PRESS RELEASE

DisCoVeRy: Remdesivir does not expose hospitalised patients with Covid-19 to an increased risk of cardiac effects

Paris, 02 May 2024

The role of the antiviral agent remdesivir in the management of patients hospitalised with Covid-19 has evolved over time with the accumulation of new data. Numerous cases of adverse cardiac events, in particular bradycardia, have been reported at individual level and in observational studies without a comparator group. In this context, and as part of the European response, the Clinical Research Vigilance Department of the ANRS Emerging Infectious Diseases, with the support of research teams from various institutions, including Inserm,* the Hospices civils de Lyon, AP-HP and the Université libre de Bruxelles (ULB), has just carried out a *post-hoc* analysis of the phase III DisCoVeRy study. This analysis assessed the incidence of adverse cardiac events in hospitalised patients suffering from the moderate to severe form of Covid-19 and receiving the usual standard of care alone or combined with remdesivir. No increased risk of cardiac adverse events was demonstrated with remdesivir compared to the comparator group. The results were published in the March 2024 issue of *Clinical Infectious Diseases*, along with an editorial by the journal (1,2).**

At the start of the pandemic, there was an urgent need to find therapeutic options to treat patients with a moderate or severe form of Covid-19, *i.e.* hospitalised patients with respiratory symptoms requiring oxygen. The antiviral agent remdesivir was one of the first treatment options in the context of the rapid development of therapeutic strategies.

The DisCoVeRy clinical trial, initially launched in March 2020 by Inserm-PRC* in France and subsequently expanded to Europe through the EU-Response project **(3)** funded by the European Commission, was designed to evaluate several possible treatments for Covid-19. In this study, remdesivir, like the other antivirals tested (lopinavir/ritonavir, hydroxychloroquine, interferon, etc.), showed no clinical benefit in adult patients hospitalised and placed on supplemental oxygen compared with those receiving standard care alone **(4).**

Subsequently, studies on another population at risk of developing severe Covid (non-hospitalised, non-oxygen dependent population - Pinetree **(5)**) and a meta-analysis (Prospero **(6)**) demonstrated the efficacy of early remdesivir administration before the onset of severe Covid.

As with any newly authorised medicine, a large number of post-authorisation safety studies have been carried out. Several clinical cases and observational studies have warned of the occurrence of cardiac concerns at the start of treatment, in particular mild to moderate sinus bradycardia (arrhythmia corresponding to an abnormally slow heartbeat). The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) analysed this safety signal for sinus bradycardia. In June 2021, it concluded that a causal relationship between the use of the medicine and this adverse event was at least a 'reasonable possibility' with an undetermined frequency.

Under those circumstances, a *post-hoc* analysis of the DisCoVeRy data was undertaken. In this study, participants had been allocated to 'homogeneous' groups, meaning that on inclusion they were not significantly different from each other on a number of key characteristics, such as co-morbidities.

The results of the analysis showed that, compared to the comparator group and regardless of severity, antiviral treatment was not associated with an increased risk of cardiac adverse events, including arrhythmias. Cardiac adverse events were reported in 46 of 410 patients receiving remdesivir and in 48 of 423 patients in the comparator group. The difference between the two groups was not significant. The incidence of arrhythmia, the most common cardiac disorder in both groups, was mainly associated with a favourable outcome, without the need to discontinue remdesivir. These results reflect the already well-documented cardiovascular complications associated with the disease itself. They also highlight the role of other risk factors, such as pre-existing co-morbidities and exposure in both groups to numerous drugs that can cause cardiac problems, particularly in intensive care.

