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Appropriate WHO Confidentiality Undertakings were signed and submitted to WHO by all participating experts

INTRODUCTION

Sofosbuvir and daclatasvir are antiviral drugs, which are approved for treatment of Hepatitis C infection.

Sofosbuvir is a polymerase inhibitor, it inhibits the hepatitis C NS5B protein. Sofosbuvir appears to have a high barrier to the development of resistance. Sofosbuvir is a prodrug of the Protide type, whereby the active phosphorylated nucleotide is granted cell permeability and oral bioavailability.

Daclatasvir is an inhibitor of NS5A, a non-structural protein encoded by HCV. Daclatasvir binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly.

There are published in silico studies suggesting docking affinity for sofosbuvir and daclatasvir to structural proteins of SARS-CoV-2. In vitro evaluation of both drugs is in progress. There is a high variability of results from in vitro studies of sofosbuvir against a range of viral infections. The results seem to depend on the cell type used in the assays.

OBJECTIVES OF THE CONSULTATION

The objective of the call was

- To summarize in vitro results made by Fiocruz
- To summarize the preliminary results of 3 clinical studies in Iran
- To discuss the potential for SOF/DCV to be tested in a larger study

Agenda items

1) Presentation by Thiago Moreno from Fiocruz – In vitro assays
2) Presentation by Andrew Hill from Liverpool University – Clinical results from Iran
3) Discussion
4) Recommendations and next steps

**Working group members**

Chair: Marco Cavaleri

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
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<tbody>
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<td>Manager- Advisory</td>
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COVID-19: Therapeutics Working Group Informal consultation on the potential inclusion of Sofosbuvir/Daclatasvir in a clinical trial

**Name** | **Position** | **Institutional Affiliation**
--- | --- | ---
Helen Rees | Professor, Wits Reproductive Health and HIV Institute | University of Witwatersrand, South Africa
Matthew Frieman | Associate Professor, Microbiology and Immunology | University of Maryland School of Medicine, USA

**Additional experts:**

Michael Jacobs, Andrea Antinori, Vicente Estrada, Richard Peto, Peter Smith, Tom Fleming, Uli Fruth.

WHO Secretariat: Alejandro Costa, Janet Diaz, Ana Maria Henao-Restrepo, Kolawole Salami, Emer Cooke, Deusdedit Mubangizi, Matthias Mario Stahl, Raymond Corrin, Philip Coyne

**OVERVIEW OF THE DELIBERATIONS**

**Presentations:**

In vitro results

In vitro studies in Vero E6 measuring PFUs or number of copies/mL did not show sofosbuvir or daclatasvir to inhibit SARS-CoV-2 replication, however showed synergism with remdesivir and simeprevir. In vitro studies using HuH-7 and Calu-3 cells SOF and DCV showed inhibition of virus replication.

Daclatasvir shows consistent anti-SARS-COV-2 activity among different cell types, DCV showed to be 10 times more potent than SOF (DCV 0.6-1.1 µM vs SOF 6.2-9.5 µM)

Daclatasvir’s pharmacological parameters against SARS-COV-2 are within its AUC in humans.

Besides inhibition of SARS-COV-2, sofosbuvir has been associated with anti-Zika, Dengue, yellow fever and chikungunya activities (list of works below knowledge)

Sofosbuvir’s PK within specific anatomical compartments is necessary to interpret its biological activity

Clinical preliminary results

Three clinical trials have been conducted to assess sofosbuvir/daclatasvir versus control, in a total of 176 hospitalised patients.
The pharmacokinetics of SOF concentration in plasma indicates that the approved dose of 400 mg is lower than the concentration needed for antiviral activity. On the contrary Daclastivir at the suggested dose of 60 mg the concentration in plasma is above the EC50.

Three trials have been conducted in Iran:
1- Tehran with 66 patients, LPV/RTV + SOF/DCV (33) versus LPV/RTV (33)
2- Abadan with 62 patients, HCQ+LPV/RTV + SOF/DCV (35) versus HCQ + LPV/RTV + RBV (27), not randomized
3- Sari with 48 patients, LPV/RTV + SOF/DCV (24) + RBV versus LPV/RTV (24)

All patients were moderate/severe

In a meta-analysis of these three clinical trials, the analysis was looking at time to discharge from hospital and survival

When the 3 studies are combined death rates were 5/92 (5%) on sofosbuvir/daclatasvir versus 17/84 (20%) on control treatment (p=0.005). In the same meta-analysis, the time to discharge from hospital was significantly shorter in the sofosbuvir/daclatasvir arms, compared with the control arms (p<0.001).

In the meta-analysis, the benefits of sofosbuvir/daclatasvir versus control treatment were fairly consistent across the three trials. However, one of these trials was not properly randomized and the overall sample size is limited. These results need to be confirmed in larger trials to support potential regulatory approval of sofosbuvir/daclatasvir to treat COVID-19 infection.

Advantages of the treatment are:
- Apparent faster recovery
- Safe
- Not expensive ($5 per treatment)
- Is widely available (3 million treatments in stock)
- Production capacity and easy to scale up (annual production around 8 million treatments)

Disadvantages are:
- Small studies, only 176 patients and one of the studies was not randomized.

Studies planned: Iran, South Africa, Egypt, Brazil

Discussion on the available evidence

The in vitro studies made by Fiocruz, SOF does not show in vitro activity against SARS-CoV-2. Gilead has obtained similar results in vitro. In Iran SOF was included in combination with DCV because is the treatment approved for HCV.
Fiocruz is moving forward to test SOF and in combination (to see potential synergism) in other tissue and cells like epithelial lung cells. Fiocruz does not have the capacity to test antiviral in animal models.

The use of steroids in the 3 trials was not presented and it should be clarified.

SOF/DCV was given in the Iranian trials in combination with Kaletra. Although it does not seem that drug interactions occurred, it needs to be further investigated.

Since DCV is highly protein bound, much higher doses would be required.

Determining the real concentration in the lung epithelial fluid would be important. Also matching a more stringent activity concentration than EC50 would be warranted.

In the USA SOF was not included in the ongoing trials because of the high EC50, and DCV was not part of the antiviral priority list for screening.

CONCLUSIONS:

As today, there is no enough preclinical and clinical evidence to consider SOF/DCV to be included in large clinical trials like Solidarity. This combination therapy has shown some encouraging results in small trials, but there is no enough data to know which drug and what dose regimen would be effective since SOF/DCV was given in combination with Kaletra in the Iranian trials.

According to the in vitro data presented, SOF will not achieve effective concentration is plasma, so the possibility, would be to explore if there is any synergistic effect when combined with other antivirals. Animal studies will be very important to provide a proof of concept in this sense.

There is also a need for more studies to define the adequate dose regimen of DCV before considering moving to phase III. More in vitro and in vivo data should be performed for supporting dose selection.

Antiviral combination trials (Brazil, South Africa) should be include a factorial design to allow understanding which drug is driving the response and whether there is synergism or interference.

Virological end points like viral loads in studies in mild or early disease could be valuable for proof-of-concept.

PROPOSED NEXT STEPS
Organize a new call when more in vitro and ideally animal model data are generated, as well as more clinical information from the already planned clinical trials (Brazil and South Africa)

Note that above prioritization decisions are preliminary and may change as further information is provided to WHO.
# ANNEX – Sofosbuvir-Daclatasvir

Prioritisation Therapeutics

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Sofosbuvir/daclatasvir</th>
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<tr>
<td><strong>Basic criteria</strong></td>
<td><strong>Sofosbuvir/daclatasvir</strong></td>
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</table>
| Preclinical efficacy data in non-human primates (NHP) | Pre-clinical efficacy in NHP under well-controlled and documented conditions  
  - Evidence of efficacy should include improved survival of COVID-19 inoculated rhesus macaques (or other NHPs) following treatment with the drug versus controls.  
  There is no data from animal studies evaluating sofosbuvir/daclatasvir against COVID-19 infection                                                                                                                                 |
| Safety profile from non-clinical studies       | In the absence of human data, safety results from animal studies, as well as relevant in vitro data should be assessed with respect to safety in humans.  
  There are published in silico studies suggesting docking affinity for sofosbuvir and daclatasvir to structural proteins of SARS-CoV-2. In vitro evaluation of both drugs is in progress. There is a high variability of results from in vitro studies of sofosbuvir against a range of viral infections. The results seem to depend on the cell type used in the assays. |
| Quality of manufacturing (cGMP)                | It is expected that the product will be manufactured in compliance with GMP (Good Manufacturing Practice).  
  - Information on the active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) preparation, FPP composition, controls (specifications), known and potential impurities, as well as stability data supporting a reasonable shelf-life should be provided.  
  Sofosbuvir/daclatasvir is manufactured to GMP standards by several large generic companies. These companies already have been granted WHO pre-qualification to supply sofosbuvir/daclatasvir to treat Hepatitis C |
COVID-19: Therapeutics Working Group Informal consultation on the potential inclusion of Sofosbuvir/Daclatasvir in a clinical trial

