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

September 2021; Version 22

Preliminary note

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.

This document is periodically revised 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 COVID-19 cases during the epidemic in Belgium. This guideline primarily targets hospital care but refers whenever necessary to other guidelines.

The guidance has been developed from March to December 2020 by a task force of Infectious Diseases Specialists (IDS): Dr Sabrina Van Ierssel, Universitair Ziekenhuis Antwerpen; Dr Nicolas Dauby, Hôpital Universitaire Saint-Pierre Bruxelles; Dr Emmanuel Bottieau, Instituut voor Tropische Geneeskunde (ITG), and Dr Ralph Huits, ITG, supported by Sciensano (Dr Chloe Wyndham-Thomas;), the AFMPS/FAGG (Dr Roel Van Loock) and ad-hoc contributions from colleagues of other disciplines. Since January 2021, the COVID-19 therapeutic guideline has officially been taken over by the Belgian Society of Infectiology and Clinical Microbiology (BVIKM/SBIMC), and the new task force is composed of IDS representatives from all Belgian University Hospitals, with the additional collaboration of the Belgian Societies of Intensive Care Medicine and of Pneumology. The complete list of members is available below. This guidance is based on the best clinical evidence (peer-reviewed scientific publications) that is available at the moment of writing each update, and is purposed to be a “living guideline” which can always be found via the same link. Keeping the guidelines regularly updated is however particularly challenging due to the incredible speed of knowledge generation for this disease. Readers are warmly invited to send any additional comment, relevant publications, including from the grey literature, and contribution in priority to Dr Maya Hites (maya.hites@erasme.ulb.ac.be) and Dr Emmanuel Bottieau (ebottieau@itg.be). We take this opportunity to thank again the countless readers who, since this guideline was initially released, flagged the inconsistencies, typos or unclear text, as well as those who sent all types of contributions related to this rapidly evolving field.

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); the strengths of the recommendations are now provided using the GRADE score [2].

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**, clinical evidence for treatment with monoclonal antibodies (Table 2) and *in vitro*/*in vivo* efficacy of select antiviral drugs (Table 3).

4. **An overview of the ongoing clinical trials in Belgium** (Table 4).

5. **Annexes**

6. **References**

**IMPORTANT**

As a rule, only manuscripts ACCEPTED after a rigorous PEER-REVIEW process will be used for the strong recommendations in this guidance. 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.

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 preclinical pipeline.

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.

**Members of the working group**

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A conflict of interest list for the members is available here
### 1. Executive summary

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

<table>
<thead>
<tr>
<th>Clinical category</th>
<th>Supportive Care</th>
<th>Additional therapy (Strength of recommendation - GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicion of COVID-19</td>
<td>Symptomatic treatment</td>
<td>No (Strong recommendation, low-quality or very low quality evidence – 1C)</td>
</tr>
<tr>
<td>Suspected disease of COVID-19</td>
<td>Symptomatic treatment</td>
<td>Monoclonal antibodies (mAbs) should be proposed to patients at high risk for complications after balancing individual risks and benefits within a multidisciplinary team, provided these therapeutics are administered in a hospital setting within 10 days after COVID-19 symptom onset (Strong recommendation, moderate quality of evidence – 1B). There is currently little evidence on efficacy of this treatment among immunocompromised patients. Follow the algorithm to assess eligibility criteria for treatment with mAbs for adult patients with mild or moderate COVID-19 infection.</td>
</tr>
<tr>
<td>Confirmed mild or moderate COVID-19</td>
<td>Symptomatic treatment</td>
<td>Optimal supportive care in hospital WARD (or ICU)</td>
</tr>
<tr>
<td>Confirmed COVID-19 severe disease</td>
<td>Optimal supportive care in hospital WARD (or ICU)</td>
<td>Dexamethasone 6 mg once a day for up to 10 days (or until hospital discharge if sooner), IV or PO; (Strong recommendation, high-quality evidence - 1A). 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) (Strong recommendation, moderate quality of evidence - 1B). Case by case decision for children and pregnant women pending additional results and with the respective specialists.</td>
</tr>
<tr>
<td>≥ 1 of the following:</td>
<td></td>
<td>Combination of dexamethasone and remdesivir is no longer to be considered in patients, even those rapidly progressing with &lt; 5 days of symptoms.</td>
</tr>
<tr>
<td>Respiratory rate ≥30/min (adults); ≥40/min (children &lt; 5y)</td>
<td></td>
<td>Tocilizumab and other interleukin-6 blockers: consider early administration of IL6-receptor antagonists in addition to corticosteroids in hospitalized patients with rapidly progressive COVID-19 (Conditional recommendation, moderate quality of evidence).</td>
</tr>
<tr>
<td>Blood oxygen saturation ≤93% or requires supplemental oxygen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2/FiO2 ratio &lt;300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung infiltrates &gt;50% of the lung field within 24-48 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical category</td>
<td>Supportive Care</td>
<td>Additional therapy</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Confirmed COVID-19 critically ill disease</strong></td>
<td>Optimal supportive care in ICU</td>
<td><strong>Dexamethasone</strong> 6 mg IV (or equivalent doses of corticosteroids, see row above) once a day for up 10 days; case by case decision for children and pregnant women pending additional results and with the respective specialists (Strong recommendation, high-quality evidence - 1A).</td>
</tr>
<tr>
<td>≥ 1 of the following:</td>
<td>Mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>➢ Acute Respiratory Distress Syndrome</td>
<td>Administer prophylactic LMWH if not contra- indicated</td>
<td><strong>Consider early administration of IL6-receptor antagonists in addition to corticosteroids in hospitalized patients with rapidly progressive COVID-19 (Conditional recommendation, <strong>moderate</strong> quality of evidence).</strong></td>
</tr>
<tr>
<td>➢ Sepsis</td>
<td>Specific prevention &amp; treatment of ARDS</td>
<td></td>
</tr>
<tr>
<td>➢ Altered consciousness</td>
<td>Track secondary bacterial and opportunistic (Aspergillus) infections</td>
<td></td>
</tr>
<tr>
<td>➢ Multi-organ failure</td>
<td>Prevention of subsequent lung fibrosis</td>
<td></td>
</tr>
</tbody>
</table>

ARDS: Acute respiratory distress syndrome. LMWH: low molecular weight heparin
Precautions of use & additional information

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

**Dexamethasone:** Usual contraindications. It is currently unknown whether the use of corticosteroids in COVID-19 is independently associated with an increased risk for bacterial or fungal infection. The use of dexamethasone may reduce the discriminatory potential of C-reactive protein (CRP) and procalcitonine (PCT) as biomarkers for the diagnosis of secondary bacterial infection (see comments).

**Monoclonal antibodies (mAbs):** Treatment is authorized through CHMP review but they are not commercially available. In Belgium, mAbs can only be administered in the hospital setting, after the authorization of a multidisciplinary team including at least an infectious disease physician and one immunologist.

- **Warning/precautions:**
  - Intrinsic resistance has to be considered (e.g. delta variant resistance to bamlanivimab monotherapy, beta/gamma variant resistance to bamlanivimab + etesevimab combination therapy).
  - Health care providers must have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis and patient should be observed for a least one hour following infusion completion.
  - Subcutaneous route should only used when intravenous route is not feasible and will result in treatment delay.
  - **Renal impairment:** No dosage adjustment is required in patients with altered kidney function (including those in dialysis), hepatic impairment or for geriatric patient.
  - **Hepatic impairment:** mAbs have not been studied in individuals with severe hepatic impairment.
  - **Pregnancy:** The risk of severe COVID-19 is increased in pregnant women and COVID-19 infections risks adverse pregnancy outcomes. mAbs should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus considering all associated health factors.

- **Interactions:**
  - mAbs could interfere with the immune response to COVID-19 vaccination and CDC recommends deferring vaccination for at least 90 days after receiving mAbs.

- **Contraindications:**
  - Hypersensitivity to monoclonal antibodies or to any of the excipients.

**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:** Pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. In patients with eGFR < 30mL/min, the benefits & risks are to be weighed [3]
  - **Possible bradycardia:** Post-marketing study based on the World Health Organization pharmacovigilance database identified increased reports of serious bradycardia among patients treated with remdesivir. Remdesivir was the sole suspected drug among 93% of 88 patients [4]. Following Pharmacovigilance Risk Assessment Committee (PRAC) advice, EMA has recommended to include bradycardia as a possible side-effect of Veklury (link).

- **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](https://www.gilead.com/).
- 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 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 (grade 1A). Background data and rationale behind these recommendations are detailed here. Latest results concerning additional antiviral and immunomodulatory treatments are also covered hereunder.