" *The study of any Covid-19 therapeutic must be gauged in terms of its risk profile in the Covid-19 population by accounting for the cardiovascular risk of Covid-19 disease, along with pre-existing patient comorbidities, always including a randomized controlled trial.*" *Robert L Gottlieb (Center for Advanced Heart and Lung Disease, Baylor University Medical Center, Dallas, Texas) and Andre C Kalil (Division of Infectious Diseases, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska)*

The results of DisCoVeRy, a randomised controlled trial, complement existing data on the safe use of remdesivir in hospitalised patients with Covid-19. They are consistent with those of meta-analyses and other randomised controlled trials. New research, including meta-analyses with a larger sample size enabling sub-population analyses, is expected in the near future.

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** Analysis of experimental data after a study has been concluded and the data collected

References:

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(3) https://cordis.europa.eu/project/id/101015736

Funded by the European *Union (European Union's Horizon 2020 research and innovation programme under grant agreement No* 101015736), DisCoVeRy is now research axis 1 of the EU-RESPONSE project (European Research and Preparedness Network for Pandemics and Emerging Infectious Diseases), which brings together 22 partners (clinics, hospitals, universities, etc.) from 13 countries in the European Union, Norway, Switzerland, Luxembourg and Turkey.

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About the ANRS MIE: *The ANRS Emerging Infectious Diseases (MIE), created on 1 January 2021, is an autonomous Inserm agency headed by Professor Yazdan Yazdanpanah. Its remit is to lead, evaluate, coordinate and fund research into HIV/AIDS, viral hepatitis, sexually transmitted infections, tuberculosis and emerging and re-emerging infectious diseases (in particular emerging respiratory infections - including Covid-19 - viral haemorrhagic fevers and arboviruses). Under the authority of the France's Ministry of Higher Education and Research and Ministry of Health and Prevention, the ANRS MIE federates an interinstitutional network of national and international physicians and researchers, patient organisations and civil society representatives, all fully involved in theagency's governance and operation. This dynamic co-construction guarantees project implementation in line with the expectations of the affected communities, and aims to limit the health, economic and social impact of epidemics. The Agency's vaccine research programme is led by the Vaccine Research Institute (VRI). For more information: https://anrs.fr/en/*

About Inserm: *Founded in 1964, Inserm is a public scientific and technological institute dedicated to biomedical research and human health, and is involved in the entire range of activities from the laboratory to the patient's bedside. It also partners with the most prestigious research institutions in the world that are committed to scientific challenges and progress in these fields. For more information:* https://www.inserm.fr/en/home/

About the Hospices Civils de Lyon: *Backed by 200 years of medical history, the Hospices Civils de Lyon are 13 public hospitals of excellence, bringing together all medical and surgical disciplines and committed to a threefold mission: to care, to innovate and to pass on knowledge. For more information: https://www.chu-lyon.fr/*

About AP-HP: *Europe's leading university hospital centre (CHU), AP-HP and its 38 hospitals are organised into six university hospital groups (AP-HP. Centre – Université Paris Cité; AP-HP. Sorbonne University; AP-HP. Nord – Université Paris Cité; AP-HP. Université Paris-Saclay; AP-HP. Henri-Mondor University Hospitals and AP-HP. Hôpitaux Universitaires Paris Seine-Saint-Denis) and are structured around five Paris Region universities. In close collaboration with major research organisations, the AP-HP has eight world-class university hospital institutes (ICM, ICAN, IMAGINE, FOReSIGHT, PROMETHEUS, InovAND, Re-Connect, THEMA) and France's largest healthcare data warehouse (EDS). A major player in applied research and innovation in healthcare, the AP-HP holds a portfolio of 810 active patents, its clinician-researchers produce more than 11,000 scientific publications every year and nearly 4,400 research projects are currently under development, all sponsors included. In 2020, the AP-HP obtained the Carnot Institute label, which rewards the quality of its partnership research: the Carnot@AP-HP offers applied and clinical research solutions in the field of healthcare to industrial players. In 2015, the AP-HP also set up the Fondation de l'AP-HP, which works directly with healthcare professionals to support the organisation of care, hospital staff and research within the AP-HP. For more information:* https://www.aphp.fr/

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