INTERIM CLINICAL GUIDANCE FOR ADULTS WITH SUSPECTED OR CONFIRMED COVID-19 IN BELGIUM

1 December 2020; Version 15
Addition 2 December

Preliminary note

This document has been revised on the 1 December 2020 to provide support to the diverse groups of Belgian clinicians (general practitioners, emergency physicians, infectious disease specialists, pneumologists, intensive care physicians) who have to face suspected/confirmed COVID19 cases, during the epidemic in Belgium.

The guidance has been first developed by a task force: Dr Sabrina Van Ierssel, Universitair Ziekenhuis Antwerpen, UZA (Sabrina.VanIerssel@uza.be); Dr Nicolas Dauby, Hôpital Universitaire Saint-Pierre Bruxelles, HSP (Nicolas_Dauby@stpierre-bru.be); Dr Emmanuel Bottieau, Instituut voor Tropische Geneeskunde, ITG (ebottieau@itg.be), and Dr Ralph Huits, ITG (rhuits@itg.be). It was initially based on the therapeutic protocols elaborated in the two reference institutions (UZA and HSP). It has been revised in fast track by a larger group of physicians and scientists from different specialties/disciplines including experts from ScienSano (Dr Chloe Wyndham-Thomas; Chloe.WyndhamThomas@sciensano.be) and from AFMPS/FAGG (Dr Roel Van Loock; Roel.VanLoock@fagg-afmps.be). From January 2021 onwards the COVID-19 therapeutic guideline will be officially taken over by the Belgian Society of Infectiology and Clinical Microbiology (BVIKM/SBIMC), with the further contribution of the current task force, and with the additional collaboration of the Belgian societies of Intensive Care Medicine and of Pneumology.

This guidance is based on the best (but still incomplete) clinical evidence that is currently available, and is purposed to become a “living guideline” which will be regularly updated each time new relevant scientific data will emerge (latest version will always be found via the same link).

Keeping the guidance regularly updated is however particularly challenging due to the incredible speed of knowledge generated for this disease. Readers are warmly invited to send any additional comment, relevant publication, including from the grey literature, and contribution in priority to the small core group (ideally to all six provided mails). We thank the countless readers who, since this guideline was initially released, flagged the inconsistencies, typo’s or unclarities, as well as those who sent all types of contribution with regards to this rapidly evolving field.

COVID-19 is a mild viral illness in the vast majority of the patients (80%) but may cause severe pneumonitis and disseminated endotheliitis [1] (and subsequent complications) with substantial fatality rates in elderly and individuals with underlying diseases. About 20% of infected patients need to be admitted, including 5% who require intensive care.

Of note, this document will not describe in detail the generic and supportive management of COVID-19 (except if there are some pathogen-specific interventions). It is also not aimed at providing an extensive review on all potential investigational treatments in the pipeline.
We have opted for a document with the following structure:

1. **Executive Summary**, with the current therapeutic recommendations for each category of COVID-19 patients, with indications and precautions (Table 1);
2. **The Belgian recommendations for supportive care and adjunctive antiviral/immunomodulatory treatment for suspected/confirmed COVID-19 cases**, detailing latest evidence and rationale behind this consensus;
3. **A summary of the efficacy data of selected antiviral drugs**, with information on in vitro/in vivo efficacy (Table 2);
4. **An overview of the clinical trials ongoing in Belgium** (Table 3).
5. **Annexes**, covering compassionate use and import procedures, and detailed safety profiles
6. **References**

**IMPORTANT:**
As a rule, only manuscripts ACCEPTED after a rigorous PEER-REVIEW process will be referred to for the strong recommendations in this guideline. Important (pre-publication) communications by well-established research groups will be however mentioned if the findings may strongly impact the clinical care within a rather short timeframe.

Use of off label or investigational antiviral or immunomodulatory drugs should be reserved to clinical studies/trials only and efforts are undertaken by the KCE to support non-commercial multicentric studies in Belgium. In addition, use of standardized case report forms is strongly encouraged during patient management, in order to obtain a fast feedback on safety issues and patient outcomes.

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### 1. Executive summary

**Table 1**: Supportive care & antiviral/immunomodulatory treatment of hospitalized adults patients with suspected or confirmed COVID-19

<table>
<thead>
<tr>
<th>Clinical category</th>
<th>Supportive Care</th>
<th>Additional therapy</th>
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<tbody>
<tr>
<td>Suspicion of COVID-19</td>
<td></td>
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<tr>
<td>➢ Mild-to-moderate symptoms (no dyspnea)</td>
<td>Symptomatic</td>
<td>No</td>
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<tr>
<td>➢ No risk group ex. Hospitalization for social-related reasons</td>
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| Suspicion or confirmed COVID-19          | Symptomatic     | Insufficient data to recommend for or against this drug in routine in mild to moderate disease. Use only in clinical trials. |
| ➢ Mild-to-moderate symptoms (no dyspnea) | treatment       |                    |
| ➢ Risk group¹                           |                 |                    |

¹ Risk groups: age > 65 years AND/OR underlying end organ dysfunction (lung, heart, liver,…), diabetes, coronaropathy, chronic obstructive pulmonary disease, arterial hypertension
### Clinical category | Supportive Care | Additional therapy
--- | --- | ---
**Confirmed COVID-19 Severe disease** | Optimal supportive care in hospital WARD (or ICU) | **Dexamethasone** 6 mg once a day for up to 10 days (or until hospital discharge if sooner), IV or PO, for which more evidence is available in those with symptom duration > 7 days; case by case decision for children and pregnant women pending additional results and with the respective specialists. If dexamethasone is not available, equivalent doses of corticosteroids can be used (hydrocortisone 150 mg/d or methylprednisolone 32 mg/d or prednisone 40 mg/d)
- Respiratory rate ≥30/min (adults); ≥40/min (children < 5)
- Blood oxygen saturation ≤93%
- PaO2/FiO2 ratio <300
- Lung infiltrates >50% of the lung field within 24-48 hours

**Confirmed COVID-19 Critical disease** | Optimal supportive care in ICU | **Dexamethasone** 6 mg IV (or equivalent doses of corticosteroids, see row above) once a day for up to 10 days; case by case decision for children and pregnant women pending additional results and with the respective specialists.
- Acute Respiratory Distress Syndrome
- Sepsis
- Altered consciousness
- Multi-organ failure

Additional therapy:

- Mechanical ventilation
- Specific prevention & treatment of ARDS
- Track secondary bacterial and opportunistic (*Aspergillus*) infections
- Prevention of subsequent lung fibrosis

Combination of **dexamethasone** and **remdesivir** has not been studied in clinical trials, but can be considered, based on an individual risk/benefit analysis**, in rapidly progressing COVID-19. **Remdesivir** preferentially for patients <5 days of symptom onset
- 200 mg loading dose (IV, within 30 min)
- 100 mg once daily for day 2 to day 10*

**Note that recent data suggests potential kidney toxicity, to take into account in the individual decision. As with all adverse events, occurrence of renal toxicity with Remdesivir should be reported to AFMPS/FAGG.**

* A minimal 5-day treatment course should be given, with a possibility of a one-off extension of 5d if unsatisfactory clinical response. Given the limited availability of remdesivir the treatment should not be given longer than necessary (cfr annex 1 for details on remdesivir availability)

**NB: tocilizumab and other interleukins (6 or 1) blockers:** Clinical experience and small observational studies suggest a favorable effect in
the most critical patients suffering from persistent and overwhelming inflammation resembling cytokine release syndrome (CRS). Recent evidence provides however conflicting results. At this moment, this class of drugs should only be used in clinical trials. Ongoing studies with dexamethasone, tocilizumab, anakinra, otilimab, siltuximab etc...are ongoing in Belgium.

Precautions of use & additional information

**General**: Use paracetamol in first-line (usual dosage), and NSAIDs with caution (if really required)

**Dexamethasone**: Usual contraindications

**Remdesivir** (Veklury®): *at this moment very restricted availability of remdesivir in Belgium.*

- **Contraindications**:  
  - Hypersensitivity to active substance(s) or any of excipients

- **Warnings/precautions**:  
  - **Hepatic impairment**: Remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk. Remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal at baseline
  - **Renal impairment**: Remdesivir should not be used in patients with eGFR <30 mL/min

- **Interactions**:  
  - Strong inducers of CYP2C8, CYP2D6 and CYP3A4 (e.g. rifampicin) may decrease plasma concentrations and are not recommended.
  - Co-administration of remdesivir with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy
  - Still limited information on drug interaction is available. Risk-benefit assessment should be made individually. Close monitoring of remdesivir toxicity or diminished efficacy of concomitant drug is recommended. Check also for interaction with remdesivir at [http://www.covid19-druginteractions.org](http://www.covid19-druginteractions.org) (Liverpool).

- **More information on warnings/precautions of use in Veklury product information** (Annex 2)

- **Registered for treatment of COVID-19 in adults and adolescents from 12 years of age (with at least a body weight of 40kg). For pregnant women & children**: compassionate use is possible, request on [https://rdvcu.gilead.com/](https://rdvcu.gilead.com/)

2. Belgian recommendations for supportive care and adjunctive antiviral/immunomodulatory treatment for suspected/confirmed COVID-19 cases.

As summarized in the executive summary table, we recommend that **dexamethasone** [or if not available equivalent doses of corticosteroids] be considered as a standard of care in severe and critical COVID-19 disease. In patients requiring supplemental oxygen, **remdesivir** may be considered but with a number of key precautions to follow. Background data and rationale behind these recommendations are detailed here. Latest results concerning additional antiviral and immunomodulatory treatments are also covered: **chloroquine and**
hydroxychloroquine, lopinavir/ritonavir, favipiravir, camostat mesylate, azithromycin, interferons, immunomodulatory agents, convalescent plasma and monoclonal antibodies. These treatments are currently only to be prescribed in the context of clinical trials.

Additional notes are also given on ACE inhibitors/AREBs, pregnant women, children, anticoagulation, oxygen therapy and ambulatory care.

**Corticosteroids**: In accordance with WHO interim guidance [2] and a Correspondence in the Lancet [3], corticosteroids have been up to now not recommended as a systemic adjunctive treatment. Low dose dexamethasone (6 mg/day once daily for 10 days) is a treatment option which has been however investigated in one of the UK-RECOVERY study arms. In a publication reporting on preliminary results, dexamethasone significantly reduced the overall 28-day mortality rate (age-adjusted rate ratio, 0.83 [95% CI 0.75 to 0.93]; P=0.001) [4]. In a pre-specified subgroup analysis according to the level of respiratory support that the patients were receiving at randomization, there was a trend showing the greatest absolute and proportional benefit among patients who were receiving invasive mechanical ventilation (11.5 by chi-square test for trend). Compared with standard of care, dexamethasone reduced incidence of death in ventilated patients (29.3% vs. 41.4%, rate ratio 0.64 [95% confidence interval 0.51 to 0.81]) and in other patients receiving oxygen only (23.3% vs. 26.2%, 0.80 [0.70 to 0.92]). No evidence of benefit for patients who did not require oxygen was found, and patients outside the hospital setting were not included in the study. In a sub-group analysis, dexamethasone was associated with a reduction in 28-day mortality among those with symptoms for more than 7 days but not among those with more recent symptom onset (12.3 by chi-square test for trend). Based on this survival benefit in the sickest patients, the manageable toxicity of low-dose/short course dexamethasone in hospitals and the strong biological plausibility of an anti-inflammatory treatment in the second phase of COVID-19 (the majority of admitted patients), the task force has recommended in the version v12 low-dose dexamethasone for admitted patients requiring oxygen, in particular requiring mechanical ventilation and with a symptom onset > 7 days. Following the publication of the RECOVERY results, three other large RCTs evaluating various doses and types of steroids in critical COVID-19 stopped prematurely patient inclusion before reaching the respective target sample sizes, i.e. REMAP-CAP (multicountry) [5], CoDEX (Brazil) [6], and CAPE COVID (France) [7]. The results of RECOVERY, of the last 3 published (“incomplete”) RCTs and of another three ongoing smaller trials were then pooled and meta-analyzed by the WHO REACT working group [8]. The conclusion was robust throughout all trials (n=678 in total versus 1025 in placebo/usual care arm, all critically ill patients): administration systemic corticosteroids in critically ill patients with COVID-19 is associated with decreased 28-day mortality (0.66 [95% CI 0.53-0.82]; p<0.001). This association was similar for dexamethasone and hydrocortisone, for higher versus lower doses of steroids, and in admitted patients with fewer or greater than 7 days of symptoms, requiring oxygen either through mechanical ventilation or not. While exact details concerning the implementation in clinical practice is lacking, the consistent findings of benefit provide definitive data that corticosteroids should be first-line treatment for critically ill patients with COVID-19 [9]. In case dexamethasone is not available, WHO recommends using equivalent doses of other corticosteroids (see Table 1; executive summary) [8].

Nb. Effect of lose-dose and short-course DXM on risk of Strongyloides reactivation is not well known. Nevertheless, for high risk patients, such as originating from Strongyloides endemic area, empirical ivermectin treatment should be considered before, or early during, DXM administration treatment [10].

**Remdesivir** (RDV) seemed promising in vitro and in non-human primates models [11]. An initial Chinese trial did not show any survival benefit with remdesivir, but the study could not include enough cases and was discontinued at the end of the local epidemic [12]. In this study (where median delay from symptom onset to enrolment was quite long, 11 days in the RDV group), there was no effect of RDV on viral load over time in both upper and lower respiratory tract suggesting the absence of antiviral effect.
Meanwhile, a final report of the ongoing NIAID-ACTT NCT04280705 trial conducted in the US has been published [13] confirming a faster recovery in remdesivir-treated hospitalized COVID-19 patients with evidence of pneumonia (n=541) compared to patients given placebo (10 days instead of 15 days; recovery rate ratio 1.29; [95% CI 1.12 to 1.49], p<0.001). The benefit was most apparent in those COVID-19 patients receiving low-flow oxygen, the largest group of patients included in the study, and when remdesivir was given before the 10th day of symptom onset. Results were not conclusive for other groups of patients (those not requiring supplemental oxygen, or in patients requiring mechanical ventilation). No statistical difference was seen for mortality by Day 15 (6.7% mortality versus 11.9%) and by Day 29 (11.4 versus 15.2%), but there was a positive trend compared to placebo (hazard ratio: 0.73 95% CI 0.52 to 1.03).

In addition, a randomized, open-label, phase 3 trial, comparing 5-day and 10-day treatment with remdesivir in patients with severe/critical disease (O2 requirement), did not find a significant difference in efficacy between these two treatment durations. After adjustment for baseline imbalances in disease severity (patients assigned to 10 day course had significantly worse clinical status than those in the 5-day group), outcomes were similar as measured by a number of end points: clinical status at day 14, time to clinical improvement, recovery, and death from any cause. Post-hoc analysis showed that patients receiving mechanical ventilation or ECMO may benefit from 10 days of remdesivir treatment. Further evaluation of this subgroup and of other high-risk groups, such as immunocompromised persons, is needed to determine the shortest effective duration of therapy in these patients [14].

A third RCT sponsored by Gilead (Spinner et al.) assessed the role of RDV in hospitalized patients with non-severe COVID-19 (not requiring oxygen supplementation) [15]. The patients (n=584) were randomized 1:1:1 to 10-day course of RDV, 5-day course of RDV and standard of care. Mortality was low (1%). The study found a benefit for a better clinical status with the 5-day course but not the 10-day course. The clinical significance of this finding remains uncertain as the patients in the 5-day and 10-day courses received almost the same number of doses (5 and 6, respectively).

It is important to highlight that in both the ACTT-1 and Spinner trials, no impact of RDV on viral shedding was reported. In both trials, the median duration of symptoms before enrollment was 9 days, limiting the potential of a significant antiviral effect as it was also observed in the Wang et al trial [12]. In a study performed in the rhesus macaque, initiation of RDV very early after infection (12 hours) obtained better clinical outcome and reduced lung viral replication [11]. This suggests that the impact of RDV would only be expected very early on in the infection.

On 3 July 2020, following EMA evaluation, the European Commission granted a conditional marketing authorization for remdesivir, for the treatment of COVID-19 in adults and adolescents from 12 years of age (with at least a body weight of 40kg) with pneumonia who require supplemental oxygen (dosage and precautions see Table 2).

The effect of remdesivir may appear as clinically modest but a reduction of hospital stay could be very useful when resources are overstretched. All in all however, the precise indication remains uncertain because the optimal patient population, the optimal treatment duration and the actual impact on outcome are still unclear [16].

At the time of writing the current version, the WHO has communicated the results concerning the SOLIDARITY multicenter worldwide pragmatic trial that did not demonstrate any clinical benefit of remdesivir use in hospitalized patients with COVID-19 (link). Peer-review publication is not available at this moment. In addition, EMA is currently evaluating full mortality and viral data from NIAID ACTT-1 data and the data from SOLIDARITY trial. This guidance, that already considers remdesivir as having a modest effect and small window of use, will be further updated when this additional information become available.
In addition, as dexamethasone is now considered the standard of care for the hospitalized patients requiring oxygen or on mechanical ventilation, it is important to highlight that there is no data about the impact of combining dexamethasone and remdesivir on outcome.

- **Chloroquine and hydroxychloroquine** inhibits replication of SARS-CoV-2 *in vitro*. Chloroquine (CQ) inhibits the virus at concentrations (EC50 = 1.13 to 5.47 µM) that cannot be achieved in human plasma [17], but possibly in the intracellular compartment. This drug (not available in Belgium since 2015) has been used for decades (at a total of 25 mg/kg within 3 days) for malaria treatment without any monitoring and side effects, including in pregnant women. However, the therapeutic window is quite narrow (cardiotoxicity/arrhythmia), requiring caution for use at higher cumulative dosages in patients with comorbidities and co-medication.

Hydroxychloroquine (HCQ, drug marketed in Belgium as Plaquenil®) has appeared to be more potent than chloroquine *in vitro* (EC50=0.72 µM), so that lower dosages (than initially recommended) could be used [18]. It has also a better safety profile than chloroquine (larger therapeutic window).

Several small retrospective studies could not demonstrate any independent benefit of hydroxychloroquine use compared to non-exposed hospitalized patients [19–23]. Some larger retrospective studies did find an independent association between HCQ use (low dosage, similar to the “Belgian” recommendations) and a reduction in COVID-19 associated in-hospital mortality [24–27]. No particular safety signals were observed with the use of HCQ (alone) in these large cohorts. However, the major limitation of all these studies was the retrospective observational design that precluded any definitive conclusion about treatment efficacy. The prospective randomized controlled trial (RCT) RECOVERY in UK has stopped enrolling patients on the 5th of June after finding no beneficial effect of high dose hydroxychloroquine (9600 mg in total over 10 days) in patients hospitalized with COVID-19. For the same reason (absence of efficacy in hospitalized patients), the SOLIDARITY trial has communicated the suspension of recruitment in the HCQ arm (9600 mg over 10 days) on 18th of June (link). Similarly, the DisCoVeRy trial stopped enrolling participants in the HCQ arm (5600 mg in total over 10 days) at the same period. The results of the large RECOVERY trial on HCQ efficacy in hospitalized COVID-19 patients have demonstrated that mortality at Day 28 was similar in HCQ recipients compared to standard of care (421/1561, 27% versus 790/3155, 25%; p=0.15). No benefit was observed for all secondary outcomes and subgroups of patients [28]. Another smaller RCT in Brazil conducted in mild-to-moderate hospitalized patients did not find any improvement of the clinical status (seven-level ordinal scale) in participants having received HCQ (total dosage: 5600 mg), alone or with azithromycin (500 mg/day for 7 days) [29].

