Creon New Formulation Clinical Study (PANC-GRP-3001)—Results Summary

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A. CLINICAL TRIAL INFORMATION

1. Clinical trial identification

- Protocol Number: PANC-GRP-3001
- Title of Clinical Trial:
  Open-label, single-arm, multicentre clinical trial to evaluate patient acceptability of a new CREON formulation of Pancreas Powder gastro-resistant pellets in patients with cystic fibrosis suffering from pancreatic exocrine insufficiency.

2. Identifiers

- EU Trial Number: 2023-503256-27-00
- Other identifiers: Not applicable

3. Sponsor details

- **Sponsor name and contact:**
  Meda Pharma GmbH & Co. KG (A Viatris Company), Benzstraße 1, 61352 Bad Homburg, Germany
- **Scientific and public contact details:**
  Email address: EUClinicalTrials@viatris.com
  Phone: +49 (0) 6172 888 -01.

4. Pediatric investigation plan:

Not applicable.

5. Results analysis stage:

- Final analysis stage: Yes
- Global end date of clinical trial: 19 December 2024

6. General Information

- **Main objectives:**
  - Primary: To evaluate acceptability of CREON new formulation.
  - Secondary: To assess lipase dose use, switch potential, clinical symptoms, and safety/tolerability.
- **Trial design:**
  Open-label, single-arm, multicentre (8 sites in UK and Germany)
- **Scientific background and rationale:**
  Pancreatic exocrine insufficiency (PEI) in cystic fibrosis (CF) requires pancreatic enzyme replacement therapy (PERT). CREON capsules are standard but may be inconvenient for high-dose regimens. A new CREON new formulation was developed to improve flexibility and ease of administration.

- **Start Date:** First subject enrolled: 28 May 2024
- **Subject protection measures:** Conducted per ICH-GCP, Declaration of Helsinki, Regulation (EU) 536/2014 and approved by German Federal Institute for Drugs and Medical Devices, Medicines and Healthcare Products Regulatory Agency, and Institutional Review Board/ Independent Ethics Committee.
- **Background therapy:** CREON capsules; Pancreatic Enzyme Replacement Therapy (PERT)
- **Statistical methods:** Descriptive analysis (medians, means, standard deviation, confidence interval); categorical and continuous endpoints; no interim analysis.

7. Population of subjects:

- **Number of Subjects:**
  - Planned to be enrolled: up to 120
  - Enrolled: 58 (Germany: 50; UK: 8)
  - Mean age: 35.0 years (range: 19–62)
  - Gender: 52.6% female, 47.4% male
- **Inclusion criteria:**

  To be eligible for inclusion into the study, a subject had to comply with all of the following criteria:

  - Male and female subjects of any ethnic origin
  - At least 18 years of age
  - Cystic fibrosis (documented by two sweat tests or by gene analysis or medically confirmed diagnosis)
  - On treatment with PERT with CREON capsules on the current dose for at least 4 weeks prior to entry in the study and with satisfactory symptom control (e.g., stool frequency and consistency, meteorism/flatulence, abdominal pain) with a dose of at least two CREON capsules per main meal
  - Willing to comply with the requirements of the study protocol.
  - Written informed consent.
  - Adults (≥18 years) with CF and PEI, on stable CREON capsule therapy ≥4 weeks.
- **Exclusion criteria:**

  Subject candidates were not enrolled in the study if they had met any of the following criteria:

  <u>Safety concerns</u>

  - Evidence of severe disease, or any other relevant condition (other than CF) as revealed by history or physical examination potentially limiting participation in or completion of the study.
  - History of allergic reaction or hypersensitivity to pancreatin or excipients of CREON
  - Known predisposition to allergies (relevance as judged by the investigator)
  - Positive β-hCG pregnancy test, established pregnancy, or breast-feeding at Visit 1. Women of childbearing potential not using at least one effective method of contraception (preferably one whose effectiveness is not dependent on the user, such as an intrauterine

device or implant). Women on oral hormonal contraceptives or vaginal ring must agree to use another non-hormonal acceptable highly effective method of contraception in addition to the oral hormonal contraception or vaginal ring.
- Clinically relevant acute infections, febrile disease or any acute condition (illness) 2 weeks prior to Visit 1, as judged by the investigator.

Lack of suitability for the study

- History of alcohol or drug abuse within the last 2 years
- Exposure to another investigational product within the last 3 months

Administrative reasons

- Lack of willingness to have personal study-related data collected, archived, or transmitted according to protocol.
- Lack of willingness or inability to co-operate adequately
  - Anticipated non-availability for study visits/procedures.
  - Vulnerable subjects (such as persons kept in detention)
  - Lack of ability or willingness to give informed consent

B. SUBJECT DISPOSITION:

1. Recruitment:

- **Number of subjects recruited:** 58
- **Withdrawals:** 3 (2 due to non-compliance, 1 due to adverse events)
- **Inclusion criteria:** Adults (≥18 years) with CF and PEI, on stable CREON capsule therapy ≥4 weeks (*for detailed inclusion criteria refer to CLINICAL TRIAL INFORMATION section*)
- **Exclusion criteria:** Severe disease, hypersensitivity to pancreatin/pork products, pregnancy, febrile disease, or any acute condition (illness) 2 weeks prior to Visit 1, as judged by the investigator (*for detailed inclusion criteria refer to CLINICAL TRIAL INFORMATION section*)
- **Randomization:** Not applicable.
- **Blinding:** Not applicable as this was an open-label study.
- **Investigational medicinal products used:** CREON new formulation (Pancreas Powder gastro-resistant pellets)

2. Pre-assignment Period:

One-week of Run-in period in which patients took CREON capsules

3. Post Assignment Periods:

Telephone call 8 days post-treatment

C. BASELINE CHARACTERISTICS

1. Age range:

19–62 years

2. Gender:

30 (52.6%) females, 27 (47.4%) males

D. ENDPOINTS

1. Primary endpoint:

Acceptability assessed via 12- parameters of study treatment at Visit 3 (Day 8). The assessed parameters included aspects of handling and formulation (Table 1).

Table 1: Primary Endpoint: List of Acceptability Questionnaire Variables (n=12)

Acceptability Questionnaire Variables (n=12)	**Characterisation on Rating Scale**
Handling Variables (n=6)	
Opening package of the new formulation	Very difficult (0) to very easy (10)
Getting the new formulation out of package	Very difficult (0) to very easy (10)
Time spent taking the dose	Very troublesome (0) to no problem at all (10)
General convenience taking the dose	Very difficult (0) to very easy (10)
Preparation of final dose to be ingested	Very difficult (0) to very easy (10)
Number of dose units to be ingested	Very troublesome (0) to no problem at all (10)
Formulation Variables (n=6)	
Colour	Very bothersome (0) to very appreciated (10)
Experience during intake	Very bothersome (0) to very good (10)
Taste	Very bad (0) to very good (10)
Ease of swallowing	Very difficult (0) to very easy (10)
Experience of aftertaste after ingestion	Very strong (0) to no aftertaste (10)
Feeling of fulness after ingestion	Very full (0) to not full at all (10)

The primary endpoint was summarised using the new formulation set and the number of valid and missing observations (N_{valid} and $N_{missing}$), the median, the mode, and the min, max, and interquartile range **(**IQR). Additionally, a 95% confidence interval (CI) for the median was estimated. A bar chart was used for the graphical representation displaying the frequencies of each answer category. Two panels of bar charts were provided as follows:

The results of 6 of the 12 variables from acceptability questionnaire related to handling aspects are summarised below in Table 2.

Table 2: Primary Endpoint: Acceptability Questionnaire – Handling Scores – New Form Set

Category - Visit 3 (n=55)	Mean (SD)	Median [95% CI]	Min	Max
Opening package of the new formulation	9.2 (1.42)	10.0 [9.00, 10.00]	3	10
Getting the new formulation out of package	8.5 (1.76)	9.0 [8.00, 10.00]	3	10
Time spent taking the dose	4.8 (2.69)	5.0 [4.00, 6.00]	0	10
General convenience taking the dose	5.1 (3.05)	5.0 [4.00, 7.00]	0	10
Preparation of final dose to be ingested	6.5 (2.83)	7.0 [5.00, 8.00]	0	10
Number of dose units to be ingested	8.4 (2.10)	9.0 [8.00, 10.00]	0	10

n=number of subjects in Analysis population with valid values.
CI: Confidence interval; Max: Maximum; Min: Minimum; SD: Standard deviation.
Source: PANC-GRP-3001 CSR.

