# Clinical trial results:
# An Open-Label, Multicenter Study to Evaluate the Safety and Effectiveness of Intravenous CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus

## Summary

| | |
|---|---|
| EudraCT number | 2018-004572-35 |
| Trial protocol | HU CZ PL ES |
| Global end of trial date | 06 March 2020 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 10 October 2021 |
| First version publication date | 10 October 2021 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | CR845-CLIN3105 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03998163 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Cara Therapeutics, Inc. |
| Sponsor organisation address | 107 Elm Street, 9th Floor, Stamford, United States, |
| Public contact | Regulatory Affairs, ICON Clinical Research Limited, 44 07831653684, markas.marriott@iconplc.com |
| Scientific contact | Regulatory Affairs, ICON Clinical Research Limited, 44 07831653684, markas.marriott@iconplc.com |
| Sponsor organisation name | Cara Therapeutics, Inc. |
| Sponsor organisation address | 107 Elm Street, 9th Floor, Stamford, United States, |
| Public contact | Cara Clinical Trials, Cara Therapeutics, Inc., 1 203-406-3700, |
| Scientific contact | Cara Clinical Trials, Cara Therapeutics, Inc., 1 203-406-3700, |

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 | 06 March 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 February 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 March 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety of IV CR845 at a dose of 0.5 mcg/kg in hemodialysis patients with moderate-to-severe pruritus

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 06 May 2019 |
| 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 | Poland: 3 |
| Country: Number of subjects enrolled | Czechia: 4 |
| Country: Number of subjects enrolled | Hungary: 12 |
| Country: Number of subjects enrolled | United States: 203 |
| Worldwide total number of subjects | 222 |
| EEA total number of subjects | 19 |

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) | 150 |

| | |
|---|---|
| From 65 to 84 years | 71 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study was conducted in a total of 222 subjects.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | CR845 |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CR845 |
| Investigational medicinal product code | |
| Other name | Difelikefalin |
| Pharmaceutical forms | Solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

IV CR845 0.5 mcg/kg administered after each dialysis session (3 times/week)

| **Number of subjects in period 1** | CR845 |
|---|---|
| Started | 222 |
| Completed | 197 |
| Not completed | 25 |
| Adverse event, serious fatal | 2 |
| Consent withdrawn by subject | 7 |
| Administrative | 1 |
| Adverse event, non-fatal | 11 |
| other | 2 |
| Lost to follow-up | 1 |
| Lack of efficacy | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall Study (overall period) |

Reporting group description: -

| Reporting group values | Overall Study (overall period) | Total | |
|---|---|---|---|
| Number of subjects | 222 | 222 | |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br>58.1<br>± 12.81 | <br><br><br>- | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 101 | 101 | |
| Male | 121 | 121 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | CR845 |

Reporting group description: -

### Primary: Number of Participants With AEs

| | |
|---|---|
| End point title | Number of Participants With AEs[1] |

End point description:

Assessed by monitoring of adverse events.

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

End point timeframe:

Up to Follow-Up Visit (Week 13-14)

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: No statistical analyses have been specified for this primary end point.

| End point values | CR845 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 222 | | | |
| Units: Participants | 143 | | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: Up to Follow-Up Visit (Week 13-14) | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 22.0 |

| Reporting groups | |
|---|---|
| Reporting group title | CR845 |

Reporting group description: -

| Serious adverse events | CR845 | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 45 / 222 (20.27%) | | |
| number of deaths (all causes) | 3 | | |
| number of deaths resulting from adverse events | 0 | | |
| Vascular disorders | | | |
| Hypertensive urgency | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive emergency | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |

| | | | | |
|---|---|---|---|---|
| Asthenia | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Death | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Non-cardiac chest pain | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Respiratory failure | | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute pulmonary oedema | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute respiratory failure | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchospasm | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chronic obstructive pulmonary disease | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | |
|---|---|---|---|
| Hypoxia | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Corynebacterium test positive | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Arteriovenous fistula thrombosis | | | |
| subjects affected / exposed | 3 / 222 (1.35%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arteriovenous fistula aneurysm | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Head injury | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lumbar vertebral fracture | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Procedural hypotension | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorders | | | | |
| Cardio-respiratory arrest | | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Acute myocardial infarction | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Angina pectoris | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial flutter | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chronic left ventricular failure | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Palpitations | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 3 / 222 (1.35%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radiculopathy | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|---|---|---|---|
| Faecaloma | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haematemesis | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal ischaemia | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vomiting | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Skin and subcutaneous tissue disorders | | | | |
| Erythema nodosum | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endocrine disorders | | | | |
| Primary adrenal insufficiency | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal and connective tissue disorders | | | | |
| Diffuse idiopathic skeletal hyperostosis | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Muscular weakness | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tenosynovitis | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thoracic spinal stenosis | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |
| Clostridium difficile colitis | | | | |
| subjects affected / exposed | 3 / 222 (1.35%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 3 / 222 (1.35%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteomyelitis | | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 2 / 222 (0.90%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchitis | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cystitis | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endocarditis | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Localised infection | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Orchitis | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumococcal sepsis | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia respiratory syncytial viral | | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia viral | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pseudomonas infection | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rhinovirus infection | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 5 / 222 (2.25%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fluid overload | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | CR845 | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 222 (4.95%) | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 11 / 222 (4.95%) | | |
| occurrences (all) | 12 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 12 February 2019 | Modify the Inclusion criteria to add an upper age limit and clarify the acceptable hemodialysis modality<br>Update the study procedures |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported