Statistical Analysis Plan

Protocol No. MT-1186-J04

Clinical Pharmacology Study of Oral Edaravone in Patients with Amyotrophic Lateral Sclerosis (ALS)

Prepared By:	Mitsubishi Tanabe Pharma Corporation
Version:	Version 1.0
Date:	28Nov2019

NCT number: NCT04176224

APPROVAL FORM

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ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
CV	coefficient of variation
DP	decimal places
ECG	electrocardiogram
MedDRA	medical dictionary for regulatory activities
MTPC	Mitsubishi Tanabe Pharma Corporation
PK	pharmacokinetics
PT	preferred term
SAP	statistical analysis plan
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse events
WHO	World Health Organization

LIST OF PK PARAMETERS

Parameters	Definitions
AUC_{0-24}	Area under the plasma concentration-time curve from zero up to 24 hour
AUC_{0-t}	Area under the plasma concentration-time curve from zero up to the last quantifiable concentration time point
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from zero up to infinity with extrapolation of the terminal phase
$AUC\%_{ex}$	Area under the (plasma) concentration-time curve extrapolated from the last quantifiable concentration time point to infinity in % of the total $AUC_{0-\infty}$
Ae_{0-24}	Cumulative urinary excretion amount of drug from zero to 24 hour
C_{max}	Maximum plasma concentration after administration
C_{last}	Last quantifiable concentration
CL/F	Apparent total clearance
CLr	Renal clearance
Kel	Elimination rate constant from the central compartment
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
MRT	Mean residence time
NC	Not calculated
$t_{1/2}$	Terminal elimination half-life in plasma concentration-time course
V_{ss}/F	Apparent volume of distribution at steady state
V_z/F	Apparent volume of distribution during terminal phase
Ae%	Urinary excretion ratio of drug

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol (v1.0) dated 13-Mar-2019. The plan covers statistical analysis, tabulations and listings of the study data to investigate the pharmacokinetics (PK) and safety.

The SAP is prepared by Mitsubishi Tanabe Pharma Corporation (MTPC). The statistical analysis and production of the outputs described in the SAP and QC will be conducted by [redacted] The final analysis and outputs will be checked by [redacted] and approved by MTPC Data Science Deparment.

Any statistical analysis details described in this document supersede any description of statistical analysis in the protocol.

2. STUDY OBJECTIVE AND ENDPOINTS

2.1. Study Objective(s)

To evaluate the pharmacokinetics (PK) of single doses of edaravone oral suspension in patients with Amyotrophic Lateral Sclerosis (ALS)

2.2. Safety Assessments

(1) Adverse events and adverse drug reactions
(2) 12-lead ECG
(3) Laboratory tests
(4) Vital signs

2.3. Pharmacokinetic Assessments

(1) Drug concentration (in plasma and urine)
Unchanged edaravone, sulfate conjugate, and glucuronide conjugate
(2) Pharmacokinetic parameters
Unchanged edaravone: AUC_{0-t}, AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT, CL/F, V_z/F, V_{ss}/F, Ae, Ae%, CLr
Sulfate conjugate and glucuronide conjugate: AUC_{0-t}, AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, Ae, Ae%
(t: Final concentration measurable time point)
Other PK parameters (for all PK profiles for which the Kel has been calculated): $AUC\%_{ex}$, Adjusted R^2, Number of Kel points, Lower limited of Kel, Upper limiter of Kel

3. STUDY DESIGN

3.1. Phase and Type of the Study

Phase of the study: Phase I

Type of the study: Clinical pharmacology study

3.2. Study Design

3.2.1. Type and Details of Cohorts

Single-dose, open-label

3.2.2. Study Period and Evaluation Period

Study period: The study period is defined as the period from the time of obtaining the informed consent to the time of completion of the end-of-study assessment or discontinuation assessment (for subjects who have entered into the follow-up period, to the time of completion or termination of the follow-up).

Screening: Subjects providing informed consent will be screened for eligibility to select subjects meeting all of the inclusion criteria and none of the exclusion criteria.

