+11 (11 heures après l'incision)

| Number of subjects in period 1 | Placebo | Exacyl court | Exacyl Long |
|---------------------------------------|---------|--------------|-------------|
| Started | 75 | 75 | 77 |
| Completed | 70 | 74 | 74 |
| Not completed | 5 | 1 | 3 |
| Consent withdrawn by subject | 2 | - | - |
| Protocol deviation | 3 | 1 | 3 |

Baseline characteristics

Reporting groups

| | |
|--|--------------|
| Reporting group title | Placebo |
| Reporting group description: placebo d'Exacyl® selon le schéma suivant : 1g de placebo d'Exacyl® en IVL à H0 (moment de l'incision) puis 1g de placebo d'Exacyl® à H+3 puis 1g de placebo d'Exacyl® à H+7 et H+11 | |
| Reporting group title | Exacyl court |
| Reporting group description: 1 g d'Exacyl® en IVL à H0 (moment de l'incision) puis 1g d'Exacyl® à H+3 puis 1g de placebo d'Exacyl® à H+7 et H+11 | |
| Reporting group title | Exacyl Long |
| Reporting group description: 1 g d'Exacyl® en IVL H0 (moment de l'incision) puis 1g d'Exacyl® à H+3 puis 1g d'Exacyl® à H+7 et H+11 | |

| Reporting group values | Placebo | Exacyl court | Exacyl Long |
|--|---------|--------------|-------------|
| Number of subjects | 75 | 75 | 77 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 34 | 33 | 27 |
| From 65-84 years | 39 | 39 | 48 |
| 85 years and over | 2 | 3 | 2 |
| Age continuous Units: years | | | |
| arithmetic mean | 64.4 | 65.0 | 67.1 |
| standard deviation | ± 11.64 | ± 11.99 | ± 10.59 |
| Gender categorical Units: Subjects | | | |
| Female | 42 | 44 | 43 |
| Male | 33 | 31 | 34 |
| Missing | 0 | 0 | 0 |
| Score ASA Units: Subjects | | | |
| Score 1 | 21 | 18 | 26 |
| Score 2 | 37 | 47 | 40 |
| Score 3 | 16 | 10 | 8 |
| Missing | 1 | 0 | 3 |
| Comorbidités Units: Subjects | | | |
| Non | 64 | 65 | 69 |
| Oui | 11 | 10 | 8 |
| Missing | 0 | 0 | 0 |
| Taux d'hémoglobine Units: g/dL | | | |
| arithmetic mean | 14.0 | 14.0 | 13.9 |
| standard deviation | ± 1.38 | ± 1.42 | ± 1.18 |
| Taux d'hématocrite Units: pourcentage | | | |
| arithmetic mean | 42.3 | 42.0 | 41.7 |

| | | | |
|--------------------|--------|--------|--------|
| standard deviation | ± 3.66 | ± 3.70 | ± 3.29 |
|--------------------|--------|--------|--------|

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 227 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 94 | | |
| From 65-84 years | 126 | | |
| 85 years and over | 7 | | |
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 129 | | |
| Male | 98 | | |
| Missing | 0 | | |
| Score ASA Units: Subjects | | | |
| Score 1 | 65 | | |
| Score 2 | 124 | | |
| Score 3 | 34 | | |
| Missing | 4 | | |
| Comorbidités Units: Subjects | | | |
| Non | 198 | | |
| Oui | 29 | | |
| Missing | 0 | | |
| Taux d'hémoglobine Units: g/dL arithmetic mean standard deviation | - | | |
| Taux d'hématocrite Units: pourcentage arithmetic mean standard deviation | - | | |

End points

End points reporting groups

| | |
|--|--------------|
| Reporting group title | Placebo |
| Reporting group description: placebo d'Exacyl® selon le schéma suivant : 1g de placebo d'Exacyl® en IVL à H0 (moment de l'incision) puis 1g de placebo d'Exacyl® à H+3 puis 1g de placebo d'Exacyl® à H+7 et H+11 | |
| Reporting group title | Exacyl court |
| Reporting group description: 1 g d'Exacyl® en IVL à H0 (moment de l'incision) puis 1g d'Exacyl® à H+3 puis 1g de placebo d'Exacyl® à H+7 et H+11 | |
| Reporting group title | Exacyl Long |
| Reporting group description: 1 g d'Exacyl® en IVL H0 (moment de l'incision) puis 1g d'Exacyl® à H+3 puis 1g d'Exacyl® à H+7 et H+11 | |

Primary: Perte sanguine totale

| | |
|--|--------------------------------------|
| End point title | Perte sanguine totale ^[1] |
| End point description: Les pertes sanguines totales en ml de globules rouges (PST) calculées par la formule de Mercuriali en 100% d'hématocrite | |
| End point type | Primary |
| End point timeframe: Jour 3 | |
| 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: Modèle linéaire ajusté sur le centre (effet aléatoire) analyse de supériorité analyse hiérarchique | |

| End point values | Placebo | Exacyl court | Exacyl Long | |
|--------------------------------------|------------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 70 | 74 | 74 | |
| Units: ml | | | | |
| arithmetic mean (standard deviation) | 633.1 (± 371.79) | 374.5 (± 259.06) | 394.9 (± 213.04) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Inclusion to Month 3

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Overall study and subject |
|-----------------------|---------------------------|

Reporting group description: -

| Serious adverse events | Overall study and subject | | |
|--|---------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 29 / 218 (13.30%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Electrocardiogram repolarisation abnormality | | | |
| subjects affected / exposed | 1 / 218 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Troponin increased | | | |
| subjects affected / exposed | 1 / 218 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) cancer | | | |
| subjects affected / exposed | 2 / 218 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| procedural complications | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 16 / 218 (7.34%) | | |
| occurrences causally related to treatment / all | 0 / 16 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 218 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 218 (0.46%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 218 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial thrombosis | | | |
| subjects affected / exposed | 1 / 218 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 218 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Hip arthroplasty | | | |
| subjects affected / exposed | 1 / 218 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia postoperative | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 15 / 218 (6.88%) | | |
| occurrences causally related to treatment / all | 0 / 15 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Malaise, pyrexia | | | |
| subjects affected / exposed | 3 / 218 (1.38%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 218 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Disorientation | | | |
| subjects affected / exposed | 1 / 218 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Overall study and subject | | |
|---|---------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 159 / 218 (72.94%) | | |
| Vascular disorders | | | |
| HAEMATOMA, HYPERTENSION, HYPOTENSION, WOUND | | | |
| HAEMATOMA | | | |
| subjects affected / exposed | 9 / 218 (4.13%) | | |
| occurrences (all) | 9 | | |
| General disorders and administration site conditions | | | |
| malaise | | | |
| subjects affected / exposed | 10 / 218 (4.59%) | | |
| occurrences (all) | 10 | | |
| general disorder | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 14 / 218 (6.42%) 14 | | |
| Immune system disorders Immune system disorders subjects affected / exposed occurrences (all) | 3 / 218 (1.38%) 3 | | |
| Respiratory, thoracic and mediastinal disorders COPD, DYSPNEA, SINUSITE subjects affected / exposed occurrences (all) | 3 / 218 (1.38%) 3 | | |
| Psychiatric disorders ANXIETY, DISORIENTATION subjects affected / exposed occurrences (all) | 6 / 218 (2.75%) 6 | | |
| Investigations TROPONIN INCREASED subjects affected / exposed occurrences (all) | 32 / 218 (14.68%) 32 | | |
| Injury, poisoning and procedural complications post procedural complication subjects affected / exposed occurrences (all) | 51 / 218 (23.39%) 54 | | |
| Cardiac disorders Cardiac disorder subjects affected / exposed occurrences (all) | 7 / 218 (3.21%) 7 | | |
| Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all) | 17 / 218 (7.80%) 17 | | |
| Blood and lymphatic system disorders Anaemia postoperative subjects affected / exposed occurrences (all) Anemia, THROMBOCYTOPENIA subjects affected / exposed occurrences (all) | 86 / 218 (39.45%) 86 3 / 218 (1.38%) 3 | | |