No clear difference in the characterisation of the parameters on handling was detected among responses to acceptability questionnaire from subjects in Germany and the UK. However, a similar trend for the questions on 'Opening package of the new formulation', 'Getting the new formulation out of package' and '*number of dose units to be ingested*' between the 2 countries was detected. Both, subjects from Germany and UK provided a positive characterisation for these variables. The variables with lower median scores including the question on '*general convenience taking the dose*', '*time spent taking the dose*' and '*preparation of the final dose to be ingested*' were assessed with similar variability between countries.

The results of 6 of the 12 variables from acceptability questionnaire related to formulation aspects are summarised in Table 3.

Table 3: Primary Endpoint: Acceptability Questionnaire – Formulation Scores – New Form Set

Category - Visit 3 (n=55)	Mean (SD)	Median [95% CI]	Min	Max
Colour	8.1 (2.29)	9.0 [8.00, 10.00]	0	10
Experience during intake	6.0 (2.66)	6.0 [5.00, 8.00]	0	10
Taste	6.4 (2.44)	6.0 [5.00, 7.00]	0	10
Ease of swallowing	6.7 (2.85)	7.0 [6.00, 9.00]	0	10
Experience of aftertaste after ingestion	8.3 (1.95)	9.0 [8.00, 10.00]	3	10
Feeling of fullness after ingestion	8.8 (2.05)	10.0 [9.00, 10.00]	1	10

n=number of subjects in analysis population with valid values.
CI: Confidence interval; Max: Maximum; Min: Minimum; SD: Standard deviation.
Source: PANC-GRP-3001 CSR.

No clear difference in the characterisation of the parameters on formulation was detected among responses to acceptability questionnaire from subjects in Germany and the UK. However, a similar trend for the questions on '*feeling of fulness after ingestion*', '*experience of aftertaste after ingestion*', and '*colour'* was detected for the 2 countries. Both, subjects from Germany and UK, provided a rather positive characterisation for those variables. The variables with lower median ratings including '*experience during intake'*, *'experience of aftertaste after ingestion',* and *'ease of swallowing'* were assessed with a similar variability between countries.

2. Secondary endpoints:

The following secondary endpoints were summarised descriptively by study period using the information of the diary (safety set):

- Lipase dose used per main meal, snack and over the day, used number of capsules/new formulation.
    - Capsules: Mean daily dose 224.5 units; 11.2 capsules/day
    - New formulation: Mean daily dose 183.5 units; 4.7 new form/day

- Closing switch questionnaire:

i. Would you switch your current treatment to the new formulation? Yes/No/Partly:

- Yes: To the new formulation in general
- No: Not to the new formulation at all
- Partly: To a combination of capsules and new formulation

Switch Potential Outcomes:

- Yes: 1.8% (n=1)
- Partly: 33.9% (n=19)
- No: 62.5% (n=35)

ii. If you would switch to a combination of capsules and new formulation: under which circumstances, would you use the new form?

- At home
- At office/work/school
- On travel/vacation
- For social events (e.g., restaurant visits)
- Other, please specify (e.g., to succeed in taking the prescribed dose)

Circumstances of CREON new formulation usage:

- At home: 17 subjects (89.5%)
- At office/work/school: 8 subjects (42.1%)
- On travel/vacation: 2 subjects (10.5%)
- Other (e.g., to succeed in taking the prescribed dose): 2 subjects (10.5%)

iii. To what extent would you use the CREON new formulation?

- Rarely (up to 10%)
- Occasionally (up to 25%)
- Frequently (up to 50%)
- Very frequently (up to 75%)

Frequency of the use of new formulation of CREON:

- Very frequently (up to 75%): 3 subjects (15.8%)
- Frequently (up to 50%): 9 subjects (47.4%)
- Occasionally (up to 25%): 6 subjects (31.6%)
- Rarely (up to 10%): 1 subject (5.3%)

- Clinical symptoms

i. Stool frequency per day.