Evaluation period: The evaluation period is defined as the period from provision of informed consent to completion of the end-of-study assessment or discontinuation assessment.

Hospitalization period: 2 nights and 3 days (Day -1 to Day 2)

End-of-study assessment: The prespecified observations and tests will be performed as the end-of-study assessment, 7 days (allowance±2 days) after the dose of the investigational product.

3.3. Schedule of Study Procedures

Day (time window)	Informed consent	Screening Day -30 to -2	-1	1												2	End-of-study[c] Assesment Day 8 (±2)
Time after dosing		Visit	Admission	Pre-dose	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8 h	10 h	12 h	24 h Discharge	Visit
Written informed consent	X																		
Subject characteristics		X																	
Eligibility assessment		X	X	X															
Dosing of edaravone					X														
Height, weight, BMI[a]		X	X																X
Physical examination		X	X	X														X	X
Vital signs		X	X	X														X	X
12-lead ECG		X	X	X														X	X
Laboratory tests		X	X																X
Serological tests		X																	
Drug/alcohol abuse screening		X																	
Pregnancy test (only female)		X	X																X
Adverse events	←	→																	→
Concomitant medications		←																	→
Blood sampling for edaravone				X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine sampling for edaravone[b]				←														→	

a) Height: Only at screening; Body weight: At screening, hospitalization and end-of-study assessment (discontinuation assessment). BMI: At screening and hospitalization assessment.

b) Urine volume will be measured for each void. A portion of the urine will be collected, dispensed into a tube containing stabilizer, and stored frozen. Urine will be forced to void at 24 hours after administration. Urine will not be collected from subjects if collection is difficult.

c) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.

3.4. Sample Size and Power Considerations

9 subjects

[Rationales for setting]

The target number of subjects was set on the assumption that it would allow obtaining results that will meet the study objectives although it is not based on statistical calculations.

4. PLANNED ANALYSIS

4.1. Final Analysis

This SAP will be finalized before database lock. Final data analysis will be conducted after database lock.

5. ANALYSIS POPULATIONS

PK analysis will be performed on the PK analysis set. Safety analysis will be performed on the safety analysis set (SAF). The definitions of the analysis sets are provided below. The detailed handling of subjects was determined by the sponsor, by the time of the data lock.

(1) PK analysis set

The PK analysis set will consist of all subjects who received at least 1 dose of the investigational product and had evaluable PK data.

(2) SAF

The SAF will consist of all subjects who received at least 1 dose of the investigational product.

6. STATISTICAL CONSIDERATIONS

6.1. Descriptive Statistics

(1) Non-PK related

Continuous data will be summarized descriptively using the number in the analysis set (N), the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects and analysis population being presented, unless otherwise specified.

(2) PK related

Plasma concentrations will be summarized descriptively using N, n, mean, SD, CV%, median, minimum and maximum.

The plasma and urine PK parameters will be summarized descriptively using N, n, arithmetic mean, SD, median, CV%, range (minimum, maximum), geometric mean and geometric CV%

CV% and Geometric CV% will be calculated as follows:

$$\text{CV\%} = \frac{\text{standard deviation}}{\text{arithmetic mean}} \times 100$$

$$\text{Geometric CV\%} = \sqrt{[\exp(\sigma^2) - 1]} \times 100$$

where σ represents the standard deviation computed on the natural logarithmic transformed concentrations.

6.2. Data Review Meeting

Prior to database lock, a data review meeting (DRM) was conducted at November 22, 2019. Protocol deviation and handing of subjects and records, for analysis sets and evaluations, was confirmed during DRM.

No protocol deviation was observed during the study. As a results of DRM, all subject was included in SAF and PK analysis set.

The PK data handling was assessed during DRM. All PK data were considered valid and included in the calculation of PK parameters and in the summary tables and figures.

7. DATA CONVENTIONS

7.1. Analysis Variable Definitions

7.1.1. Study Subjects

7.1.1.1. Demographic and Other Baseline Characteristics

(1) BMI

BMI will be recalculated using the formula below and reported to 1DP

BMI (kg/m^2) = weight at Day-1 (kg) / {height at screening (m)}^{2}

(2) Age at informed consent

Age (year) = year of informed consent – year of birth

Subtract 1 from the age (years) calculated above, if [Month of informed consent < Month of birth] or [Month of informed consent = Month of birth AND Day of informed consent < Day of birth].

7.1.1.2. Medical History

Medical history will be coded according to the MedDRA version 22.0.

7.1.1.3. Prior or Concomitant Medication

Medications will be coded according to the WHO Drug Dictionary (WHO-DD) Global B3 Format March 1, 2019.

(1) Prior Medication

Prior medication is any medication that was stopped prior to the investigational product administration.

(2) Concomitant Medication

Concomitant medication is any medication (including commercially available drugs) other than the investigational product, between the start of investigational product administration and completion of the end-of-study assessment.

7.1.2. Safety Assessments

7.1.2.1. Adverse Events

Adverse events will be coded according to the MedDRA version 22.0.

(1) Treatment Emergent Adverse Events/ Treatment Emergent Serious Adverse Events (TEAEs/TESAEs)

A TEAE/TESAE is classified as treatment emergent if it newly occurred after the first dose of study drug or if a pre-dose event increases in severity following the first dose of study drug.

(2) Adverse Drug Reaction

A TEAE is considered "adverse drug reaction" if it has been assessed as having a "reasonable possibility" in relationship to the study drug.

(3) Time to Adverse Events

Time to Adverse Events occurrence (days) = AE start date – date of first administration + 1

(4) Duration of Adverse Events

Duration of Adverse Events (days) = AE stop date – AE start date + 1

7.1.2.2. Laboratory Tests

Values for out of pre-defined clinically relevant will have clinically relevant values flagged set (L=Lower than normal range, H=Higher than normal range or A=Abnormal).

7.1.2.3. 12-Lead ECG

(1) Criteria for pre-defined limit

12-lead ECG:

- QTcF > 500msec
- 500 >= QTcF > 480msec
- 480 >= QTcF > 450msec
- QTcF <= 450 msec
- Change from baseline in QTcF > 30 msec
- Change from baseline in QTcF > 60 msec

7.1.3. Pharmacokinetics Evaluation

7.1.3.1. Plasma Concentration

For the calculation of the summary statistics, concentration values reported as below the limit of quantification (BLQ) will be set to 0.

7.1.3.2. Pharmacokinetic Parameters

Below the limit of quantification

For the calculation of PK parameters, actual sampling time (in hours rounded to 3 DPs) relative to dosing should be used. Concentration below the limit of quantification (BLQ) will be

imputed with a value of 0. For calculation of AUCs, missing data will be treated as if the respective sample never had been scheduled for the calculation by the linear-linear trapezoidal rule. For Ae, Ae% and CLr, geometric mean and geometric CV% will be calculated only when all the individual Ae, Ae% and CLr is greater than 0 in each sampling time point.

7.2. Analysis Visit Definitions

(1) Non-PK related

The date of the first dose of study drug is defined as Day 1.

Unless otherwise specified, baseline will be the last observed value of the parameter of interest prior to the first intake of study drug (this includes unscheduled visits). No analysis visit window will not be perfomed for safety evaluation.

(2) PK related

The allowable time window will be the following.

Plasma PK sampling

Nominal Time Point	Window
Predose	Within 60 min before dosing
0.083 h after dosing	Nominal time point ± 1 min
0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12 h after dosing	Nominal time point ± 5 min
24 h after dosing	Nominal time point ± 15 min

Urine PK sampling

Nominal Time Point	Window
Predose	Within 60 min before dosing
Voluntary Urine	–
Forced micturition at 24 h after dosing	Nominal time point ± 30 min

7.3. Data Handling Convention for Missing Data

(1) Non-PK related

Adverse events:

If severity or relationship is found to be missing the most severe occurrence will be imputed for the summary of interest.