| | | | |
|---|------------------------------------|--|--|
| <p>Eye disorders</p> <p>Eye disorders</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 218 (1.38%)</p> <p>3</p> | | |
| <p>Gastrointestinal disorders</p> <p>Gastrointestinal disorders</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>19 / 218 (8.72%)</p> <p>20</p> | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>ERYTHEMA, RASH</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 218 (1.83%)</p> <p>4</p> | | |
| <p>Renal and urinary disorders</p> <p>Renal and urinary disorders</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>7 / 218 (3.21%)</p> <p>7</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Musculoskeletal and connective tissue disorders</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>24 / 218 (11.01%)</p> <p>25</p> | | |
| <p>Infections and infestations</p> <p>INFLUENZA, URINARY TRACT INFECTION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>6 / 218 (2.75%)</p> <p>6</p> | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 28 August 2015 | <p>1. Nous souhaitons modifier le délai de recueil des critères de jugement principal et secondaires afin de prendre en compte le temps réel moyen d'hospitalisation des patients. Dans la pratique courante, il est rare que les patients restent hospitalisés jusqu'à J5. En effet, la sortie se passe le plus souvent à J3. Aussi, afin de respecter les procédures réalisées en pratique courante et de recueillir le critère de jugement principal à la même date pour tous les patients, le recueil de données et les examens prévus initialement à J5 seront réalisés à J3. Cette modification nécessite :</p> <ul style="list-style-type: none">- La modification du critère de jugement principal- La modification des critères de jugement secondaires- La modification du calendrier protocolaire- La modification des paramètres d'évaluation de l'efficacité- La modification des paramètres d'évaluation de la sécurité <p>2. Modification d'un critère d'inclusion : Suppression du terme 'non cimentée' concernant le critère d'inclusion suivant : Patients opérés pour une arthroplastie totale de hanche, non cimentée, de première intention, non traumatique, programmée. Par conséquent, tous les patients de plus de 18 ans devant bénéficier d'une arthroplastie totale de hanche de première intention, cimentée, et bénéficiant d'une prophylaxie antithrombotique par Rivaroxaban se verront proposer de participer à l'essai. La modification de ce critère n'aura pas d'impact sur les risques encourus par les patients ni sur la qualité des données de l'étude.</p> <p>3. Précision d'un critère de non inclusion : Initialement nous avons noté que les patients ayant présenté un Infarctus du myocarde (IDM) ne pourront pas être inclus. Nous pensions sans l'avoir précisé que comme l'IDM est un syndrome coronarien aigu (SCA), cela excluait également les SCA. Or, si l'IDM est bien un SCA, le SCA n'atteint pas toujours le stade de l'IDM. Le SCA étant également une contre-indication à la mise en place des traitements prévus dans le protocole, nous souh</p> |
| 03 June 2016 | <p>Modification et mise à jour de la définition d'une hémorragie majeure (critère de jugement secondaire, événement adjudiqué), selon le contexte de l'étude (opération chirurgicale orthopédique) article de S. SCHULMAN, Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patient, Journal of Thrombosis and Haemostasis, 8: 202-204.</p> |
| 30 November 2016 | <p>Afin de répondre aux hypothèses du protocole, et avec une puissance nominale de 90%, 207 patients évalués sont requis dans l'essai. Aussi, le nombre de patients non évalués avait été prévu autour de 5% (soit 12 patients supplémentaires, ce qui fait un total de 219 patients inclus, 73 par groupe) mais il est en réalité de l'ordre de 10% à ce jour. Le nombre de sujets à inclure doit donc être revu à la hausse, soit 231 patients au total (77 patients par groupe).</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported