Results Summary

Nº CHRD	CoPreDex
CHRD1520	
Study coordinator :	Dr Edouard DEVAUD
Department :	Infectious and Tropical Diseases
Adresse :	NOVO Hospital – Site de Pontoise 6 avenue de l'Ile de France CS 90079 95303 CERGY-PONTOISE Cedex

1	**Sponsor :**	NOVO Hospital (Formerly Centre Hospitalier René-Dubos – Pontoise (95))
2	**Name of the investigational medicinal product(s) :**	Dectancyl Solupred
3	**Name of the active substance(s) :**	Dexamethasone Prednisolone
4	**Official Title :**	Comparison Between Prednisolone and Dexamethasone on D28 Mortality in Patients on Oxygen Therapy, With CoViD-19: Multicenter, Randomized, Open-label Non-inferiority Study
5	**Investigator (s)[1] :**	Study coordinator : Dr Edouard DEVAUD Total number of investigators: 8 (Dr Edouard Devaud : study - coordinator and principal investigator site 01 and 7 principal investigators from the remaining 7 sites)
6	**Study locations and centres [2] :**	8 centres
7	**Publications[3] :**	NA
8	**Duration of the clinical study :**	11 months (19 months theoretical)
8.1	• **date of first inclusion:**	2021/03/03
8.2	• **end date of participation of the last person included in the clinical study.**	2022/02/10
9	**Study Phase:**	III
10	**Primary and secondary outcome measure:**	Primary Outcome : Mortality assessment at D28 Secondary Outcome: - Assessment of clinical course in both groups - Measurement of evolution of respiratory symptoms in both groups - Assessment of patient satisfaction towards the treatment - Comparison betwween D1 and D28 of patient quality of life evolution between randomization groups - Comparison betwween D1 and D28 of adverse events and adverse effects between randomization groups
11	**Clinical study methodology [4] :**	Prospective, multicenter, randomised, non-inferiority study

[1] If the study is multicentric, indicate the name(s) of the coordinating investigators and the total number of investigators

[2] Indicate the number of research sites and centres (if different from the number of sites)

[3] Specify in order: the name of the authors, the title of the publication, the name of the journal, the year, the volume number, the pages concerned

[4] Specify in particular whether the research involves a random draw, whether it is comparative, open-label, single-blind, double-blind, parallel group, cross-over, types of comparators used

12	**Number of people who took part in the Clinical Study**	89
12.1	• **number of people expected**	220
12.2	• **number of people analysed:**	71 per-protocol analysis – 80 intention-to-treat analysis
13	**Medical condition or disease studied and inclusion and non-inclusion criteria:**	Medical condition or disease studied : Covid-19 infection Inclusion Criteria : - Patient ≥ 18 years old - Patient with SARS-CoV-2 pneumopathy documented by nasopharyngeal or bronchoalveolar lavage fluid RT-PCR or any documented clinical symptoms support by CT scan. - Patient with SpaO2 ≤ 94 % in room air (90% for patient with respiratory failure) and requiring an oxygen therapy - Negative pregnancy test for women of childbearing age - Informed and written informed consent obtained - Patients with affiliation to the social security system Non-inclusion criteria : - Patients with a contraindication to the use of corticosteroids (allergy…) - Patient with corticosteroids as background treatment (≥ 10 mg equivalent) - Patient under supplemental oxygen > 6 L/min - Immunocompromised patient (AIDS, bone marrow or solid organ transplants …) - Patient who received a corticosteroid dose within 3 days for Covid-19 - Medical history of hypersensitivity to Prednisolone or Dexamethasone; or lactose / galactose (excipients with known effect) - Another active virus such hepatitis, herpes, varicella, shingles .... - Psychotic state not controlled by treatment - Pregnant or breastfeeding woman - Patient under guardianship/ curatorship
14	**Investigational drug(s) studied**[5] **:** *(name, dose, route of administration and batch numbers)*	- Dexamethasone (INN) = Dectancyl 6mg/day or 12 tablets in the morning for 10 days per os - Prednisolone (INN) = Solupred 60mg/day or 2 orodispersible tablets in the morning (40mg) and 1 orodispersible tablet in the evening (20mg) for 10 days per os Batch number not available.
15	**Duration of treatment** [6] **:**	10 days
16	**Reference investigational medicinal product(s), if any :**	- Dexamethasone (INN) = Dectancyl 6mg/day or 12 tablets in the morning for 10 days per os

[5] Specify, if applicable, for each investigational medicinal product studied, the maximum duration of treatment for the person who underwent the research

[6] Repeat the section if the research involves more than one investigational drug being studied