Regarding other potential indications, an RCT using HCQ (low-dose) as post-exposure prophylaxis (PEP), showed no prevention of “illness compatible with COVID 19” [40]. This trial had however several limitations such as undocumented treatment adherence and no laboratory confirmation of SARS-CoV-2 infection in 85% of the participants. No serious adverse events were notified. Another RCT by the same group studied early administration of HCQ in mild/ambulatory patients with laboratory-confirmed or symptomatic contacts (n=423), and no substantial symptom reduction was observed in the HCQ arm compared to masked placebo [30]. Here again, many participants (about 40%) were not tested. In a well-designed Spanish RCT evaluating early treatment with HCQ in adults with mild disease (n=293), no clinical (shortening of symptoms) nor viral (reduction of shedding) benefits were observed [31]. A **cluster-randomized trial by the same Spanish group did not show any reduction in the incidence of SARS-CoV-2 infection nor symptomatic COVID-19 when HCQ was used in post-exposure prophylaxis in healthy persons exposed to a PCR-positive case patient** [32]. Some trials using HCQ are still ongoing, including ANTICOV in Africa.
Meanwhile, several preclinical studies have not demonstrated any antiviral effect of HCQ in animal models (hamsters, macaques, including one study from the KUL [33–36]. Overall, based on these preclinical observations and the reported trial results it has been decided since beginning of June (version 10) not to recommend its off-label use for COVID-19 in Belgium anymore, except within ongoing clinical registered trials, and after timely interim analysis of the study-related risk/benefit.

- **Lopinavir/ritonavir** (LPV/r 400 mg/100 mg BID), initiated more than 12 days post symptom onset (median, IQR [11–17 days]) did not show clinical benefits in hospitalized patients with COVID-19. Moreover, there was no impact on viral excretion. This is in line with in *vitro* experiments with SARS-CoV2 but also SARS-CoV1 (cfr. Table 2). In this trial however, a possible benefit (clinical improvement) was suggested in patients who were treated before 12 days of symptom onset, HR 1.25 (0.77-2.05). Another small RCT conducted in China did not show any viral or clinical benefit however (or at best very marginal) [37]. On the 4th of July 2020, the WHO announced that the Lopinavir/ritonavir arm was discontinued in the SOLIDARITY trial because of lack of benefit ([link](#)). This arm was also stopped in RECOVERY (press release) and DisCoVeRy for the same reason. Finally, a benefit risk-assessment performed by the BRAT (Benefit-Risk Action Team) network and published on the 23 June 2020, concluded that the benefit-risk profile for lopinavir-ritonavir in severe COVID-19 cannot be considered positive until further efficacy and effectiveness data become available [38]. The results of the large RECOVERY trial in hospitalized patients with COVID-19 confirmed that lopinavir/ritonavir had no beneficial effect on mortality at Day 28 (374/1616, 23% versus 767/3424, 22%, p=0.60) nor on any secondary endpoint (duration of hospital stay, progression of disease) [39]. In light of all these recent data, we no longer suggest off-label LPV/r as an alternative in severe COVID-19 disease. Its use should be limited within ongoing clinical registered trials, after reassessment of risk/benefit.

- **Favipiravir** has a half-cytotoxic concentration (CC50) > 400 µM and the EC50 of favipiravir against SARS-CoV-2 in Vero E6 cells was 61.88 µM/L (much higher than the EC50 of favipiravir for influenza), resulting in a selectivity index (SI) > 6.46 [40]. The half-life is approximately 5 hours. Therefore, higher dosing ranges are considered for the treatment of COVID-19 than for influenza (loading dose of 2400mg to 3000mg BID followed by a maintenance dose 1200mg to1800mg BID) [41]. In another non-randomized study, favipiravir showed shorter viral clearance time (4 days (IQR 2.5 - 9) vs. 11 days (8–13), p < 0.001), significant improvement in chest imaging (91.43% versus 62.22% (p = 0.004)) and fewer adverse reactions compared with lopinavir /ritonavir [42]. Favipiravir has not been selected for these recommendations, as this molecule is not available in Belgium outside clinical trials. An antiviral effect has been observed in animal models (hamsters) at high dosage [35]. **An interim analysis of a small phase 2 trial showed a lower rate of PCR positivity at day 5 post-favipiravir initiation but no difference at day 10** [43]. Larger trials are ongoing.

- **Camostat mesylate** is a serine protease inhibitor used in Japan, which is being evaluated as repurposed drug after it has been shown to reduce SARS-CoV-2 infection of primary human lung cells (Calu-3 cell line) in *vitro* [44]. Camostat mesylate is under investigation in monotherapy or in combination with either hydroxychloroquine or azithromycin (eg. NCT04355052 (Israel), NCT04321096 (Denmark)). The drug is not available in Belgium. **A phase 2 trial looking for antiviral activity has been initiated in UZ Gent (Table 3).**

- **Azithromycin (AZM)** : this antibiotic shown to have some antiviral and immunomodulatory effect has been promoted by some groups based on observational viral and clinical data [45]. The potential benefit of using AZM alone or with other drugs has not been demonstrated so far. Two large RCTs have explored in Brazil the usefulness of this drug in association with HCQ, both in mild/moderate [29] and severe hospitalized patients [10], and did not find any added-value compared to HCQ alone. **This drug is still being evaluated in RECOVERY and DAWN-AZITHRO (Table3).**

- **Interferons (IFN)** have antiviral effects and modulate the immune response [46]. There are a limited number of case series, case-control trials and three small RCT’s published so far. Hung *et al* compared
combination therapy including Interferon IFN ß-1b, ribavirin and lopinavir-ritonavir (n=86) vs lopinavir-ritonavir alone (n=41) in an open label RCT [47]. Only 52 patients starting therapy <7d of symptom onset received at least one dose of interferon, as by study protocol. They found a shortened viral shedding and faster clinical improvement in the IFN-containing arm. Another RCT evaluated IFN ß-1b with or without standard of care including hydroxychloroquine plus lopinavir/ritonavir or atazanavir/ritonavir (both groups n=33). They found a faster clinical improvement, in primary outcome; and a decreased ICU admission, although the study was probably underpowered for this [48]. The same group also evaluated IFN ß-1a in addition to the same standard of care (n=42) vs standard of care alone (n=39), and could not find any difference in clinical response [49]. Decreased mortality was found in the IFN group. This study has several limitations: >30% of patients had no laboratory-confirmed infection, a very high mortality was observed in the control group and a large drop-out was seen in each study group. Furthermore IFN therapy was associated with more adverse events. Pre-print results from the WHO-SOLIDARITY trial show that Interferon IFN ß-1a given with lopinavir/ritonavir did not provide any survival benefit vs lopinavir/ritonavir alone (12.7% vs 12.5% mortality, respectively) in hospitalized patients, and this study arm has been interrupted [50]. A few studies have looked at IFN administration by spray or atomization, to improve local effects and avoid systemic adverse reactions [51,52]. Questions remain on optimal dosing, administration, etc. and no RCT is available for this type of administration. Further studies are needed to clarify the role of Interferons in the treatment of COVID-19.

- **Immunomodulatory agents** are a varied group of drugs that may prevent or dampen hyper-inflammatory responses which are associated with clinical deterioration and mortality [53,54]. Several interleukin blockers used in inflammatory diseases such as giant cell vasculitis or rheumatoid arthritis have been proposed for repurposing based on limited clinical experience and small observational studies. These drugs include tocilizumab [55,56] and anakinra. Three randomized trials assessing the use of tocilizumab (TCZ) in hospitalized COVID-19 patients have been recently published [57–59]. These trials were highly heterogeneous regarding the severity of the patients included. None of these three studies demonstrated a survival benefit. The RECOVERY trial is still including patients in the TCZ arm and should provide substantial information regarding benefit in predefined subgroups of patients. The REMAP-CAP trial platform has announced through press release a benefit of TCZ administration in term of clinical improvement and/or mortality (combined outcome measure). These results have not been peer-reviewed and must be considered preliminary (link).

These drugs are intensively investigated including in Belgium (see Table 3). Notably, the COV-AID trial is still recruiting. Inclusion is based on a combination of biological factors (to better select suitable candidates), in contrast with other trials. Recently, clinical trials using Anakinra have been suspended in France. Of note, the French trials used higher dosages as compared to the one used in Belgium and the DSMB of the COV-AID trial has considered that Anakinra could be further evaluated in Belgium. There is no RCT evidence yet for recommending their use outside studies. Potential adverse events and drug interactions have to be carefully taken into consideration.

- **Convalescent plasma**: Animal studies with SARS-CoV-1 and SARS-CoV-2 infections indicate a protective role of neutralizing antibodies. Several observational studies, non-controlled and controlled non-randomized trials, and two RCT’s have been published [60]. Observational studies show survival benefit of transfusing convalescent plasma (CP) with high antibody titers [61]. In contrast, the prematurely terminated randomized controlled trial in severely ill COVID-19 patients in Wuhan didn’t show faster clinical improvement nor decreased mortality in patients receiving convalescent plasma. This study was however underpowered, furthermore the plasma was administrated late in the course of the disease (median time from symptom onset to randomization: 30 days)[62].
Recently an Indian multicenter open label RCT in severe non critically ill COVID-19 patients (P/F 200-300mmHg or RR>24 + SatO2 ≤ 93% with FiO2 21%) did not show any reduction in disease progression and all-cause mortality at D28 (19% vs 18%). However, an antiviral effect was demonstrated as well as a faster resolution of dyspnea. In this study post-hoc analysis showed low levels of neutralizing antibodies in the administered plasma and detected neutralizing antibodies in 79% of patients at baseline [63]. This concurs with the Dutch RCT that was stopped early due to the finding of comparable amounts of neutralizing antibodies in patients as in their convalescent plasma, as early as median 10 days after symptom onset, (preprint/non peer-reviewed data) [64]. A large placebo-controlled randomized trial from Argentina did not find an impact on mortality of administration of CP containing high titers of neutralizing antibodies. However, 29% of the patients in the plasma arm were critically ill [65]. We only recommend the administration of convalescent plasma within clinical trials in Belgium such as the multicentric study DAWN-plasma and CONFIDENT that are currently ongoing. Both Rode Kruis and Croix Rouge are collecting plasma from patients who have experienced COVID-19. Whenever possible, patients should be informed at discharge on the possibility to donate plasma and to contact their local RKV/CR center. AFMPS/FAGG has recommended that donation should only take place more than 28 days after symptoms have ended. Of note, administration of CP could be considered in case of persistent viral shedding (>1 month) in severe COVID-19 patients with B cell-related immunosuppression (including patients on Rituximab and other B-cell depleting agents) unable to mount an antibody response, as shown in a French case series by Heuson et al [66] and in a case series of 5 Belgian patients by Betrains et al (article accepted for publication in British Journal of Haematology). A MEURI (Monitored Emergency use of unRegistered investigational Interventions) protocol, similar to the Urgent Medical Need program of the FAGG/AFMPS/AFMHP was established by RKV/CR to obtain CCP for these very restricted situations where inclusion in the current clinical trials (CONFIDENT and DAWN-plasma) is not possible. CCP is a standard fresh frozen plasma from convalescent voluntary donors with SARS-CoV-2 neutralising antibodies and conforms to all legal criteria. Criteria for this MEURI delivery, including the requirement for registration of clinical data, are defined and available via your hospital’s bloodbank laboratory or RKV/CR.

- **Monoclonal antibodies**: Dozens of monoclonal antibodies targeting the S protein domains (RBD) have been developed [67]. Some have entered phase II trials this summer. Given the long half-life, a single infusion is generally used and could prevent disease progression [68]. Animal studies with the SARS-CoV-2 model are encouraging [69]. A preliminary evaluation of a phase II RCT still in progress with bamlanivumab (LY-CoV555) in mild and moderate COVID-19 showed promising results on viral decline, symptom resolution and hospitalization. Further evaluation in clinical trials will be necessary to evaluate these antibodies [70].

- **Ivermectin**: *In vitro* inhibition of SARS-CoV-2 replication in Vero/hSLAM cells [28] has been reported with ivermectin (IVM), but at concentrations 50- to 100 times higher than those clinically attainable in human patients (150-400 µg/kg). *In vitro* high doses should not however be compared as such with plasma concentrations, as the distribution volume of ivermectin is very high. Preprint results from a study in the hamster model (Pasteur Institute) indicate that IVM is associated with less severe disease related to decreased production of pro inflammatory cytokines and increased levels of IL-10. Preliminary evidence from observational studies suggest beneficial treatment effects for the use of ivermectin; e.g. After multivariate adjustment for confounders and mortality risks, the mortality difference in favour of ivermectin remained significant (OR, 0.27; 95% CI, 0.09-0.80; P< 0.03) [71]. The committee withholds recommendations until more robust data from RCTs become available.
Note – ACE inhibitors or ARBs: There is currently no evidence from clinical or epidemiological studies that establishes a link between their use and severe COVID 19 [72,73]. It is important that patients do not interrupt their treatment with ACE inhibitors or ARBs nor be switched to other medicines, in spite of concerns raised in the social media related to the theoretical interferences between ACE2 receptors (used for viral entry). The same type of concerns were raised for non-steroid anti-inflammatory drugs (NSAIDs), with also no evidence so far to advise for or against these drugs in COVID-19 patients. However, to be safe, and while waiting pending results, paracetamol may be preferred as first-line symptomatic treatment of pain and fever (at usual dosage), while NSAIDs should be used with caution (as in common practice) and according to common practice (contra-indicated in case of renal failure for example).

Note – pregnant women: Specialized care and close monitoring for complications is absolutely necessary in COVID-19 pregnant women. A COVID positive patient, if maternal condition allows it, can deliver vaginally. Large organizations like WHO, RCOG and ACOG support the practice of breastfeeding even in the context of active SARS-CoV-2 disease, but with application of necessary preventive measures (mask, nipple cleaning, frequent handwashing). See additional guidance on newborns of COVID-19 positive mothers via the following link. Antiviral treatment of COVID19 confirmed pregnant women should be considered depending on the safety profile, maternal risk factors (diabetes, hypertension, asthma) and pregnancy outcome (possible risk of premature delivery in the setting of viral infection) (see also SmPCs in annex 2) [74]. Remdesivir is available for compassionate use in pregnant women with severe disease and the first observational data provide reassurance about safety [75]. A working group is preparing a more elaborated guideline for COVID-19 and pregnancy, to which we will refer as soon as finalized. International guidelines are available, including from NIH, RCOG and WHO guidance.


Note – anticoagulation in COVID-19 patients: Evidence is emerging that COVID-19 is associated with an increased risk of thromboembolic disease, with pulmonary embolism (as well as cerebrovascular accident or myocardial infarction) regarded as an important risk factors for increased mortality.

A consensus guideline on anticoagulation management in COVID-19 positive patients has been published by the Belgian Society on Thrombosis and Haemostasis and available here. Of note, a KCE report on thrombo prophylaxis in COVID-19 diseases concluded that the BSTH management algorithms are of good quality and in agreement with international guidance.

Note – Oxygen therapy in COVID-19 patients: A working group coordinated by AFMPS/FAGG has prepared guidelines for oxygen therapy in:

(1) Hospitalized patients: FR , NL

(2) Patients after hospital discharge and residents of nursery homes: FR, NL

Note – Treatment of COVID-19 patients in nursing homes: Collège de Médecine Générale : Mise à jour du protocole thérapeutique des résidents d’institutions âgés de plus de 75 ans atteints de Covid-19: link
3. Summary of efficacy data of selected antiviral drugs

Table 2: *In vitro / in vivo* efficacy of antiviral drugs selected for treatment of suspected/confirmed COVID-19

*Note: all ongoing clinical treatment trials/studies over COVID-19 (> 300) are compiled in a real-time dashboard at LitCovid website, see The Lancet [76]; we try to summarize the relevant information for the selected drugs*

<table>
<thead>
<tr>
<th>Drug</th>
<th><em>In vitro</em> activity</th>
<th><em>In vivo</em> activity (animal models)</th>
<th>Clinical studies SARS-CoV-2 (non-exhaustive)</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SARS-CoV-1</td>
<td>MERS-CoV</td>
<td>SARS-CoV-2</td>
<td>SARS-CoV-1</td>
</tr>
<tr>
<td>Remdesivir / GS5734 (Veklury®); Limited availability in Belgium</td>
<td>+++ [77]</td>
<td>+++ [77–80]</td>
<td>+++ [17]</td>
<td>+++ [81]</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>Rating</td>
<td>Rating</td>
<td>Rating</td>
<td>Rating</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Chloroquine phosphate (CQ)</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Not marketed in Belgium. Available via import or as magistral preparation (500mg CQ = 300mg chloroquine base); Used for malaria</td>
<td>[82,83]</td>
<td>[84]</td>
<td>[17]</td>
<td>[85]</td>
</tr>
<tr>
<td>Hydroxy-chloroquine (HCQ) (Plaquenil®); Used for lupus, rheumatoid arthritis</td>
<td>+/-?</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>[86]</td>
<td></td>
<td>[18]</td>
<td></td>
</tr>
<tr>
<td>Lopinavir /ritonavir (Kaletra®); Used in HIV infection</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>[88–90]</td>
<td></td>
<td>[91]</td>
<td></td>
</tr>
</tbody>
</table>

Although in initial SOLIDARITY (WHO) protocol, the trial was only ever pursued with hydroxychloroquine despite initial SOLIDARITY (WHO) protocol, the trial was only ever pursued with hydroxychloroquine.

Fusion and uncoating blockade, by lysosomal alkalization [82,83]; Interaction with the ACE2 receptor [82]; “Immuno-modulation”?

2020-000890-25: Reduction of the proportion of SARS-CoV-2 RNA positivity (RT-PCR) in nasopharyngeal swabs of treated patients compared to external control group with symptomatic care only (weak evidence) [87]

Was under investigation in the SOLIDARITY (WHO), RECOVERY (UK) and DisCoVeRy (INSERM) trials, at high dosages (9600 mg in total over 10 days for the former two trials and 5600 mg in total over 10 days for the latter). All three trials stopped enrolling patients in hydroxychloroquine arm: no clinical benefit in patients hospitalized with COVID-19 (press releases).

