Het document is in deze staat aangeleverd ter beoordeling van het onderzoeksdossier. Daarbij was de informatie in de met blauw omkaderde vakken reeds onleesbaar gemaakt.

SYNOPTIC CLINICAL STUDY REPORT

RDN 929-103

NCT 03963973

EudraCT 2019-000831-26

Study Title:	A two-part, parallel group study to assess the safety, tolerability, and pharmacokinetic profile of multiple oral doses of RDN-929 in healthy older adults and subjects with early symptomatic Alzheimer's disease
Phase of Study:	1
Indication:	Alzheimer's disease
Date of First Subject's First Visit:	Part 1: 16 May 2019 Part 2: 09 Sep 2019
Date of Last Subject's Last Visit:	Part 1: 30 Aug 2019 Part 2: 21 Jan 2020
Date of Study Termination:	22 Jan 2020
Document Date:	21 Dec 2020
Sponsor:	Rodin Therapeutics, Inc., now a subsidiary of Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA

This study was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Council on Harmonisation (ICH) Harmonised Tripartite Guideline.

CONFIDENTIAL

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Name of Sponsor/Company: Rodin Therapeutics, Inc., now a subsidiary of Alkermes, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: RDN-929		
Name of Active Ingredient: RDN-929		

Study Title: A two-part, parallel group study to assess the safety, tolerability, and pharmacokinetic profile of multiple oral doses of RDN-929 in healthy older adults and subjects with early symptomatic Alzheimer's disease

Investigators and Study Centers: Part 1 of this study was conducted at 1 site in the Netherlands. Part 2 of this study was conducted at 2 sites in the Netherlands; each of these 2 sites had an affiliated site where subjects underwent magnetic resonance imaging (MRI) and positron emission tomography (PET) scans.

Publications: As of the date of this clinical study report, the data from this study have not been published.

Study Period: First subject's first visit: Part 1, 16 May 2019; Part 2, 09 Sep 2019 Last subject's last visit: Part 1, 30 Aug 2019; Part 2, 21 Jan 2020	**Phase of Development:** 1

Reason for Study Termination: Elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed in 2 among 20 subjects in Part 1 and in 1 among 7 subjects in Part 2 of the study; all 3 subjects had been administered RDN-929. Given this occurrence in 3 subjects, with similar patterns of serum transaminase elevations and probable relation to the study drug, the decision was made to terminate the study.

Objectives:

Primary: To assess the safety and tolerability of multiple, once-daily oral doses of RDN-929 over 28 days in healthy older adult subjects and subjects with early symptomatic Alzheimer's disease (AD).

Secondary: To assess the plasma and cerebrospinal fluid (CSF) pharmacokinetics of RDN-929 in healthy older adult subjects and subjects with early symptomatic AD.

Criteria for Evaluation:

Safety: The primary endpoints were safety parameters, including adverse events (AEs), serious adverse events (SAEs), physical and neurological examination, clinical laboratory values, vital signs, 12-lead electrocardiogram (ECG), and C-SSRS scores.

PK: The secondary endpoints were plasma and CSF PK of RDN-929. Population PK analysis was also performed to estimate the PK parameters of C_{max} (maximum observed plasma concentration) and AUC_{tau} (area under the concentration time curve over the dosing interval) for RDN-929.

Methodology: This was a randomized, double-blind, parallel, 28-day, 4-arm study in healthy older adults (Part 1) and an open-label, single-arm, 28-day study in subjects with early symptomatic AD (Part 2). [redacted]

5.1.1.c

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5.1.1.c

5.1.1.c

Three dosage levels of RDN-929 were studied in 25 healthy older adult subjects. Subjects received RDN-929 once daily for 28 days. 5.1.1.c

5.1.1.c

5.1.1.c

Number of Subjects:

Planned: Part 1 planned for 25 healthy older adult subjects. Part 2 planned for up to 20 early symptomatic AD subjects.

Actual: 5.1.1.c

Analyzed: All 5.1.1.c subjects who were enrolled were analyzed.

Main Criteria for Subject Inclusion: Healthy adults aged 55 to 85 years were eligible for Part 1, and adults age 50 to 85 years with a diagnosis of AD were eligible for Part 2. Subjects had to have a body mass index (BMI) of ≥18.0 kg/m^2 and <35.0 kg/m^2, and no evidence of current suicidal ideation or previous history of suicide attempt as evaluated by the Columbia Suicide Severity Rating Scale (C-SSRS).

