NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

Minutes of the Teleconference Meetings held on Thursday 21st May 2020 at 10:00 and Friday 22nd May 2020 at 10:00 via zoom network communication due to the Covid-19 virus crisis currently affecting the UK

Commissioners Participated

Professor S Ralston (Chair)
Ms S Bradford
1 Professor J Coleman
Dr J Fraser
Professor J S Friedland
Dr R J C Gilson
Professor M R Macleod
Dr R Mann
Professor S Meredith
Dr S Misbah
2 Professor Sir M Pirmohamed
Professor S Price
Dr M Wilson

Invited Experts

3 4 3 4 3 **Name Redacted**

Observers

3 Ms J Dilkes
3 **Name Redacted**
5 Ms J Prescott

Secretariat

Name Redacted

MHRA Legal

5 **Name Redacted**

Professional Staff of MHRA Participated

Principal Assessors

Dr K Prasad – Licensing (LD)

Licensing Division Presenters[6]

Name Redacted

VRMM Presenters[6]

Name Redacted
Name Redacted
Name Redacted

17.3 **Irrelevant & Sensitive**

18. **Paper**

18.1 **Hydroxychloroquine or chloroquine with or without a macrolide antibiotic for treatment of COVID-19: a multinational registry analysis**

The following Commissioners declared non-personal non-specific (NPNS) and other relevant interests; however, this did not debar them from taking part in the proceedings:

- Dr NR – NPNS: Pfizer, Teva
  Other relevant interest: co-investigator for COVID-SOLES (systematic online living evidence summary), a web-based platform curating primary research in COVID, which will be funded from 1st June by a small grant from the Institutional Strategic Support Fund, which is in turn funded by the Wellcome Trust

- Professor Ralston – NPNS: Pfizer

- Professor Friedland – NPNS: Pfizer

- Professor Gilson – NPNS: Mylan

18.1.1 The Commission noted Tabled Paper VI.

18.1.2 The Commission was presented with the findings from a pre-print publication by Mehra et al. entitled "Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis" which had been shared in confidence by The Lancet. It was noted that online publication was expected later on Friday 22nd May and was under embargo until 2 PM.

18.1.3 The Commission noted that this was a large study including more than 96,000 patients with COVID-19 infection from over 670 hospitals across 6 continents. The study concluded that treatment with hydroxychloroquine alone, hydroxychloroquine with a macrolide antibiotic, chloroquine alone, and chloroquine with a macrolide antibiotic were each independently associated with an increased risk of in-hospital mortality and de-novo ventricular arrhythmia in patients admitted to hospital with confirmed SARS-CoV-2 infection.

18.1.4 The Commission noted the observational nature of the study, which was conducted using data from the Surgical Outcomes Collaborative registry. The potential for bias caused by differences in the underlying severity of COVID-19 in patients treated with hydroxychloroquine or chloroquine compared to those admitted to hospital with severe infection but who did not receive therapeutic treatment for COVID-19 was discussed, although it was noted that patients already requiring mechanical ventilation were excluded and that only approximately 20% of treated patients included in the study went on to require this. Furthermore, analysis conducted to explore the potential impact of unmeasured confounding suggested that it was highly unlikely that there was sufficient bias to be masking a benefit of treatment in terms of reduced mortality rates.

18.1.5 While data on the exact doses of hydroxychloroquine used by patients in the Mehra et al. study were not available at the time of review, the Commission agreed that it could be reasonably estimated that these were higher than those doses currently recommended for licensed indications. This, coupled with differences in the underlying risk profiles of those receiving treatment for COVID-19, meant that the findings of the study were not considered to impact on the licensed indications for hydroxychloroquine or chloroquine for which the benefits continue to outweigh any risks.

18.1.6 The Commission also noted a number of other recent publications and pre-print papers describing data from epidemiological studies which explored the benefits and risks of hydroxychloroquine and chloroquine used for the treatment of COVID-19. These included a pre-print paper by Singh et al (medRxiv, 21st May 2020). which suggested no difference in 7 or 14-day mortality between patients treated and untreated with hydroxychloroquine using data from 1,125 treated COVID-19 patients identified in a US electronic medical record network. A further study by Rosenberg et al. JAMA published 11th May 2020, using data from 1,438 COVID-19 patients hospitalised in metropolitan New York also showed no difference in the rate of in-hospital mortality. Two smaller studies, Mercuro N et al. (JAMA Cardiology May 1st 2020) and Bessiere F et al. (JAMA Cardiology May 1st 2020) found significant risks of QT prolongation in COVID-19 patients treated with hydroxychloroquine with or without azithromycin. Another study by Borba M et al (JAMA April 24th 2020) had reported QT prolongation in COVID-19 patients given high dose chloroquine

18.1.7 The Commission agreed that the observational study by Mehra M et al., combined with the growing body of evidence regarding the potential risks associated with hydroxychloroquine in the treatment of COVID-19, and the current absence of data on a benefit, was concerning. It was also noted that some patients with COVID-19 who are otherwise considered to be at low risk, even without HCQ exposure, still get arrhythmias. It was agreed that these new data raised serious questions about the potential for a positive benefit risk balance of hydroxychloroquine and chloroquine for the treatment of COVID-19.

18.1.8 The Commission noted that there were 8 trials approved in the UK which include the use of hydroxychloroquine for the treatment of, or prophylaxis for, COVID-19. It was agreed that each of these needed consideration in the light of the findings of the emerging evidence.

18.1.9 The Commission were presented with, and discussed, the range of regulatory options for managing the clinical trials involving hydroxychloroquine for treatment or prevention of COVID-19 in light of the emerging evidence. They recommended that the trial sponsors for all relevant trials should be contacted to request that they urgently ask the investigators and data monitoring committees to provide a re-assessment of the benefit-risk balance of the trial and justify any proposed continuation. The Commission advised that all responses would be assessed and if the benefit-risk balance of the trial was no longer justified then further regulatory action would be taken under The Medicines for Human Use (Clinical Trials) Regulations 2004.

18.1.10 The impact of the above decisions for trials that were not yet approved but were currently under review by MHRA was also discussed. The Commission advised that no further trials using hydroxychloroquine should be approved until the review has been completed and a stronger potential for benefit has been established.

18.1.11 The Commission also discussed what advice should be given regarding patients taking hydroxychloroquine or chloroquine for other indications who go on to develop COVID-19 infection. It was agreed that treatment should be stopped in these situations until the patient had recovered.

19. Abridged

19.1 **I&S**

19.1.1 Professor Friedland, Professor Meredith and Professor Macleod declared non-personal non-specific interests in Boehringer Ingelheim Limited; however, this did not debar them from taking part in the proceedings.

19.1.2 **I&S**

19.2