- The average daily stool frequency was 1.8 per day during the Run-in period and 1.7 per day during the Study treatment period.
- Percentage of days with stool: The mean was 94.4% during the Run-in period and 93.9% during the Study treatment period.

ii. Stool consistency (hard, formed, loose)

- Percentage of days with hard stool consistency: The mean was 9.3% during the Run-in period and 12.0% during the Study treatment period.
- Percentage of days with formed stool consistency: The mean was 69.0% during the Run-in period and 71.6% during the Study treatment period.
- Percentage of days with loose stool consistency: The mean was 21.7% during the Run-in period and 16.4% during the Study treatment period.

iii. Abdominal pain on average (none, mild, moderate, severe)

- Percentage of days with no abdominal pain: The mean was 85.2% for both Run-in period and Study treatment period.
- Percentage of days with mild abdominal pain on average: The mean was 11.0% for both Run-in period and Study treatment period.
- Percentage of days with moderate abdominal pain on average: The mean was 3.8% during the Run-in period and 3.6% during the Study treatment period.
- Percentage of days with severe abdominal pain on average: The mean was 0. 0% during the Run-in period and 0.2% during Study treatment period.

iv. Flatulence on average (none, mild, moderate, severe)

- Percentage of days with no flatulence: The mean was 64.2% during the Run-in period and 66.0% during the Study treatment period.
- Percentage of days with mild flatulence on average: The mean was 29.6% during the Run-in period and 31.5% during the Study treatment period.
- Percentage of days with moderate flatulence on average: The mean was 6.2% during the Run-in period and 2.3% during the Study treatment period.
- Percentage of days with severe flatulence on average: The mean was 0.0% during the Run-in period and 0.2% during the Study treatment period.

- Local tolerability (inspection of oral cavity):

i. Incidence of stomatitis: No subjects experienced stomatitis during all the visits

ii. Incidence of oral mucosal irritation: During Visit 1, no subjects experienced oral mucosal irritation. At Visit 2, 1 subject experienced oral mucosal irritation and 2 subjects experienced oral mucosal irritation at Visit 3.

iii. Incidence of oral cavity bleeding: No subjects experienced oral cavity bleeding during all the visits.

iv. Incidence of oral cavity ulcers: During Visit 1 and Visit 2, no subjects experienced oral cavity ulcers and 1 subject experienced oral ulcer at Visit 3.

v. Incidence of pain in mouth: During Visit 1, no subjects experienced pain in mouth and by Visit 2 and Visit 3, 1 subject experienced pain in mouth each during the visits.

The endpoints have only been derived for a subject if there were at least 3 days per study period with a non-missing assessment and only days with non-missing assessments were considered. The denominator is based on the number of non-missing assessments.

3. Other endpoints:

- General feedback on the new formulation:
  - If you had the opportunity to modify the new CREON new formulation, what would you change?
    - I would not change anything: 13 (23.2%) subjects indicated that they would not change anything regarding the new CREON new formulation.
    - I would change the following:
      - Twenty-one subjects recommended improvements to the formulation, such as improving the taste, colour, texture, creating a ready-to-take formulation, and the size of pellets.
      - Seventeen subjects expressed their inconvenience.
      - 4 subjects found the handling method too complicated and suggested making the new formulation more convenient.
      - Two subjects provided feedback on packaging, recommending alternatives to packaging and reducing packaging in general.

E. ADVERSE EVENTS

1. Adverse events reporting group

- **Subjects**
  - Subjects documented the presence or absence of AEs in their daily diaries.
- **Clinic/Study Site Staff**
  - Subjects were routinely queried using open-ended questions by study staff.
  - Medical staff at the study site evaluated any symptoms reported before drug administration.
- **Principal Investigator or Medical Sub-Investigator**
  - Principle investigators or medical sub-investigators were notified before dosing if any symptoms were reported, to determine the course of action.

2. Serious adverse events

No serious adverse events were reported in this study.

3. Non-serious adverse events

In total 202 adverse events (AEs) were reported during the study. Out of which two hundred were categorised as treatment emergent adverse events (TEAEs). These TEAEs included 86 events which occurred in 27 (47.4%) subjects during the Run-in period and 114 in 40 (70.2%) subjects during the Study treatment period.

Most frequently, AEs were related to gastrointestinal disorders (Run-in period: 35.1% and Study treatment period: 45.6%). A summary of TEAEs is presented in Table 4 (Run-in period) and Table 5 (Study treatment period) respectively.

