A MULTI-CENTRE, MULTI-COUNTRY RETROSPECTIVE COHORT STUDY TO EVALUATE THE CLINICAL OUTCOMES IN ADULTS WITH COVID-19 WHO HAVE BEEN TREATED WITH REMDESIVIR.

- 909REM -

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Sponsor Protocol ID: NEAT ID 909REM

IRAS: 293273

SPONSOR: NEAT ID

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SPONSOR AND CHIEF INVESTIGATOR SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the guidelines of Good Pharmacoepidemiology Practice (GPP) and Heads of Medicines Agencies (HMA) GCP guidelines, Data Protection legislation, the Sponsor's SOPs, and other regulatory requirements as applicable.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the trial Sponsor:

Signature:
..... Date: ...../...../.....

Name: (please print):
.....

Chief Investigator:

Signature:
..... Date: ...../...../.....

Name: (please print):
.....

STATISTICIAN OR STUDY ANALYST SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Statistician or Study Analyst agrees to conduct the trial in compliance with the approved protocol, Statistical Principles for Clinical Trials, ICH E10 and will adhere to the principles outlined in the guidelines of Good Pharmacoepidemiology Practice (GPP) and Heads of Medicines Agencies (HMA) GCP guidelines, the Sponsor's SOPs and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Statistician or Study Analyst:

Signature:
..... Date: ...../...../.....

Name: (please print):
.....

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the trial in accordance with principles outlined in the guidelines of Good Pharmacoepidemiology Practice (GPP) and Heads of Medicines Agencies (HMA) and ICH-GCP, Data Protection legislation, and the applicable regulatory requirements and with the approved protocol.

I agree to comply with the procedures for data recording/reporting

I agree to permit monitoring, auditing and inspection at this site and to retain all trial related essential documentation for the duration of the study as required according to the applicable regulatory requirements.

Principal Investigator:

Signature:
..... Date: ...../……../……..

Name: (please print):
.....

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KEY TRIAL CONTACTS

Chief Investigator	Anton Pozniak NEAT ID Foundation Registered address: PL 709 Rue Haute 322, 1000 Brussels, Belgium Administrative office: 27 Old Gloucester Street, London WC1N 3AX, UK anton.pozniak@chelwest.nhs.uk
Sponsor	NEAT ID Foundation (NEAT ID) Registered address: PL 709 Rue Haute 322, 1000 Brussels, Belgium Administrative office: 27 Old Gloucester Street, London WC1N 3AX, UK
Project Management	909-REM Project Manager Research Organisation (KC) Ltd. (ROKC) The Stanley Building, 7 Pancras Square, London,UK, N1C 4AG 909REM@rokcservices.com
Data Management	Clinical Informatics Team Research Organisation (KC) Ltd. (ROKC) The Stanley Building, 7 Pancras Square, London, UK, N1C 4AG

STUDY SYNOPSIS

Full study Title	A Multi-centre, Multi-country Retrospective Cohort Study to Evaluate the Clinical Outcomes in Adults with COVID-19 who have been treated with Remdesivir.	
Short title/Acronym	NEAT ID 909REM	
Clinical Phase	IV	
Trial Design	A multi-centre, multi-country retrospective cohort study	
Name of Non-Investigational Product	Remdesivir	
Trial Participants population	At least 450 cases	
Planned Sample Size	At least 450 cases, at least 450 controls (if required, controls will be included in Part 2)	
Eligibility Criteria	**Cases** All Adult participants with COVID-19 confirmed by PCR who meet the following criteria: 1. Hospitalised after August 31st 2020 2. Received Remdesivir (RDV) at any time during hospitalisation	
Indication	COVID-19	
Number of sites	up to 20	
Objectives	**Primary** The primary objectives of this study are to assess the clinical course and outcome of adults with COVID-19 who have been treated with Remdesivir assessed by: 1. All-cause mortality at Day 28; 2. duration of hospitalisation	**Secondary** The secondary objectives are to assess the clinical course and outcome of adults with COVID-19 who have been treated with Remdesivir with respect to the following: 1. a 7-point ordinal clinical status scale on Day 7 and Day 14 2. timing (from first symptoms and from hospitalisation) and duration of use of Remdesivir 3. clinical severity at Day 7, 14, 28 as assessed by the NEWS 2 score 4. clinical status as assessed a 7-point ordinal scale on Day 28 (or at last observation if discharged or died