For AE start missing or partial dates, the AE will be treated as TEAE if it cannot be determined to be a non-TEAE.

Other safety:

For safety summaries, only observed data will be used. Unless otherwise specified, missing safety data will not be imputed.

(2) PK related

For PK summaries, only observed data will be used. Missing PK data will not be imputed. When calculating Ae and Ae%, missing PK data will be imputed to 0.

8. STATISTICAL METHODOLOGY

8.1. Study Subjects

8.1.1. Subject Disposition

Subject disposition will be summarized on the SAF and listed on the enrolled subjects.

8.1.2. Analysis Populations

Analysis populations including the inclusion and exclusion criteria deviation at screening will be summarized and listed on the enrolled subjects.

8.1.3. Study Drug Exposure

Exposure data will be listed on the SAF.

8.1.4. Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be used.

	Category	descriptive
Sex	Male, Female	
Age at informed consent(years)		Yes
Height(cm)		Yes
Weight(kg)		Yes
BMI(kg/m^2)		Yes
Race	Japanese	
El Escorial Revised Airlie House Criteria	Clinically definite ALS, Clinically probable ALS, Clinically probable-laboratory-supported ALS	
Total ALSFRS-R Score		Yes
Medical History	No, Yes	
Complication	No, Yes	
Concomitant Medication	No, Yes	
Allergic History (including drug allergies)	No, Yes	
Drinking status	No (if 'Never'), Yes (if otherwise)	
Smoking Status	No (if 'Never'), Yes (if otherwise)	
Edaravone Histrory	No, Yes (if any record at "Edaravone Intravenous History")	

Demographic and other baseline characteristics will be summarized and listed on the SAF.

8.1.5. Medical History and Allergic History

Medical history and allergic history will be listed on the SAF.

8.1.6. Prior or Concomitant Medications

Prior medication and concomitant medication will be listed on the SAF.

8.2. Efficacy Assessments

N/A

8.3. Safety Assessments

Safety assessments will be made on the SAF.

8.3.1. Adverse Events

Overall summary for the following will be conducted.

- Subjects with at least one TEAE
- Subjects with at least one adverse drug reaction
- Subjects with at least one TESAE
- Subjects with at least one serious adverse drug reaction
- Subjects with TEAE leading to death

The following summaries also will be conducted. These table will be ordered by International Agreed Order for SOC and then by alphabet order for PT.

- TEAEs by SOC and PT
- Adverse drug reactions by SOC and PT
- TEAEs by SOC, PT and severity

Each of the summaries will be done at the subject level - multiple occurrences of the same event within a subject will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a subject will be counted once in the maximum severity category (severe > moderate > mild) and/or maximum drug relationship category (reasonable possibility/no reasonable possibility) and/or the earliest duration.
All AEs, TEAEs and SAEs will be listed.

8.3.2. Laboratory Tests

Absolute values and changes from baseline, except for urinalysis will be summarized by scheduled visit.
For urinalysis, number and percentage will be presented. Shift tables will present the changes in clinically relevant categories from baseline to each scheduled post-baseline visit.

Below in a list of the laboratory test.

Laboratory Test	Parameters
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, MCH, MCHC, MCV, differential white blood count
Biochemistry	Na, K, Cl, Ca, inorganic phosphorus, urea nitrogen, creatinine, uric acid, total bilirubin, direct bilirubin, ALT, AST, γ-GTP, ALP, LDH, CK, amylase, total cholesterol, triglycerides, LDL-C, HDL-C, total protein, albumin, glucose
Coagulation	Prothrombin time, activated partial thromboplastin time
Urinalysis	pH, specific gravity, protein, glucose, occult blood, urobilinogen, bilirubin, ketones, sediment (listing only), hCG (listing only)

All data including clinically relevant flagged will be listed. Any BLQ data will be treated as 0 in summary statistics.

8.3.3. Vital Signs

Absolute values and changes from baseline will be summarized for the following parameters by scheduled visit.

