Clinical trial results:
Prevention of paclitaxel-related neurological side effects with lithium – a randomized, double-blind, placebo-controlled, explorative proof-of-concept phase II clinical trial to counteract chemotherapy induced neurotoxicity

Summary

EudraCT number	2015-004172-30
Trial protocol	DE
Global end of trial date	18 December 2024

Results information

Result version number	v1 (current)
This version publication date	06 February 2026
First version publication date	06 February 2026

Trial information

Trial identification

Sponsor protocol code	PREPARE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02753036
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00027165

Notes:

Sponsors

Sponsor organisation name	Charité Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Department of Neurology / NCRC, Charité – Universitätsmedizin Berlin, +49 30450 560 102, prepare-studie@charite.de
Scientific contact	Department of Neurology / NCRC, Charité – Universitätsmedizin Berlin, +49 30450 560 102, prepare-studie@charite.de

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	12 March 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2024
Global end of trial reached?	Yes
Global end of trial date	18 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this proof-of-concept exploratory clinical trial is to test the hypothesis that a co-medication with lithium carbonate (Quilonum® retard) is able to reduce the burden of chemotherapy induced neuropathy (CIN) as measured by the "Total Neuropathy Score reduced" (TNSr) in breast cancer patients undergoing neurotoxic chemotherapy with weekly (q1w) or biweekly (q2w) paclitaxel infusions.

Protection of trial subjects:

The study was conducted in accordance with the ICH E6 (R2) Guideline for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, German Medicinal Products Act (AMG)), and with the ethical principles that have their origins in the Declaration of Helsinki (version 2013). The Investigator also had to comply with all applicable privacy regulations (e.g., Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR)).

Background therapy:

Chemotherapy-induced polyneuropathy (CIPN) and postchemotherapy cognitive impairment (PCCI) are frequent side effects of paclitaxel treatment. CIPN/PCCI are potentially irreversible, reduce quality of life and often lead to treatment limitations, which affect patients' outcome. We previously demonstrated that paclitaxel enhances an interaction of tthe Neuronal calcium sensor-1 protein (NCS-1) with the Inositol-1,4,5-trisphosphate receptor (InsP3R), which disrupts calcium homeostasis and triggers neuronal cell death via the calcium-dependent protease calpain in dorsal root ganglia neurons and neuronal precursor cells. Prophylactic treatment of rodents with lithium inhibits the NCS1-InsP3R interaction and ameliorates paclitaxel-induced polyneuropathy and cognitive impairment, which is in part supported by limited retrospective clinical data in patients treated with lithium carbonate at the time of chemotherapy. Currently no data are available from a prospective clinical trial to demonstrate its efficacy.

Evidence for comparator: -

Actual start date of recruitment	01 April 2022
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	Germany: 86
Worldwide total number of subjects	86
EEA total number of subjects	86

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)	79
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between August 2, 2022 and July 8, 2024 in 8 study sites in Germany.

Pre-assignment

Screening details:

4952 were to bee assessed for eligibiilty in weekly tumor board meetings. The study included n=94 patients of which 86 patients were randomized divided into 2 groups.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Lithium carbonate group

Arm description:

IMP add-on to SMP

Arm type	Experimental
Investigational medicinal product name	Lithium carbonate
Investigational medicinal product code	N05AN01
Other name	Quilonum
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encapsulated lithium carbonate 225mg (Quilonum® retard), taken twice per day, starting 14 days prior to the first (nab-) paclitaxel infusion and ending 3 days after the last (nab-) paclitaxel infusion, respectively a maximum of 6 or 12 (nab-) paclitaxel infusions [approx. 9 (PTX q2w) or 14 (PTX q1w) weeks in total for each patient]

Arm title	Placebo control group

Arm description:

Placebo add-on to SMP

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Commercially available placebo tablets (P-Tablets 8mm Lichtenstein) containing lactose-monohydrate, cellulose powder, magnesiumstearate (Ph. Eur.) and microcrystalline cellulose were provided and encapsulated identical to Lithium carbonate for blinding purposes by the trial pharmacy.
Placebo were taken twice per day, starting 14 days prior to the first (nab-) paclitaxel infusion and ending 3 days after the last (nab-) paclitaxel infusion, respectively a maximum of 6 or 12 (nab-) paclitaxel infusions [approx. 9 (PTX q2w) or 14 (PTX q1w) weeks in total for each patient].