		prior to this time point) in those still hospitalised after Day 14. 5. SpO2 > 94% on room air on day 7, 14 and 28 6. duration and type (low versus high flow) of oxygen therapy (days) 7. admitted to ICU (yes versus no) 8. Number of days spent on ICU/ITU 9. use of mechanical ventilation/ECMO (extracorporeal membrane oxygenation); start and stop dates 10. re-admission with COVID-19 complications or recurrence within 28 days of discharge and outcome (discharged or deceased)
Criteria for Evaluation	**Primary** 1. All-cause mortality at day 28 2. Clinical status assessed by a 7-point ordinal scale on Day 14 or at last observation if discharged or died prior to this time point, where the 7-point ordinal scale is defined as: 1. Death 2. Hospitalised, on invasive mechanical ventilation or ECMO 3. Hospitalised, on non-invasive ventilation or high flow oxygen devices 4. Hospitalised, requiring low flow supplemental oxygen 5. Hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise) 6. Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care 7. Not hospitalised	**Secondary** 1. Proportion of clinical improvement at Day 14, defined as a ≥ 2-point improvement from Day 1 on a 7-point ordinal scale 2. Timing and duration (days) of Remdesivir 3. Severity of disease on Day 7, Day 14 and Day 28 based on NEWS 2 score 4. Clinical status assessed by a 7-point ordinal scale on Day 28 (or at last observation if discharged or died prior to this time point) in those still Hospitalised after day 14. 5. Time to SpO2 > 94% on room air (number of days when evaluation made on day 7, 14 or 28) 6. Duration of oxygen therapy (total days) 7. Admitted to ICU 8. Need for and time on mechanical ventilation/ECMO of hospitalisation 9. Duration of hospitalisation

FUNDING AND SUPPORT

FUNDER(S)	COLLABORATORS/KEY CONTRIBUTORS
Gilead Sciences 333 Lakeside Drive Foster City, CA 94404	NEAT ID Foundation Registered address: PL 709 Rue Haute 322, 1000 Brussels, Belgium Administrative office: 27 Old Gloucester Street, London, UK, WC1N 3AX
	Research Organisation King's Cross (KC) Ltd. The Stanley Building, 7 Pancras Square, London, UK, N1C 4AG
	Dr Lambert Assoumou (Director) INSERM Centre de méthodologie et de gestion (CMG) Equipe 3 Epidémiologie clinique de l'infection à VIH : stratégies thérapeutiques et comorbidités Institut Pierre Louis d'Epidémiologie et de Santé Publique Sorbonne Université, 56, Boulevard Vincent Auriol CS 81393 - 75646 Paris Cedex 13

2. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

2.1 Primary objective

The primary objectives of this study are to assess the clinical course and outcome of adults with COVID-19 who have been treated with Remdesivir assessed by:

1. all-cause mortality at Day 28
2. duration of hospitalisation

2.2 Secondary objectives

The secondary objectives are to assess the clinical course and outcome of adults with COVID-19 who have been treated with Remdesivir with respect to the following:

1. a 7-point ordinal clinical status scale on Day 7 and Day 14
2. timing (from first symptoms and from hospitalisation) and duration of use of Remdesivir
3. clinical severity at Day 7, 14, 28 as assessed by the NEWS 2 score
4. clinical status as assessed a 7-point ordinal scale on Day 28 (or at last observation if discharged or died prior to this time point) in those still hospitalised after Day 14.
5. SpO2 > 94% on room air on day 7, 14 and 28
6. duration and type (low versus high flow) of oxygen therapy (days)
7. admitted to ICU (yes versus no)
8. number of days spent on ICU/ITU
9. use of mechanical ventilation/ECMO (extracorporeal membrane oxygenation); start and stop dates
10. re-admission with COVID-19 complications or recurrence within 28 days of discharge and outcome (discharged or deceased)