	(name, dose, route of administration and batch numbers)	
17	**Evaluation criteria :**	The primary outcome is the mortality assessment at D28
17.1	• **Efficacy**	• Comparison of the clinical course between the Dexamethasone and Prednisolone groups for : o Number of oxygen therapy days o Number of patients requiring oxygen therapy increase (High-Flow Oxygen Therapy, CPAP/BIPAP, mechanical ventilation, ECMO) o Number of hospital days o Number of patient admitted in Resuscitation Unit /Intensive care Unit o Number of patient with organic damage other than lung o Number of disease-related infection other than SARS-Cov-2 o Frequency and evolution of complication of corticosteroid therapy (Severity evaluated according to CTCAE (diabetes, acute psychosis or other adverse effect consider to be link to corticosteroide therapy by investigator)) • Respiratory symptoms will be defined by measuring oxygen saturation associated with oxygen flow and respiratory rate once a day for 14 days then 3 times a week until D28
17.2	• **Safety**	• Proportion of adverse events and adverse effects during the 28 days
17.3	• **Other**	• Assessment of patient satisfaction, at D12, with a satisfaction questionnaire (Likert-type scale) • Measurement of patient quality of life evolution with EQ5D self-assessment questionnaire
18	**Statistical analysis :**	This is a non-inferiority study comparing two groups. For this type of design, the analysis is performed per-protocol. The primary outcom was also assessed on an intention-to-treat to validate the result. Description of the population: simple comparison between the 2 groups (χ 2 and Wilcoxon test) <u>Primary outcome</u> : Comparison of the number of patients who died by a one-sided Dunnett and Gent χ 2 test, based on patients whose vital status was recovered (the others being excluded from the analysis). Due to the small number of patients, this test could not be performed. Only a relative risk comparison was performed. Validation by a Fisher exact test in intention-to-treat. Concerning the survival curves, the small numbers do not allow a comparative Log-Rank test to be carried out. A research of factors that could influence the result was carried out, first in univariate by Fisher and Wilcoxon tests and then a logistic regression model was used. <u>Secondary outcomes</u> : The comparison of the duration of oxygen use between the two groups

		was calculated by a Wilcoxon-Mann-Whitney test. The comparison of the number of transfers in Resuscitation Unit /Intensive care Unit between the two groups was done by a Wilcoxon-Mann-Whitney test. Changes in EQ5D-3L score, mobility, autonomy, activities of daily living, pain or anxiety were compared between the two groups by Fisher exact tests. Adverse events were listed. A simple comparison of the number of adverse events between the two groups was performed by a Fisher exact test.
19	**Abstract – conclusions of the clinical study**	The CoPreDex study is conducted in the context of known and accepted bioequivalence, pharmacokinetics and dynamics of the different steroids. Nevertheless, at the end of the originator Recovery study, it appeared important to validate these elements of equivalence by proposing a non-inferiority study of Prednisolone versus Dexamethasone. However, due to the small number of patients recruited, in relation to the involution of the epidemic on a national scale, and even though there was no statistically significant difference between the two groups studied, it was not possible to affirm this non-inferiority. For the primary outcome, mortality at D28, the statistical analysis did not show a significant difference between the two treatment arms, as the relative risk and survival curve analyses were not relevant in view of the patient numbers. In multivariate analysis, the results seem to confirm high age and diabetes, of any type, as a negative prognostic factor for CoVID 19 in contrast to the type of corticosteroid used. On the secondary outcomes, there was, again, no significant difference in the number of days of oxygen dependence, the need of intensive care with assisted ventilation, and finally the perception of the role of the treatment on quality of life.
19.1	• **Results of the efficacy assessment, if any**	The therapeutic efficacy of Prednisolone was not inferior to that of Dexamethasone in the statistical population analysed
19.2	• **Results of the safety assessment, if any**	In total, there were 106 adverse events recorded during the study involving 38 patients. There was no difference in the proportion of events between the two treatments. 54% in the Dexamethasone group and 46% in the Prednisolone group.
19.3	• **Conclusion**	The CoPreDex study of non-inferiority between Prednisolone and Dexamethasone in the treatment of severe forms of CoVID 19 was unable to gather sufficient numbers of patients for a meaningful statistical analysis. As the analyses carried out did not show any significant difference between Prednisolone and Dexamethasone on mortality at D28 in severe forms of CoVID 19, the study does not contradict the hypothesis of equivalence of these two steroids. However, it lacks the statistical power to draw a firm conclusion on the non-inferiority of Prednisolone over Dexamethasone in reducing mortality at D28 in severe forms of CoVID 19. The study also tends

		to confirm age and diabetes as independent risk factors for progression to a severe form.
20	**Reasons for the early interruption of the study**	The inclusions were initially scheduled to be completed on 02/09/2022. The rate needed to be approximately 12 patients included per month to reach the number of 220 patients. However, since June 2021, we have seen a sharp decline in the rate of inclusions (2-5 patients included per month), and no patients have been included in the study since January 2022. This sharp decrease is due to the large vaccine coverage against Covid-19 in France, and the fact that the few eligible patients are resistant to clinical trials. Therefore, the study effectively ended prematurely on March 31, 2022 .
21	**Report date :**	2023/06/29
22	**EudraCT number:**	2020-005883-78
23	**Date of report's submission :**	2023/06/29
	Signature :	
	Name / Title :	Pauline DELATTRE Responsable USRC