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (beats/min)
- Body Temperature(°C)

Vital signs data will be listed.

8.3.4. 12-Lead ECGs

Absolute values and changes from baseline will be summarized for the following parameters by scheduled visit.

- Heart Rate (beats/min)
- PR (msec)
- RR (msec)
- QRS (msec)
- QT (msec)
- QTcF (msec)

The percentage of subjects with 12-lead ECG values outside pre-defined limit will be summarized by scheduled visit.

12-Lead ECG data (including overall evaluation) will be listed.

8.3.5. Physical Examinations

Physical examination will be listed.

8.4. Pharmacokinetics Evaluation

8.4.1. Concentrations for unchanged edaravone, sulfate conjugate, and glucuronide conjugate

Plasma unchanged edaravone, sulfate conjugate, and glucuronide conjugate concentrations will be summarized at each nominal sampling point. All plasma concentrations will also be listed. Individual plasma concentrations vs. actual time for unchanged edaravone, sulfate conjugate, and glucuronide conjugate will be plotted on both linear/linear and log/linear scales. Mean plasma concentrations vs. nominal time curves will be plotted on both linear/linear (+SD) and log/linear scales.

8.4.2. Pharmacokinetic Parameters for unchanged edaravone, sulfate conjugate, and glucuronide conjugate

The PK parameters listed in Section 2.3 will be calculated for each subject using non-compartmental model. The PK parameters will be listed and summarized. The PK parameters listed as other PK parameters will not be summarized. The urinary pharmacokinetic parameters will be listed and summarized. The urinary pharmacokinetic parameters at pre-dose will not be summarized.

9. DATA PRESENTATION CONVENTIONS

9.1. Number of Digits to Report

(1) Non-PK related

Statistic	Specification	Apply to
Minimum, Maximum	Same number of DPs as the data provided in the datasets	All original (i.e. non-derived)
	see section 7.3	All derived data
Mean, Median, SD, SE, Confidence intervals	One more DP than above	All
Percentages[*1]	1 DP	All
Ratios	3 DPs	All

[*1] Percentages: use 1 place beyond the DP, except for the following cases:

If the percentage is equal to 0, then leave blank, do not use (0)

If the percentage is equal to 100, then use "(100)" without a decimal

(2) PK Plasma Concentration

Statistic	Specification
Individual value	With the number of DP to which they are reported
Mean, SD, Minimum, Median, Maximum	Same number of DPs as the individual value
CV%	1 DP

(3) PK Parameters

Plasma PK Parameters

Statistic	Specification
Individual value	C_{max}: same number of DPs as the plasma concentration t_{max}*: 2 DPs Other parameters to be summarized: number of DPs which the number of significant digits of a minimum parameter is three $AUC\%_{ex}$: 3 DPs Adjusted R^2: 3 DPs Number of Kel points: 0 DP Lower and Upper limited of Kel: 2 DPs
Mean, SD, Minimum, Maximum, Median, Geometric mean	Same number of DPs as the individual values
CV%, Geometric CV%	1 DP

*: t_{max} will be expressed basically in terms of median and range

Urine PK Parameters

Statistic	Specification
Individual value	$Ae_{pre\text{-}dose}$, $Ae\%_{pre\text{-}dose}$: 3 DPs Other parameters: number of DPs which the number of significant digits of a minimum parameter is three
Mean, SD, Minimum, Maximum, Median, Geometric mean	Same number of DPs as the individual values
CV%, Geometric CV%	1 DP

9.2. Treatments to Report

Treatment	For TFLs
MT-1186	Edaravone

9.3. Analysis Visits to Report

(1) Non-PK related

Safety:

	Apply to		
Analysis Visit	Laboratory Tests	Vital Signs	12-Lead ECGs
Screening	X	X	X
Day -1	X	X	X
Day 1		X	X
Day 2		X	X
Follow up	X	X	X

Screening, unscheduled visits and retests (same visit number assigned) will not be displayed in

by-visit summary tables, but will be included in the data listings.