2.3 Primary Criteria for Evaluation

1. All-cause mortality at day 28
2. Clinical status assessed by a 7-point ordinal scale on Day 14 or at last observation if discharged or died prior to this time point, where the 7-point ordinal scale is defined as:

    1. Death
    2. Hospitalised, on invasive mechanical ventilation or ECMO
    3. Hospitalised, on non-invasive ventilation or high flow oxygen devices
    4. Hospitalised, requiring low flow supplemental oxygen
    5. Hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
    6. Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care
    7. Not hospitalised

2.4 Secondary Criteria for Evaluation

1. Proportion of clinical improvement at Day 14, defined as a ≥ 2-point improvement from Day 1 on a 7-point ordinal scale
2. Timing and duration (days) of Remdesivir
3. Severity of disease on Day 7, Day 14 and Day 28 based on NEWS 2 score
4. Clinical status assessed by a 7-point ordinal scale on Day 28 (or at last observation if discharged or died prior to this time point) in those still hospitalised after day 14.
5. Time to SpO2 > 94% on room air (number of days when evaluation made on day 7, 14 or 28)
6. Duration of oxygen therapy (total days)
7. Admitted to ICU
8. Need for and time on mechanical ventilation/ECMO of hospitalisation
9. Duration of hospitalisation

3 TRIAL DESIGN

This is a multi-centre, multi-country retrospective cohort study. At least 450 COVID-19 cases from up to 20 participating study sites who meet all eligibility criteria will be included in the analysis. Deidentified data will be extracted from electronic medical record (EMR) databases, clinical registries, case series or additional sources from participating sites and countries, and then entered into a structured e-CRF system. addition, each site/country will be surveyed to determine the local standard of care therapy for COVID-19 infection and to determine if standard protocols were/are in place for the use of Remdesivir and if/how the protocols changed over time.

Number of Sites and Subjects Planned

Up to 20 centres with 450 cases of Covid-19 treated with at least one dose of Remdesivir

Target Population

Adults with COVID-19 diagnosed and treated with Remdesivir after Aug 31st 2020.

Comparator group-(Part 2)

Part 2, which is collecting data on non-RDV treated controls, will only be initiated, if required, and once data from Part 1, the cases, is collected and analysed. Matching criteria will be detailed in a study management document.

4 ELIGIBILITY CRITERIA

4.1 Inclusion criteria

Diagnosis and Main Eligibility Criteria - Cases(Part 1)

All Adult participants with COVID-19 confirmed by PCR who meet the following criteria:

1. Hospitalised after August 31st,2020
2. Received at least one dose of Remdesivir (RDV) at any time during hospitalisation

Diagnosis and Main Eligibility Criteria –Controls (Part 2)

Adult participants with COVID-19 confirmed by PCR who meet the following criteria:

1. Hospitalised after August 31st 2020

4.2 Exclusion criteria

Exclusion Criteria – Cases (Part 1)

1. Received Remdesivir as part of a clinical trial, compassionate use or expanded access program
2. Received Remdesivir prior to this admission at any other health facility than the research sites and whose health records are available.

Exclusion Criteria – Controls (Part 2)

1. Received Remdesivir at any time during hospitalisation

5 TRIAL PROCEDURES

Only real-world retrospective data will be used for this study. Deidentified retrospective data will be extracted at each clinical site from source data. No personal identifiable data will be transmitted to NEAT ID. Data will be extracted/transcribed in to the eCRF database with standard formatting from electronic medical record (EMR) databases, clinical registries, case series or additional sources from sites/ countries. The data elements will be extracted/transcribed from source data according to the following schedule. Mechanisms to ensure data quality and integrity will be deployed as per applicable standard operating procedures.