<table>
<thead>
<tr>
<th>Prioritization criteria</th>
<th>Scientific rationale for use in COVID-19 patients</th>
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<tbody>
<tr>
<td></td>
<td>Brief description of the biological mechanism targeted by the drug. In case of a drug that is approved, or has a large clinical trial experience base, for another indication: explanation of why this is an indicator of success for COVID-19 (e.g. in the case of targeting pulmonary pathologies)</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir and daclatasvir are antiviral drugs, which are approved for treatment of Hepatitis C infection.</td>
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<td>Sofosbuvir is a polymerase inhibitor. Sofosbuvir inhibits the hepatitis C NS5B protein. Sofosbuvir appears to have a high barrier to the development of resistance. Sofosbuvir is a prodrug of the Protide type, whereby the active phosphorylated nucleotide is granted cell permeability and oral bioavailability.</td>
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<td>Daclatasvir is an inhibitor of NS5A, a nonstructural protein encoded by HCV. Daclatasvir binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly.</td>
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<tr>
<td>Safety in humans single/repeat dose escalation</td>
<td>Evidence of acceptable risk-benefit profile, i.e. acceptable incidence of SAE, SUSARs or severe AEs with sequelae observed as documented by the DSMB.</td>
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<td>- Phase 1 clinical data should available for the drug at the exposure level proposed for treatment of COVID-19</td>
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<td></td>
<td>- If evidence on dose escalation is available that would be an advantage.</td>
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<tr>
<td></td>
<td>There are no data from Phase 1 trials of sofosbuvir/daclatasvir to treat COVID-19. The decision was to progress directly to Phase 2 trials</td>
</tr>
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</table>
| Time-efficacy window after challenge in animal models | Pre-clinical efficacy in NHP under well-controlled and documented conditions.  
- Evidence of efficacy should include improved survival of COVID-19 virus inoculated rhesus macaques (or other NHPs) following treatment with the drug versus controls. Surrogate markers, validated or reasonably expected to predict efficacy, e.g. viral load decreases, would be supportive. | There are no results available from treatment in animal models |
|---|---|---|
| Dosing rationale | A rationale should be provided for the proposed dosing in humans, with reference to drug exposures shown to be effective in suitable animal models.  
- Ideally, human pharmacokinetic data would be available, demonstrating similar levels of the drug following administration at the proposed dose, compared to blood levels seen in NHPs successfully treated with the drug. | For the clinical trials conducted so far, sofosbuvir/daclatasvir has been dosed at the standard level of 400/60mg once daily |
| Route of administration and administration challenges | What is the route of administration.  
- Over how long must the drug be administered, and  
- How many administrations are required to complete one treatment course? | Sofosbuvir/daclatasvir is given as an oral tablet, with a dose of 400/60 mg once daily |
|------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Efficacy data in humans against COVID-19 | Where clinical efficacy data from randomized controlled trials (RCTs) are available, this is clearly preferable to efficacy in animals.  
- Administration through MEURI does not generate useful information to support clinical efficacy determination due to the very high risk of bias and confounding factors.  
Surrogate markers, validated or reasonably expected to predict efficacy, e.g. viral load decreases, would be supportive.  
Information on combination with other agents, documented or potential drug and/or vaccine interactions would be desirable. | Three clinical trials have been conducted to assess sofosbuvir/daclatasvir versus control, in a total of 176 hospitalised patients.  
In a meta-analysis of these three clinical trials, death rates were 5/92 (5%) on sofosbuvir/daclatasvir versus 17/84 (20%) on control treatment (p=0.005). In the same meta-analysis, the time to discharge from hospital was significantly shorter in the sofosbuvir/daclatasvir arms, compared with the control arms (p<0.001).  
In the meta-analysis, the benefits of sofosbuvir/daclatasvir versus control treatment were fairly consistent across the three trials. One of these trials was not properly randomized and the overall sample size is limited. These results need to be confirmed in larger trials to justify regulatory approval of sofosbuvir/daclatasvir to treat COVID-19 infection. |
| Access in event of success (mandatory) | Evidence that at least 200 treatment courses compliant with GMP will be available and labeled by the trial initiation date ( | We have checked the import-export database [www.panjiva.com](http://www.panjiva.com). In the last 12 months, there was enough sofosbuvir/daclatasvir manufactured to treat 3 million people with COVID-19 infection for 14 days. |
Evidence that sufficient numbers of GMP treatment courses doses (>200) will be available for early implementation for confirmed cases (by May 2020)

Evidence that production plans are in place to meet the treatments supply demand (thousands of doses) in large-scale implementation in at-risk countries in Africa starting in October 2020.

Evidence of willingness to ensure that therapeutics will be manufactured and made available to WHO and the public health sector of the COVID-19-affected countries in sufficient amount and at an affordable price.

<table>
<thead>
<tr>
<th>Additional prioritization criteria</th>
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<tbody>
<tr>
<td><strong>Staff training</strong></td>
<td>Information on the specific training that medical staff would need to have received in order to safely and reproducibly administer the agent.</td>
</tr>
<tr>
<td><strong>Administration and monitoring equipment</strong></td>
<td>Is specific equipment that would not normally be present at COVID-19 ICUs needed to administer the agent?</td>
</tr>
<tr>
<td></td>
<td>Is specific equipment that would not normally be present at ICUs needed to monitor the agent including laboratory equipment for e.g. hematology, biochemistry (e.g. liver, renal function).</td>
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<tr>
<td><strong>Storage &amp; shelf-life</strong></td>
<td>Temperature, stability at given temperature</td>
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</table>
Origin of data: Data and evidence necessary to score the attributes will be collected from published data and information provided by the respective manufacturers.

Weighting/scoring: Scoring: Score 0 to 3 per attribute (0 = no data available; 1= does not meet minimally acceptable profile; 2=meets minimally acceptable profile; 3 likely to exceed minimally acceptable profile). Descriptive attributes are not weighted.

Output: The process based on this framework will result in a report describing the outcome of the assessment of available COVID-19 investigational therapeutics for use by the committee to make the formal decision on recommendations for inclusion in clinical trials at a given point in time. Such decisions are to be revisited upon emergence of significant new information.