Number of subjects in period 1	Lithium carbonate group	Placebo control group
Started	43	43
Completed	36	42
Not completed	7	1
Consent withdrawn by subject	3	-
Adverse event, non-fatal	4	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Lithium carbonate group
Reporting group description: IMP add-on to SMP	
Reporting group title	Placebo control group
Reporting group description: Placebo add-on to SMP	

Reporting group values	Lithium carbonate group	Placebo control group	Total
Number of subjects	43	43	86
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	38	41	79
From 65-84 years	5	2	7
85 years and over	0	0	0
Age continuous Units: years			
median	49.3	44.7	
standard deviation	± 10.5	± 9.2	-
Gender categorical Units: Subjects			
Female	43	43	86
Male	0	0	0
Comorbidies at screening Units: Subjects			
Diabetes	4	0	4
Arterial hypertension	3	7	10
none	36	36	72
Cumulative PTX dose Units: mg m-2			
median	720	960	
inter-quartile range (Q1-Q3)	700 to 960	720 to 960	-

End points

End points reporting groups

Reporting group title	Lithium carbonate group
Reporting group description: IMP add-on to SMP	
Reporting group title	Placebo control group
Reporting group description: Placebo add-on to SMP	

Primary: Change TNSr

End point title	Change TNSr
End point description: Analysis of the primary endpoint Total Neuropathy Score reduced (TNSr) after conclusion of chemotherapy	
End point type	Primary
End point timeframe: from baseline up to 2 weeks after last paclitaxel infusion	

End point values	Lithium carbonate group	Placebo control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	42		
Units: Score				
arithmetic mean (standard deviation)				
TNSr (baseline)	0.83 (± 1.44)	0.76 (± 1.38)		
TNSr (endpoint)	3.97 (± 3.15)	4.66 (± 3.21)		

Attachments (see zip file)	secondary_endpoints_PREPARE/PREPARE_secondary endpoints.

Statistical analyses

Statistical analysis title	efficacy results
Statistical analysis description: A linear mixed model was calculated to analyze the intervention effect, with the study centers as clusters. Adjustments were made for baseline TNSr values and cumulative chemotherapy doses as per the statistical analysis plan. Missing values were imputed using multiple imputation by chained equations. Thirty data sets were generated, and the results were pooled. On average, the lithium carbonate group had a TNSr value that was 0.5 points lower (90% CI: -0.6 to 1.6) than the placebo group at two	
Comparison groups	Lithium carbonate group v Placebo control group

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.6
upper limit	1.6

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall trial	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups	
Reporting group title	Lithium carbonate group
Reporting group description: -	
Reporting group title	Placebo control group
Reporting group description: -	

Serious adverse events	Lithium carbonate group	Placebo control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 43 (11.63%)	6 / 43 (13.95%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
lithium intoxication	Additional description: Hospitalization due to suspected lithium intoxication with dizziness/imbalance and muscle twitches subsequent to a urinary tract infection. Blinded laboratory report showed lithium level of 2.08mmol/l.		
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
cardiac disorder, other	Additional description: Especially cardiotoxicity of chemotherapy with epirubicin/cyclophosphamide		
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			

subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Productive cough	Additional description: Pneumonitis as a result of therapy with the immune checkpoint inhibitor pembrolizumab, atypical pneumonia DD pneumonitis		
subjects affected / exposed	0 / 43 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection	Additional description: The patient presented with severe fatigue and dry cough and was admitted to hospital for further investigation.		
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia with sepsis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Lithium carbonate group	Placebo control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 43 (93.02%)	41 / 43 (95.35%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 43 (4.65%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Hot flashes			
subjects affected / exposed	2 / 43 (4.65%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 43 (13.95%)	9 / 43 (20.93%)	
occurrences (all)	8	10	
Edema	Additional description: Edema limbs/face		
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Fever			
subjects affected / exposed	1 / 43 (2.33%)	2 / 43 (4.65%)	
occurrences (all)	1	2	
Non-cardiac chest pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
flu like symptoms			
subjects affected / exposed	2 / 43 (4.65%)	5 / 43 (11.63%)	
occurrences (all)	2	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 43 (4.65%)	3 / 43 (6.98%)	
occurrences (all)	3	3	
Dyspnea			
subjects affected / exposed	3 / 43 (6.98%)	2 / 43 (4.65%)	
occurrences (all)	4	2	
Epistaxis			
subjects affected / exposed	5 / 43 (11.63%)	4 / 43 (9.30%)	
occurrences (all)	5	4	