Table 4: Treatment-Emergent Adverse Events During Run-in Period – Safety Set

	Events	n (%)
Overall	**86**	**27 (47.4)**
Gastrointestinal disorders	**55**	**20 (35.1)**
Flatulence	22	12 (21.1)
Abdominal pain	14	8 (14.0)
Abdominal pain upper	6	2 (3.5)
Faeces soft	4	4 (7.0)
Abdominal distension	2	2 (3.5)
Gastroesophageal reflux disease	2	1 (1.8)
Diarrhoea	1	1 (1.8)
Glossodynia	1	1 (1.8)
Nausea	1	1 (1.8)
Paraesthesia oral	1	1 (1.8)
Steatorrhea	1	1 (1.8)
General disorders and administration site conditions	**1**	**1 (1.8)**
Injection site swelling	1	1 (1.8)
Infections and infestations	**4**	**4 (7.0)**
Nasopharyngitis	1	1 (1.8)
Oral herpes	1	1 (1.8)
Pneumonia	1	1 (1.8)
Respiratory tract infection	1	1 (1.8)
Injury, poisoning, and procedural complications	**1**	**1 (1.8)**
Ligament sprain	1	1 (1.8)
Investigations	**2**	**2 (3.5)**
Blood pressure systolic increased	1	1 (1.8)
Protein urine present	1	1 (1.8)
Musculoskeletal and connective tissue disorders	**2**	**1 (1.8)**
Back pain	1	1 (1.8)
Neck pain	1	1 (1.8)
Nervous system disorders	**17**	**12 (21.1)**
Headache	15	11 (19.3)
Migraine	1	1 (1.8)
Somnolence	1	1 (1.8)
Reproductive system and breast disorders	**3**	**2 (3.5)**

	Events	n (%)
Overall	**86**	**27 (47.4)**
Dysmenorrhea	3	2 (3.5)
Skin and subcutaneous tissue disorders	**1**	**1 (1.8)**
Cold sweat	1	1 (1.8)

n: number of subjects with at least one documented event/observation
Source: PANC-GRP-3001 CSR.

Table 5: Treatment-Emergent Adverse Events During Study Treatment Period – Safety Set

	Events	n (%)
Overall	**114**	**40 (70.2)**
Gastrointestinal disorders	**74**	**26 (45.6)**
Flatulence	25	14 (24.6)
Abdominal pain	17	10 (17.5)
Abdominal pain upper	8	6 (10.5)
Diarrhea	6	4 (7.0)
Faeces soft	5	3 (5.3)
Nausea	4	3 (5.3)
Constipation	2	2 (3.5)
Abdominal discomfort	1	1 (1.8)
Gastrointestinal sounds abnormal	1	1 (1.8)
Glossodynia	1	1 (1.8)
Oral blood blister	1	1 (1.8)
Oral disorder	1	1 (1.8)
Oral pain	1	1 (1.8)
Stomatitis	1	1 (1.8)
General disorders and administration site conditions	**5**	**3 (5.3)**
Asthenia	1	1 (1.8)
Fatigue	1	1 (1.8)
Influenza like illness	1	1 (1.8)
Malaise	1	1 (1.8)
Pain	1	1 (1.8)
Infections and infestations	**5**	**5 (8.8)**
Nasopharyngitis	3	3 (5.3)
Infection	1	1 (1.8)
Laryngitis viral	1	1 (1.8)
Injury, poisoning and procedural complications	**3**	**3 (5.3)**
Burn oral cavity	1	1 (1.8)

	Events	n (%)
Overall	**114**	**40 (70.2)**
Contusion	1	1 (1.8)
Mouth injury	1	1 (1.8)
Investigations	**4**	**3 (5.3)**
False positive investigation result	1	1 (1.8)
Forced expiratory volume decreased	1	1 (1.8)
Protein urine present	1	1 (1.8)
Urinary occult blood positive	1	1 (1.8)
Metabolism and nutrition disorders	**1**	**1 (1.8)**
Decreased appetite	1	1 (1.8)
Musculoskeletal and connective tissue disorders	**1**	**1 (1.8)**
Pain in extremity	1	1 (1.8)
Nervous system disorders	**11**	**10 (17.5)**
Headache	11	10 (17.5)
Renal and urinary disorders	**1**	**1 (1.8)**
Pollakiuria	1	1 (1.8)
Reproductive system and breast disorders	**2**	**2 (3.5)**
Dysmenorrhoea	1	1 (1.8)
Menstruation irregular	1	1 (1.8)
Respiratory, thoracic and mediastinal disorders	**5**	**4 (7.0)**
Cough	1	1 (1.8)
Increased bronchial secretion	1	1 (1.8)
Oropharyngeal pain	1	1 (1.8)
Pharyngeal erythema	1	1 (1.8)
Productive cough	1	1 (1.8)
Skin and subcutaneous tissue disorders	**1**	**1 (1.8)**
Rash	1	1 (1.8)
Surgical and medical procedures	**1**	**1 (1.8)**
Intrauterine contraception	1	1 (1.8)