	Day1 (Hospital Admission)	**Day7 (+/- 1 day) and Day14 (+/- 2 days) / last observation if discharged or died prior to these time points.**	**Day 28 or last observation after Day 14 if discharged or died prior to this time point.**
Medical History [a]	X		
Pregnancy test	X		
HIV test	X		
Vital Signs [b]	X	X	X
Laboratory Testing [c]	X	X	X
Oxygenation [d]	X	X	X
Clinical Status [e]	X	X	X
Other Treatments for COVID-19 [f]	X	X	X
NEWS SCORE [g]	X	X	X

a. Focused medical history and also the following information (e.g. demographics including ethnicity, baseline characteristics including DM, CV disease and COPD)
b. SpO2, body temperature, body weight and height on admission
c. Includes white blood cell count, creatinine, total bilirubin, ALT, AST at admission Day 7 and day 14 or at discharge if before day 14 , radiographic findings at baseline and as available and SARS-CoV-2 pcr, antigen and/or antibody testing.
d. Includes oxygen supplementation: room air, low flow O2 (L/min and %), high flow O2 (L/min and %), non- invasive

positive pressure ventilation (FiO2 or %), mechanical ventilation (FiO2 or %), ECMO (extracorporeal membrane oxygenation)

e. The ordinal scale is as: 1. Death, 2. Hospitalised, on invasive mechanical ventilation or ECMO, 3. Hospitalised, on non-invasive ventilation or high flow oxygen devices, 4. Hospitalised, requiring low flow supplemental oxygen, 5. Hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise), 6. Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care, 7. Not hospitalised
f. These include corticosteroids, anticoagulants, azithromycin/other antibiotics, anti-inflammatory agents (e.g. Tocilizumab), investigational agents (eg hydroxychloroquine) and immunotherapies such as convalescent plasma and monoclonal antibodies.
g. NEWS 2 score is based on Respiration rate (per minute), SpO2 (%) Air or oxygen. Systolic blood pressure (mmHg), Pulse (per minute) Consciousness, Temperature (°C)

6 STATISTICS AND DATA ANALYSIS

6.1 Subject population

Target Population

Adults with COVID-19 diagnosed and treated with Remdesivir after Aug 31st 2020.

Comparator group

Part 2, which is collecting data on controls, will only be initiated, if required, and once data from Part 1, the cases, is collected and analysed.

The matching criteria for controls, who were given standard of care but not Remdesivir, and who were admitted in a 2 week time window of the cases will be determined once the target population of Part 1, the cases, data has been collected and analysed.

6.2 Study size

This is a non-interventional, observational study where no formal samples size calculation is to be performed. It is anticipated that at least 450 adults with COVID-19 and treated with Remdesivir could be recruited across centres from NEAT ID Network. In addition, 450 other adults with COVID-19 treated with standard of care (control group) will be recruited if needed.

6.3 Statistical analysis

Summary statistics will be generated for the cohort overall and by disease severity at baseline (2 vs 3/4 vs 5). For categorical variables, numbers and percentages of participants will be reported including the 95% confidence intervals. For continuous variables, mean, standard deviation (SD), minimum, first and third quartile (Q1, Q3), median, maximum and 95% confidence intervals will be calculated, together with the total number of observations and the number of missing values. Descriptive statistics will summarize demographics and baseline characteristics. Mortality rate (all causes) at day 28 and its associated 95% confidence interval will be calculated using Kaplan-Meier estimates.

The analysis population will be consisted of all enrolled participants with data available at baseline.

We will assess factors associated with clinical status at day 14 using proportional odds models and factors associated with survival at day 28 using Cox proportional hazards models. For continuous variables, the decision to treat the variable as a continuous or categorical variable (as tertile) will be based on the lowest Akaike information criterion value for the corresponding univariable analysis. Variables achieving $P < 0.10$ in univariable analysis will be retained for the multivariable analysis.

The following variable will be assessed:

- Participating country
- Age group: < 65 vs ≥ 65 years
- Sex at birth: female vs male
- Geographic origin: European vs Sub-Saharan Africa vs. other
- Baseline clinical status (2 vs 3/4 vs 5*)*
- Body mass index at baseline (<18.5 vs 18.5-25; 25.01-30 vs >30 kg/m^2)
- Diabetes at baseline (yes vs no)
- High blood pressure at baseline (yes vs no)
- Time from symptoms onset and date of treatment start (<7 days vs ≥ 7 days)

Secondary endpoints as well as the effect of remdesivir relative to the control group (if Part 2 is performed) will be assessed using appropriate statistical methods for non-randomized cohorts. All details of the analyses will be included in the Statistical Analysis Plan (SAP).