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For Part 2 only, subjects had to be willing to undergo genotyping for ApoE and brain-derived neurotrophic factor (Val66Met polymorphism); had to have a confirmed clinical diagnosis of early symptomatic AD, defined as Stage 3 or 4 (per the National Institute on Aging – Alzheimer's Association 2018 diagnostic criteria); had to have a mini-mental state examination (MMSE) score of 21-30 (inclusive); had to have a CSF signature of AD defined as a phosphorylated tau (181P) to amyloid-β (1-42) ratio of >0.024 within 6 weeks of the Baseline Visit; and had to have a caregiver or study partner who would be present at clinical visits and would support study drug compliance at home.

Study Treatment (including dose, mode of administration, and batch numbers): In Part 1 of the study, 5.1.1.c subjects received 25 mg of RDN-929, 5.1.1.c subjects received 100 mg of RDN-929, and 5.1.1.c subjects received 200 mg RDN-929, orally, once daily, for 28 days.

In Part 2 of the study, 5.1.1.c subjects received 50 mg RDN-929, orally, once daily for 28 days. Subjects received study drug from lots as shown in the following table:

Drug	Lot Number
RDN-929 25 mg	5.1.1.c
RDN-929 50 mg	5.1.1.c

Reference Therapy (including dose, mode of administration, and batch number): In Part 1, 5.1.1.c subjects received matched placebo. Placebo was administered orally once daily for 28 days. Subjects received placebo from lots as shown in the following table:

Drug	Lot Number
Placebo	5.1.1.c

In Part 2, no reference therapy was given.

Duration of Study: In Part 1, the duration of participation for each subject was expected to be approximately 63 days, which included up to 4 weeks for screening, 28 days of treatment, and 7 days for follow-up.

In Part 2, the duration of participation for each subject was expected to be approximately 77 days, which included up to 6 weeks for screening, 28 days of treatment, and 7 days for follow-up.

Statistical Methods:

Pharmacokinetics and/or Pharmacodynamics: 5.1.1.c

Safety: All AEs and SAEs were coded 5.1.1.c Adverse events were tabulated by severity and by relationship to study drug. Reasons for death were to be listed. Reasons for premature discontinuation of study drug were listed and summarized by frequency tables.

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Name of Active Ingredient: RDN-929		

Electrocardiogram parameters, vital sign measurements, and laboratory measurements were summarized at each time point using mean, median, standard deviation, min, max, number of available observations, and change from baseline.

Sample Size Considerations:

5.1.1.c

5.1.1.c

5.1.1.c

RESULTS SUMMARY

Subject Disposition and Baseline Characteristics:

5.1.1.c

5.1.1.c

Important Protocol Deviations:

5.1.1.c

Name of Sponsor/Company: Rodin Therapeutics, Inc., now a subsidiary of Alkermes, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
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PHARMACOKINETICS AND/OR PHARMACODYNAMICS

Because this study was terminated early by the Sponsor, no pharmacokinetic or pharmacodynamic results are described in this CSR. Links to summary tables and listings for PK and pharmacodynamic outcomes are found in Appendix 14.2 and Appendix 16.2. Links to PK and pharmacodynamic outcome reports are found in Appendix 16.1.12.

EXPLORATORY

Because this study was terminated early by the Sponsor, no exploratory results are described in this CSR. Links to summary tables and listings for exploratory outcomes are found in Appendix 14.2 and Appendix 16.2. Links to exploratory outcome reports are found in Appendix 16.1.12.

SAFETY

Extent of Exposure

Randomization and study drug administration information for each subject in Part 1 and Part 2 is provided in Listing 16.2.5.1.a and Listing 16.2.5.1.b, respectively. Study drug compliance information for each subject in Part 1 and Part 2 is provided in Listing 16.2.5.2.a and Listing 16.2.5.2.b, respectively.

Adverse Events

Part 1

[redacted]

5.1.1.c

[redacted]

5.1.1.c

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5.1.1.c

- PPD
- PPD

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PPD

Part 2

5.1.1.c

PPD

5.1.1.c

Clinical Laboratory Evaluations

Hematology

5.1.1.c

5.1.1.c

Chemistry

5.1.1.c

PPD

5.1.1.c

PPD

5.1.1.c

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5.1.1.c

5.1.1.c

Urinalysis

5.1.1.c

ECGs

5.1.1.c

C-SSRS Findings

5.1.1.c

Vital Signs

5.1.1.c

OVERALL CONCLUSIONS

Given safety concerns surrounding the cases of asymptomatic elevated serum transaminases consistent with drug-induced liver injury observed during the study, resulting in an SAE in 1 subject and in non-serious TEAEs in 2 subjects, the study was terminated. Other than the drug-induced liver injury findings with RDN-929, no other significant safety findings were identified up to a dose of 200 mg in healthy older adults and 50 mg among subjects with early symptomatic AD dementia.