No demonstrated efficacy on mortality at Day 28 in RECOVERY [28]

Weak efficacy for SARS-CoV-1; associated with ribavirin & cortico-steroids [90]

NCT04252885: Negative results for hospitalized patients with mild/moderate COVID-19 [93];

NCT04345289: No clear viral or clinical benefit in an patients hospitalized in China with severe disease [37]
<table>
<thead>
<tr>
<th>Drug</th>
<th>Study Details</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favipiravir</td>
<td>Discontinued in the SOLIDARITY because of lack of benefit (press release). Also discontinued in DisCoVeRy. No demonstrated efficacy on mortality at Day 28 in RECOVERY. [39].</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ChiCTR2000029600: Shorter viral clearance time and improved radiological evolution compared to lopinavir /ritonavir (non-randomized) [42].</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCT04373733 (PIONEER): recruiting</td>
<td>Inhibition of the activity of RNA dependent RNA polymerase (RdRp)[94,95]</td>
</tr>
<tr>
<td></td>
<td>NCT04349241: Completed, no yet published</td>
<td></td>
</tr>
<tr>
<td>Camostat</td>
<td>++[44] ++[44] ++[44] ++[96] - - NCT04355052 : recruiting</td>
<td>Inhibition of TMPRSS2, a cellular serine protease, that primes SARS-CoV-2 Spike (S) protein for cell-entry [44]</td>
</tr>
<tr>
<td>Used in Japan for reflux esophagitis and pancreatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferons</td>
<td>+[97] +[97] ++[46,98] ++[99] +[100] 3 RCT’s with small number of patients (see text). Further studies needed</td>
<td></td>
</tr>
</tbody>
</table>

**Note**: Many other antiviral/immunological treatments have been/are being investigated, including (list not exhaustive) ribavirin, fabiravir, convalescent plasma, monoclonal antibodies, complement inhibitors etc. see Landscape analysis of therapeutics WHO 17/02/2020, link. At this moment, any of these drug candidates should ONLY be evaluated in clinical trials and in Belgium, these trials should ideally be coordinated centrally.

Key points on safety profile are found in Table 1 and an extensive safety profile and/or SmPC of the proposed drugs can be found in Annex 2.
4. Clinical trials in Belgium

For an overview of all currently running clinical trials in Belgium, you can search on [https://databankklinischeproeven.be/](https://databankklinischeproeven.be/) (fill in covid-19 as search term in the ‘medical condition/pathology’ field). Additional trials are currently being set up in Belgium. The table below briefly summarizes only ONGOING trials (already recruiting).