10. CHANGE FROM THE PROTOCOL

The listing output of AE is changed from 'Adverse events that occurred will be listed regardless of whether the investigational product was administered' in the protocol to 'All AEs wil be listed on the SAF' . The reason to change the output is to enable assessment of safety on SAF instead of assessment on the enrolled subjects.

11. SOFTWARE

All statistical analyses will be performed using SAS version 9.4 or higher.
The PK parameters will be calculated using WinNonlin® software (version 6.3 or later).

12. REFERENCES

N/A

Appendix 1 Pharmacokinetic Parameter Calculations

- Actual blood sampling times will be used in the calculation of pharmacokinetic parameters
- All concentrations below the LLOQ will be set at zero for pharmacokinetic calculations
- When K_{el} is missing (or cannot be determined), $t_{1/2}$, $AUC_{0-\infty}$, $AUC\%_{ex}$, CL/F, MRT, V_z/F and V_{ss}/F will not be calculated.

PK Parameter Calculations		
Parameters	Unit	Calculation
C_{max}	ng/mL	will be determined by visual inspection
$AUC_{0-\infty}$	ng·h/mL	$AUC_{0-\infty} = AUC_{0-t} + C_{last} / K_{el}$ C_{last}: last measurable concentration
$AUC\%_{ex}$	%	$AUC\%_{ex} = (AUC_{0-\infty} - AUC_{0-t}) / AUC_{0-\infty} \times 100$
AUC_{0-t}	ng·h/mL	will be calculated using the linear trapezoidal method and actual times $AUC_{0-t} = \sum_{i=1}^{n} \frac{t_i - t_{i-1}}{2} (C_{i-1} + C_i)$
AUC_{0-24}	h·ng/mL	will be calculated using time until 24 h drug concentration
t_{max}	h	Measured time of C_{max}
$t_{1/2}$	h	$t_{½}$ will be determined as: $t_{½} = \log_e(2) / K_{el}$
K_{el}	/h	The exponential rate constant of the terminal phase, k_{el}, will be estimated by log-linear regression, if determinable. The number of data points included in the regression will be determined by visual inspection. Wherever possible, a minimum of 3 data points will be used in the estimation of k_{el}. During the analysis, this calculation method repeats regressions using the last three points with non-zero concentrations, then the last four points, last five, etc. The time of maximum concentration (t_{max}) will be excluded from the estimation of K_{el}. Points with a value of zero for the dependent variable are excluded. For each regression, an adjusted R^2 is computed $Adjusted\ R^2 = 1 - \frac{(1 - R^2) \times (n - 1)}{(n - 2)}$ where n is the number of data points in the regression and R^2 is the square of the correlation coefficient.

		The regression with the largest adjusted R^2 is selected to estimate K_{el}, with these caveats: - If the adjusted R^2 does not improve, but is within 0.0001 of the largest adjusted R^2 value, the regression with the larger number of points is used. - k_{el} must be positive, and calculated from at least three data points.
CL/F	L/h	$CL/F = \frac{Dose}{AUC_{0-\infty}}$
MRT	h	$AUMC_{0-\infty} = \sum_{i=1}^{n} \frac{(t_i - t_{i-1})(t_i \times C_i + t_{i-1} \times C_{i-1})}{2} + \frac{t \times C_t}{Kel} + \frac{C_t}{(Kel)^2}$ $MRT_{0-\infty} = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$
V_z/F	L	$V_z/F = CL/F \times \frac{1}{Kel}$,
V_{ss}/F	L	$V_{ss}/F = MRT \times CL/F$
Number of Kel points	–	will be determined using number of points used in computing Kel. If Kel cannot be estimated, zero.
Lower Limit of Kel	h	will be determined using lower limit on time to be included in the calculation of Kel
Upper Limit of Kel	h	will be determined using upper limit on time to be included in the calculation of Kel
Ae	mg	urine concentration × urine volume
Ae%	%	Ae / Dose
CLr	L/h	$CLr = \frac{Ae}{AUC_{0-\infty}}$