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Name of Active Ingredient: RDN-929		
Date of Final Report: 21 Dec 2020		

APPENDICES

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic and Baseline Data Summary Figures and Tables

14.1.1 Summary of Subject Disposition

Part 1

Part 2

14.1.2 Summary of Demographics and Baseline Characteristics

14.1.2.a1 Part 1 – Safety Set

14.1.2.a2 Part 1 – Per Protocol Set

14.1.2.b1 Part 2 – Safety Set

14.1.2.b2 Part 2 – Per Protocol Set

14.1.3 Summary of Subject Apolipoprotein E (APOE) Genotyping (Part 2 Only)

14.1.3.a1 Part 2 – Safety Set

14.1.3.a2 Part 2 – Per Protocol Set

14.1.4 Summary of Subject Val66Met Genotyping (Part 2 Only)

14.1.4.a1 Part 2 – Safety Set

14.1.4.a2 Part 2 – Per Protocol Set

14.2. Exploratory

14.2.1 Summary of Mini-Mental State Examination (MMSE) (Observed)

Part 1

Part 2

14.2.2 Summary of Repeat Measurement of MMSE (Part 1 Only) (Repeated Measures Approach)

14.2.3 Summary of Repeat Measurement of MMSE - Treatment Difference (Part 1 Only)

14.2.4 Summary of CSF Diagnostic Biomarkers (Part 2 Only)

14.2.5 Summary of Plasma Concentration by Dose Group by Nominal Time (Part 1)

14.2.6 Summary of Plasma Concentration by Nominal Time (Part 2)

14.2.7 Summary of Cerebral Spinal Fluid Concentration by Dose Group by Nominal Time (Part 1)

14.2.8 Summary of Cerebral Spinal Fluid Concentration by Nominal Time (Part 2)

14.3. Safety

14.3.1.1.1 Treatment-Emergent Adverse Events_1/2

14.3.1.1.1.a1 Part 1 – Safety Set

14.3.1.1.1.a2 Part 1 – Per Protocol Set

14.3.1.1.1.b1 Part 2 – Safety Set

14.3.1.1.1.b2 Part 2 – Per Protocol Set

14.3.1.1.2 Treatment-Emergent Adverse Events_2/2

14.3.1.1.2.a1 Part 1 – Safety Set

14.3.1.1.2.a2 Part 1 – Per Protocol Set

14.3.1.1.2.b1 Part 2 – Safety Set

14.3.1.1.3.b2 Part 2 – Per Protocol Set

14.3.1.2 Treatment-Emergent Adverse Events by SOC and PT

14.3.1.2.a1 Part 1 – Safety Set

14.3.1.2.a2 Part 1 – Per Protocol Set

14.3.1.2.b1 Part 2 – Safety Set

14.3.1.2.b2 Part 2 – Per Protocol Set

14.3.1.3 Treatment-Emergent Adverse Events by SOC and PT (Preferred Term over 5%)

14.3.1.3.a1 Part 1 – Safety Set

14.3.1.3.a2 Part 1 – Per Protocol Set

14.3.1.3.b1 Part 2 – Safety Set

14.3.1.3.b2 Part 2 – Per Protocol Set

14.3.1.4 Treatment-Emergent Adverse Events by SOC, PT and Severity

14.3.1.4.a1 Part 1 – Safety Set

14.3.1.4.a2 Part 1 – Per Protocol Set

14.3.1.4.b1 Part 2 – Safety Set

14.3.1.4.b2 Part 2 – Per Protocol Set

14.3.1.5 Treatment-Emergent Adverse Events by SOC, PT and Relationship to Study Drug

14.3.1.5.a1 Part 1 – Safety Set

14.3.1.5.a2 Part 1 – Per Protocol Set

14.3.1.5.b1 Part 2 – Safety Set

14.3.1.5.b2 Part 2 – Per Protocol Set

14.3.1.6 Treatment-Emergent Serious Adverse Events by SOC and PT

14.3.1.6.a1 Part 1 – Safety Set

14.4 Narratives

Subject PPD

16. APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

16.1.2 Sample Case Report Form

16.1.3 List of Independent Ethics Committee/ Institutional Review Board and Representative Written Information for Subject and Sample Consent Forms