Rhinorrhea			
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	
occurrences (all)	4	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 43 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 43 (2.33%)	2 / 43 (4.65%)	
occurrences (all)	1	2	
Depression			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	1 / 43 (2.33%)	2 / 43 (4.65%)	
occurrences (all)	1	2	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	4 / 43 (9.30%)	1 / 43 (2.33%)	
occurrences (all)	4	1	
White blood cell decreased			
subjects affected / exposed	15 / 43 (34.88%)	20 / 43 (46.51%)	
occurrences (all)	15	20	
Platelet count decreased			
subjects affected / exposed	2 / 43 (4.65%)	2 / 43 (4.65%)	
occurrences (all)	2	2	
Creatinine increased			
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 43 (4.65%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 43 (4.65%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Cardiac disorders			

Palpitations			
subjects affected / exposed	1 / 43 (2.33%)	2 / 43 (4.65%)	
occurrences (all)	1	2	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 43 (13.95%)	4 / 43 (9.30%)	
occurrences (all)	8	4	
Tremor			
subjects affected / exposed	5 / 43 (11.63%)	2 / 43 (4.65%)	
occurrences (all)	6	2	
Peripheral sensory neuropathy			
subjects affected / exposed	15 / 43 (34.88%)	16 / 43 (37.21%)	
occurrences (all)	18	18	
Paresthesia			
subjects affected / exposed	10 / 43 (23.26%)	8 / 43 (18.60%)	
occurrences (all)	11	11	
Dizziness			
subjects affected / exposed	6 / 43 (13.95%)	5 / 43 (11.63%)	
occurrences (all)	6	5	
Dysgeusia			
subjects affected / exposed	2 / 43 (4.65%)	2 / 43 (4.65%)	
occurrences (all)	2	2	
Cognitive disturbance			
subjects affected / exposed	4 / 43 (9.30%)	4 / 43 (9.30%)	
occurrences (all)	4	4	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	30 / 43 (69.77%)	24 / 43 (55.81%)	
occurrences (all)	31	26	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Eye disorders			
Blurred vision			
subjects affected / exposed	2 / 43 (4.65%)	1 / 43 (2.33%)	
occurrences (all)	3	1	

Watering eyes			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 43 (9.30%)	4 / 43 (9.30%)	
occurrences (all)	4	4	
Diarrhoe			
subjects affected / exposed	14 / 43 (32.56%)	11 / 43 (25.58%)	
occurrences (all)	17	12	
Abdominal pain			
subjects affected / exposed	5 / 43 (11.63%)	1 / 43 (2.33%)	
occurrences (all)	5	1	
Mucositis oral			
subjects affected / exposed	4 / 43 (9.30%)	7 / 43 (16.28%)	
occurrences (all)	4	7	
Nausea			
subjects affected / exposed	6 / 43 (13.95%)	6 / 43 (13.95%)	
occurrences (all)	8	6	
Dry mouth			
subjects affected / exposed	6 / 43 (13.95%)	2 / 43 (4.65%)	
occurrences (all)	6	2	
Dysphagia			
subjects affected / exposed	2 / 43 (4.65%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Flatulence			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Gastroesophageal reflux			
subjects affected / exposed	2 / 43 (4.65%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	1 / 43 (2.33%)	3 / 43 (6.98%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	8 / 43 (18.60%)	7 / 43 (16.28%)	
occurrences (all)	8	8	
Alopecia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	2	
Dry skin			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Hyperhidrosis			
subjects affected / exposed	2 / 43 (4.65%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Nail changes			
subjects affected / exposed	1 / 43 (2.33%)	2 / 43 (4.65%)	
occurrences (all)	1	2	
Pruritus			
subjects affected / exposed	2 / 43 (4.65%)	2 / 43 (4.65%)	
occurrences (all)	2	2	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Endocrine disorders			
Hypothyreose			
subjects affected / exposed	1 / 43 (2.33%)	5 / 43 (11.63%)	
occurrences (all)	2	6	
Adrenal insufficiency, Grad 4			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 43 (13.95%)	6 / 43 (13.95%)	
occurrences (all)	6	6	
Myalgia			
subjects affected / exposed	10 / 43 (23.26%)	9 / 43 (20.93%)	
occurrences (all)	11	9	

Back Pain			
subjects affected / exposed	4 / 43 (9.30%)	3 / 43 (6.98%)	
occurrences (all)	4	3	
Muscle cramp			
subjects affected / exposed	2 / 43 (4.65%)	3 / 43 (6.98%)	
occurrences (all)	2	4	
Bone pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 43 (4.65%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Enterocolitis infective			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Conjunctivitis			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Shingles			
subjects affected / exposed	0 / 43 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2022	update protocol V1.2 (15/03/2022)
10 November 2022	update protocol V1.3 (31/08/2022)
30 June 2023	update protocol V1.4 (05/06/2023)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/3603542