n: number of subjects with at least one documented event/observation.
Source: PANC-GRP-3001 CSR.

F. Additional Information

1. Global Substantial Modifications

The protocol Version 1.0 dated 31 August 2023 has been submitted in the UK and Germany. This Version 1.0 was amended 3 times and the 'modifications summary' pertaining to Version 2.0, Version 3.0 (not submitted) and Version 4.0 (including the changes done for Version 3.0) are listed below:

Table 6: Global substantial modifications summary:

Version	Date	Key Changes
2.0	25 Jan 2024	Updated study period; contraception methods; instructions for new formulation use; consistency edits; update to primary endpoint analysis.
3.0	09 Apr 2024	Interim version; updated site details; clarified total study duration; added exclusion criteria; expanded inclusion flexibility; clarified pregnancy test process; simplified screening; editorial consistency.
4.0	31 Jul 2024	Regulatory update; reduced site count; patient number changed to up to 120; clarified treatment duration; added medically confirmed diagnosis to inclusion; updated contraception requirements; clarified pregnancy handling; added instructions for exceptional IMP use; prohibited non-study PERT; editorial and operational updates.

IMP: investigational medical product; PERT: pancreatic enzyme replacement therapy.
Source: PANC-GRP-3001 CSR.

2. Global Interruptions and re-starts

The study was conducted as per the approved protocol without any interruption or restart.

3. Limitations, addressing sources of potential bias and imprecisions and Caveats

- **Limitations and Potential Sources of Bias**
  - **Small Sample Size and Recruitment Constraints**
    - Planned enrollment was up to 120 subjects, but only 58 were enrolled due to administrative and capacity issues.
    - This reduced sample size limits generalizability.
  - **Imbalance in country representation**
    - Fifty subjects were enrolled in Germany and 8 in the UK.
    - This imbalance may introduce regional bias and limits interpretation of country-specific trends.
  - **Open-label, single-arm design**
    - Lack of a control group and blinding introduces potential for reporting bias and subjective influence on acceptability ratings.
  - **Short treatment duration**
    - The treatment period was only 1 week, which may not capture long-term acceptability, adherence, or safety outcomes.

- **Highly experienced population**
    - Subjects were long-term users of CREON capsules (average duration ~25.9 years) with no swallowing difficulties.
    - This may bias results toward lower acceptability of the new formulation compared to naïve or newly diagnosed patients.
- **Non-standardized diet**
    - Nutritional composition was not controlled, which could affect clinical symptom outcomes (e.g., stool consistency, abdominal pain).
- **Self-reported data**
    - Diary entries and questionnaires relied on subject self-reporting, introducing recall bias and variability in compliance.
- **Protocol deviations**
    - High incidence of minor deviations (89.6% subjects) related to intake, timing, and documentation could affect data integrity.

- **Imprecisions**
    - **Variability in Acceptability Scores**
        - Wide range of responses (0–10) for several handling and formulation variables indicates heterogeneity and reduces precision.
    - **Limited Statistical Analysis**
        - Descriptive statistics only; no inferential testing or adjustment for covariates.
- **Caveats**
    - **Interpretation of Switch Potential**
        - Responses to switching questions were collected after only 1 week of exposure; long-term willingness may differ.
    - **Generalizability**
        - Findings may not apply to pediatric patients, newly diagnosed CF patients, or those with swallowing difficulties.
    - **Operational Constraints**
        - Recruitment delays and administrative limitations impacted study timelines and sample size.

4. Declaration

The submitting party confirms that the information provided is accurate and complies with Regulation (EU) No 536/2014.