16.1.4 List and Description of Investigators and Other Important Participants in the Study

16.1.5 Signatures of National Coordinating Investigator and Sponsor's Responsible Medical Officer

16.1.6 Listing of Subjects Receiving Investigational Products from Specific Batches

Not applicable

16.1.7 Randomization Scheme and Codes

Not applicable

16.1.8 Audit Certificates

16.1.9 Documentation of Statistical Methods

SAP

SAP Addendum

16.1.10 Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedures if Used

16.1.11 Publications Based on the Study

Not applicable

16.1.12 Important Documents/Publications Referenced in the Report

16.1.12.1 Part 1 Reports

Interim Safety Report – Part 1

Interim Analysis: Plasma Population PK Modeling and Plasma PK-CSF Exploration

Memo 04: Revised Dose Decision for Part 2

Cogstate Topline Report
Peripheral Blood Mononuclear Cell Report

16.1.12.2 Part 2 Reports

Cogstate Computerized Battery, ISLT

qEEG Report

PET Report

PK Report

16.1.12.3 Reports Containing Results From Part 1 and Part 2

Plasma Population PK Modeling and Plasma PK-CSF Exploration

BR-02206

BR-02205

16.2 Subject Data Listings

16.2.1 Subject Disposition and Eligibility

16.2.1.1 Subject Disposition (Completion Status)

16.2.1.1.a – Part 1

16.2.1.1.b – Part 2

16.2.1.2 Subject Disposition (Date of Visit)

16.2.1.2.a – Part 1

16.2.1.2.b – Part 2

16.2.1.3 Inclusion/ Exclusion Criteria at Screening

16.2.1.3.a – Part 1

16.2.1.3.b – Part 2

16.2.1.4 Re-evaluation of Eligibility at Treatment Period

16.2.1.4.a – Part 1

16.2.1.4.b – Part 2

16.2.2 Protocol Deviations

16.2.2 Protocol Deviation

16.2.2.a – Part 1

16.2.2.b – Part 2

16.2.3 Subjects Excluded

16.2.3 Subjects Excluded from Analysis

16.2.3.a – Part 1

16.2.3.b – Part 2

16.2.4 Demographics and Baseline Characteristics

16.2.4.1 Individual Subject Demographics

16.2.4.1.a – Part 1

16.2.4.1.b – Part 2

16.2.4.2 Medical History

16.2.4.2.a – Part 1

16.2.4.2.b – Part 2

16.2.4.3 Prior Medication

16.2.4.3.a – Part 1

16.2.4.3.b – Part 2

16.2.4.4 Concomitant Medication

16.2.4.4.a – Part 1

16.2.4.4.b – Part 2

16.2.4.5 Apolipoprotein E (APOE) Genotyping (Part 2 Only)

16.2.4.6 Val66Met Genotyping (Part 2 Only)

16.2.5 Compliance and/or Drug Concentration

16.2.5.1 Randomization and Study Drug Administration

16.2.5.1.a – Part 1

16.2.5.1.b – Part 2

16.2.5.2 Study Drug Compliance

16.2.5.2.a – Part 1

16.2.5.2.b – Part 2

16.2.5.3 Individual Concentrations in Pharmacokinetic Blood Sampling Timepoint

16.2.5.3.a – Part 1

16.2.5.3.b – Part 2

16.2.5.4 Individual Concentrations in Pharmacokinetic and Pharmacodynamic CSF Sampling Timepoint

16.2.5.4.a – Part 1

16.2.5.4.b – Part 2

16.2.5.5 Individual Subject Biomarkers in Pharmacodynamic Blood Sampling Timepoint

16.2.5.5.a – Part 1

16.2.5.5.b – Part 2

16.2.8.17 Individual Subject Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Behavior

16.2.8.17.a – Part 1

16.2.8.17.b – Part 2

16.2.8.18 Individual Subject Columbia-Suicide Severity Rating Scale (C-SSRS) – For Actual Attempts Only

16.2.8.18.a – Part 1

16.2.8.18.b – Part 2

16.2.8.19 Individual Subject Cognitive Testing

16.2.8.19.a – Part 1

16.2.8.19.b – Part 2

16.2.8.20 Individual Subject Mini-Mental State Examination (MMSE)

16.2.8.20.a – Part 1

16.2.8.20.b – Part 2

16.2.8.21 Individual Subject Brain Positron Emission Tomography (PET) Scan (Part 2 Only)

16.2.8.22 Individual Subject Quantitative Electroencephalography (qEEG) (Part 2 Only)

16.2.8.23 Clinical Laboratory Tests - Additional Hepatic Laboratory Assessments

16.2.8.23.a – Part 1

16.2.8.23.b – Part 1 (*Ad hoc*)

16.2.8.23.c – Part 1 (Comment)

16.2.8.23.d – Part 2

16.2.8.23.e – Part 2 (*Ad hoc*)

16.2.8.23.f – Part 2 (Comment)

16.3 Case Report Forms

16.3.1 Case Report Forms for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

Subject PPD