Table 3: Belgian COVID-19 Clinical Trials

<table>
<thead>
<tr>
<th>PROTOCOL CODE / EudraCT n°</th>
<th>STUDY TYPE</th>
<th>INVESTIGATED PRODUCTS</th>
<th>PATIENT PROFILE</th>
<th>PRINCIPAL INVESTIGATOR/COORDINATING CENTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>COV-AID 2020-001500-41</td>
<td>Multicentric, randomized, factorial design, interventional study</td>
<td>Six arms: Anakinra (anti-IL1), Siltuximab (anti-IL6), Tocilizumab (anti-IL6) in monotherapy, double or single combinations; standard of care (SoC)</td>
<td>COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome</td>
<td>Bart Lambrecht / UGent</td>
</tr>
<tr>
<td>SARPAC 2020-001254-22</td>
<td>Multicentric, randomized, open-label, interventional study</td>
<td>2 arms: Sargramostim (recombinant GM-CSF) vs SoC</td>
<td>Acute hypoxic respiratory failure of COVID-19 patients</td>
<td>B. Lambrecht / Ugent</td>
</tr>
<tr>
<td>DAWN – azithro 2020-001614-38</td>
<td>Multicentric, randomized, open-label, adaptive, proof-of-concept clinical trial</td>
<td>2 arms: Azithromycin vs SoC (other arms can be included later)</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td>DisCoVeRy 2020-000936-23</td>
<td>Multicentric, randomized, open-label, adaptive clinical trial</td>
<td>2 arms: Remdesivir vs SoC</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>M. Hites / Hôpital Erasme</td>
</tr>
<tr>
<td>DAWN-plasma (No IMP, therefore no EudraCT number)</td>
<td>Open-label randomized Multicenter Adaptive design</td>
<td>2 arms: convalescent plasma vs SoC</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>G. Meyfroidt/ UZ Leuven</td>
</tr>
<tr>
<td>REMAP-CAP 2015-002340-14</td>
<td>Randomized, embedded, multifactorial, adaptive platform trial for community acquired</td>
<td>Antiviral therapy: No vs Kaletra Corticosteroid therapy: No vs hydrocortisone 7d</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>AZ Sint-Jan (Brugge), CHU Charleroi, UZ Gent</td>
</tr>
<tr>
<td>Study (ID)</td>
<td>Design/Phase</td>
<td>Intervention</td>
<td>Patient Type</td>
<td>Sponsor</td>
</tr>
<tr>
<td>------------</td>
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</tr>
<tr>
<td>DAWN-antico 2020-001739-28A</td>
<td>Randomized, open-label, adaptive, proof-of-concept clinical trial</td>
<td>3 arms: High prophylactic LMWH +/- anakinra*; Apronin (antifibrinolytic) +/- anakinra*; standard dose of LMWH * anakinra only for patients in hyper-inflammatory stage</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td>Biophytis – BIO101 2020-001498-63</td>
<td>Adaptive design phase 2 to 3, randomized, double-blind, multicentre clinical trial</td>
<td>2 arms: BIO101 (activator of Mas-receptor of the renin-angiotensin system) vs SoC</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>UCL Namur St Elisabeth AZ St Maarten (Mechelen)</td>
</tr>
<tr>
<td>ZILU-COV 2020-002130-33</td>
<td>Prospective, randomized, open-label, interventional clinical trial</td>
<td>2 arms: Zilucoplan (inhibitor of complement protein C5) vs SoC</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>B. Lambrecht/UZ Gent</td>
</tr>
<tr>
<td>OSCAR (GSK) 2020-001759-42</td>
<td>Randomized, double-blind, placebo-controlled clinical trial</td>
<td>2 arms: Otilimab (anti-GM-CSF) vs SoC</td>
<td>Patients with severe pulmonary COVID-19 related disease</td>
<td>GSK</td>
</tr>
<tr>
<td>MOT-C-204 (Inotrem) 2020-001504-24</td>
<td>Randomized, double-blind, placebo controlled, adaptive, exploratory clinical study</td>
<td>2 arms: Nangibotide iv (TREM1 inhibitor) vs placebo</td>
<td>Mechanically ventilated patients due to COVID-19 and with features of systemic inflammation</td>
<td>UCL St-Luc, ZOL</td>
</tr>
<tr>
<td>TJT2012 2020-002102-58</td>
<td>Prospective open-label P1/2 clinical trial</td>
<td>Mesenchymal stromal cells</td>
<td>Patients with severe COVID-19 requiring supplemental O2</td>
<td>CHU Liège</td>
</tr>
<tr>
<td>ARGX-117-2001 (ArgenX) 2020-001546-19</td>
<td>First-in-human, open-label P1 clinical study</td>
<td>ARGX-117 iv (Humanized antibody that blocks C2b)</td>
<td>COVID-19 hospitalized patients</td>
<td>UZ Gent</td>
</tr>
<tr>
<td>AT-527 (ATEA pharmaceuticals) 2020-002869-34</td>
<td>Randomized, double blind,</td>
<td>AT-527 (guanosine nucleotide prodrug)</td>
<td>Moderate COVID-19 patients with</td>
<td>CHU St-Pierre, AZ St-Maarten (Mechelen)</td>
</tr>
<tr>
<td>Study ID</td>
<td>Type of Study</td>
<td>Details</td>
<td>Endpoint</td>
<td>Location(s)</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>ABX464-401</td>
<td>Randomized, double-blind, placebo-controlled, P2/3 trial</td>
<td>ABX464 (antiviral) vs Placebo</td>
<td>Mild-moderate COVID-19 patients with risk factors</td>
<td>UZ Gent, Erasme and CHU Saint-Pierre</td>
</tr>
<tr>
<td>VAC31518COV1001</td>
<td>Randomized, double-blind, placebo-controlled, P1/2a clinical study</td>
<td>7 arms: Ad26COV51 im (2 dose levels; single or 2-dose schedule) vs placebo</td>
<td>Healthy volunteers aged ≥18 to ≤55 years and ≥65 with or without stable underlying conditions</td>
<td>UZ Gent, CHU Liège, ZNA Jan Palfijn, UZ Leuven, UA, ZNA Stuivenbergh,</td>
</tr>
<tr>
<td>CV-NCOV-001</td>
<td>First-in-human, partially blind, placebo-controlled, dose-escalation P1 clinical study</td>
<td>Different arms: SARS-CoV-2 mRNA vaccine CVnCoV im (3 dose levels; single or 2-dose schedule) vs placebo</td>
<td>Healthy adults 18 - ≤60</td>
<td>UZ Gent</td>
</tr>
<tr>
<td>TMV-083</td>
<td>Randomized, placebo-controlled, two center, Phase I trial</td>
<td>Different arms: TMV-083 novel measles-vector based vaccine candidate (2 dose levels; single or 2-dose schedule) vs placebo</td>
<td>Healthy volunteers aged ≥18 to ≤55 years</td>
<td>SGS CPU</td>
</tr>
<tr>
<td>V591-001</td>
<td>Randomized, Double-Blind, Placebo- Controlled Phase 1/Phase 2 trial</td>
<td>Different arms: V591 measles based vaccine ascending dose levels; single or 2-dose schedule) vs placebo</td>
<td>Healthy volunteers aged ≥18 to ≤55 years and ≥60</td>
<td>UZ Gent, SGS CPU, ATC CPU Liège</td>
</tr>
<tr>
<td>COV-AAT</td>
<td>Randomized, placebo controlled, double blind Phase 2 study</td>
<td>2-arm: Camostat (antiviral, serine protease inhibitor) vs placebo</td>
<td>Ambulatory COVID-19 patients</td>
<td>UZ Gent</td>
</tr>
<tr>
<td>ETHIC trial</td>
<td>Open label, randomized, P3b trial</td>
<td>2-arm: Enoxaparin vs SoC</td>
<td>Ambulatory COVID-19 patients</td>
<td>F. Cools / Thrombosis Research Institute</td>
</tr>
<tr>
<td>AZD7442</td>
<td>Randomized, double blind, placebo controlled, Phase 3 trial</td>
<td>2-arm: AZD 7442 (cocktail of 2 mAb against SARS-CoV-2) vs Placebo</td>
<td>Healthy adults</td>
<td>Astra Zeneca</td>
</tr>
</tbody>
</table>
As pre-exposure prophylaxis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Intervention</th>
<th>Participants</th>
<th>Lead Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONVENCE 2020-002234-32</td>
<td>Open-label, factorial 2x2 design</td>
<td>Edoxaban and/or colchicine vs No intervention</td>
<td>Ambulatory COVID-19 patients</td>
<td>P Vranckx (Jessaziekenhuis Hasselt)</td>
</tr>
</tbody>
</table>

**Terminated trials**
- Antivirals for COVID-19 2020-001243-15 (itraconazole)
- COVIDAM 2020-001417-21
- SANOFI 2020-001269-35
5. Annexes

Annex 1: Availability of remdesivir

The medicine Veklury® (remdesivir) is available in the strategic stock, stored and distributed by a State-designated distributor. It is available to hospitals for patients that fill the criteria for use as defined in this guidance. Hospital pharmacists have been informed on the procedure to obtain Veklury.

The FAMHP closely monitors the evolution of stocks and, if necessary, places new order to ensure sufficient supply.

Veklury is registered for the treatment of COVID-19 in adults and adolescents from 12 years of age (with at least a body weight of 40kg). For pregnant women and children <12y, compassionate use is possible.

Emergency Compassionate use procedure (as stated in art 107/1 (link))

For pregnant women and children <12y. Request on https://rdvcu.gilead.com/)
When using Remdesivir for compassionate use, a notification to umn@fagg-afmps.be and to the ethics committee of the concerned site is to be made. The notification should include the following information:

- The name of the sponsor
- The name of the treating physician
- A sworn statement from the physician that the informed consent was obtained in accordance with the law of 22 August 2002 on patient rights
- The indication
- The motivation that without appropriate treatment, it is expected that the patient's death occurs in a short delay or that the risk for the consequences of the absence of treatment is greater than the risk for the consequences of starting the treatment is included. Please discuss the indication of the patient as well as the previous treatments that the patient received, the unmet need and the benefit/risk balance of treatment along with the urgency for this treatment.

If you have problems obtaining the medicinal products in this guideline, please contact

supply-problems@fagg-afmps.be
Annex 2: Safety profiles

Please download this document (rather than visualize in Web browser) to enable these links to pdf documents to work.

Any suspected adverse events related to these drugs should be reported through the usual channels, as part of regular pharmacovigilance activities:

www.notifieruneffetindesirable.be or
https://www.fagg.be/nl/melden_van_een_bijwerking_als_gezondheidszorgbeoefenaar
6. References