7 DATA

7.1 Authorship eligibility guidelines and any intended use of professional writers

Publication

Data from the RCS will be published independently by NEAT ID. All contributing PI investigators will have the opportunity to participate in publication (abstracts and manuscripts) on the analyses.

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practice (GPP) and Heads of Medicines Agencies (HMA) including archiving of essential documents.

7.2 Data Protection

Personal Data means any information relating to an identified or identifiable natural person (Data Participant), including without limitation pseudonymised information, as defined in the Applicable Law. The *Applicable Law* includes the Regulation (EU) 2016/679, its UK counterpart (UK GDPR) and other relevant regulations. Personal Data will only be collected in line with the study objectives as descried in this protocol, and to safeguard participants' rights, only relevant, adequate, limited and necessary data will be collected and used. It is the Data Controller's (the sponsor) responsibility to ensure compliance with the Applicable Law of a data processor (a CRO or an investigator site).

Data processor(s) to aid the Controller with the Applicable Law compliance, must ensure that persons authorised to process the data, have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality. Transfer of data must be strictly necessary for the implementation of the research or the use of the results. Transfers of data to a third country will be carried out in line with the applicable law and/or provisions ensuring adequacy (e.g. Standard Contractual Clauses for the transfer of personal data).

Data participant rights are upheld according to the applicable law. If a consent has been given, that consent may be withdrawn at any time. The withdrawal will not affect the lawfulness of the processing carried out prior. The personal data may continue to be processed where there is an appropriate legal basis for such processing. Rights to access, change or move of the collected information are limited as the information must be managed in specific ways for the research to be reliable and accurate.

7.3 Data Retention

Patient data may be retained for up to two (2) years after the last publication of the results of research or, in the absence of publication, until the signing of the final research report.

The personal data of professionals involved in research cannot be kept beyond a period of fifteen years (or in accordance with the current regulatons) after the end of the last research in which they participated.

8 APPENDICIES

APPENDIX 1 – Schedule of Procedures

	Day1 (Hospital Admission)	Day7 (+/- 1 day) and Day14 (+/- 2 days) / last observation if discharged or died prior to these time points.	Day 28 or last observation after Day 14 if discharged or died prior to this time point.
Medical History [a]	X		
Pregnancy test	X		
HIV test	X		
Vital Signs [b]	X	X	X
Laboratory Testing [c]	X	X	X
Oxygenation [d]	X	X	X
Clinical Status [e]	X	X	X
Other Treatments for COVID-19 [f]	X	X	X
NEWS SCORE [g]	X	X	X

a. Focused medical history and also the following information (e.g. demographics including ethnicity, baseline characteristics including DM, CV disease and COPD)
b. SpO2, body temperature, body weight and height on admission
c. Includes white blood cell count, creatinine, total bilirubin, ALT, AST at admission Day 7 and day 14 or at discharge if before day 14 , radiographic findings at baseline and as available and SARS-CoV-2 pcr, antigen and/or antibody testing.
d. Includes oxygen supplementation: room air, low flow O2 (L/min and %), high flow O2 (L/min and %), non- invasive positive pressure ventilation (FiO2 or %), mechanical ventilation (FiO2 or %), ECMO (extracorporeal membrane oxygenation)
e. The ordinal scale is as: 1. Death, 2. Hospitalised, on invasive mechanical ventilation or ECMO, 3. Hospitalised, on non-invasive ventilation or high flow oxygen devices, 4. Hospitalised, requiring low flow supplemental oxygen, 5. Hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise), 6. Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care, 7. Not hospitalised
f. These include corticosteroids, anticoagulants, azithromycin/other antibiotics, anti-inflammatory agents (e.g. Tocilizumab), investigational agents (eg hydroxychloroquine) and immunotherapies such as convalescent plasma and monoclonal antibodies.
g. NEWS 2 score is based on Respiration rate (per minute), SpO2 (%) Air or oxygen. Systolic blood pressure (mmHg), Pulse (per minute) Consciousness, Temperature (°C)

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