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

2.1. Corticosteroids

2.1.1. Dexamethasone, systemic corticosteroids

Main message: Systemic corticosteroids (dexamethasone) are recommended for COVID-19 patients with severe disease. In case dexamethasone is not available, the WHO recommends using equivalent doses of other corticosteroids [5]. See Executive summary Table 1 for details.

Available evidence: Although treatment with systemic corticosteroids was initially not recommended [6][7], the availability of new high-quality evidence demonstrates a reduction in mortality among COVID-19 patients with severe disease. Low dose dexamethasone (6 mg/day once daily for 10 days) is a treatment option which has been 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) [8]. 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 subgroup 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 infection, the Belgian Clinical Treatment Guidelines task force has recommended in version 12 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) [9], CoDEX (Brazil) [10], and CAPE COVID (France) [11]. The results of RECOVERY, of the last 3 published (“incomplete”) RCTs and of another three ongoing smaller trials were then pooled and metaanalyzed by the WHO REACT working group [5]. The conclusion was robust throughout all trials (n=678 in total versus 1025 in placebo/usual care arm, all critically ill patients): administration of 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 [12].

Notes on treatment with systemic corticosteroids: It is currently unknown whether the use of corticosteroids in COVID-19 is independently associated with an increased risk for bacterial or fungal infection. A systematic review with meta-analysis complemented the 7 RCTs analyzed in [5] with 37 retrospective observational studies, covering 20,197 patients [13]. Diverse corticosteroid regimens were investigated, most of which consisted of methylprednisolone; 16/29 and 11/29 studies used respectively high (>1mg/kg prednisolone) and lower (<1mg/kg prednisolone) doses. A trend towards more antibiotic use and more infections (6 studies) was noted; however overall pooled estimate showed a reduced mortality in the corticosteroid-treated patients (OR 0.72; 0.57-0.87), which is in a range similar to that found in the WHO REACT working group meta-analysis [5]. A prospective study with serial assessment of C-reactive protein (CRP) and procalcitonine (PCT) in COVID-19 patients found a lower discriminative value of both biomarkers for the early detection of secondary bacterial infections in patients treated with dexamethasone with and without tocilizumab [14].

The risk versus benefit of late corticosteroid therapy in patients with COVID-19 associated ARDS is currently not known. A post-hoc analysis of a multicenter dataset of 348 patients with moderate to severe ARDS associated with COVID-19 admitted to 21 French and Belgian ICUs, comparing with and without corticosteroid-treatment after 13 days of symptom onset did not find a difference in ICU mortality (HR 1.44; 0.83-2.50) or duration of mechanical ventilation (HR 0.89; 0.60-1.33) [15]. No studies have addressed the question whether a prolonged course or a second course of corticosteroids influence the outcome in COVID-19 patients who remain ventilator dependent following a standard course of corticosteroids as provided in the RCTs. A systematic review and trial sequential meta-analysis was performed analysing the use of corticosteroids in patients with ARDS due to COVID-19 and non-COVID-19 related etiology. The use of corticosteroids was found to probably reduce 28-d mortality (RR 0.82; 0.72-0.95) regardless of etiology, and to probably reduce the duration of mechanical ventilation (mean difference 4d fewer, 2.5-5.5), but the optimal information size was not reached in the trial sequential analysis. Among the pooled analysis of COVID-19 and non-COVID-19 patients, those who received >7d of corticosteroids had lower mortality than those who received a ≤7d course (p=0.04) [16].

Effect of low-dose and short-course corticosteroids on risk of Strongyloides reactivation is not well known. Nevertheless, for high-risk patients, such as originating from Strongyloides endemic areas, empirical ivermectin treatment should be considered before, or early during, corticosteroid administration treatment [17].

2.1.2. Inhaled corticosteroids

The possible benefit of inhaled corticosteroids in early COVID-19 (<7 days after symptom onset) was investigated in a phase-II open label RCT in the UK [18]. The trial was stopped early because of a reduced number of new cases. Independent statistical review concluded that the study outcome would not change with further participant enrolment. The patients in the budesonide group had a significantly lower probability of an urgent care visit (15% vs 3%). Number needed to treat to avoid an urgent care visit was eight. Self-
reported clinical recovery was shortened by 1 day (median 7 days [95% CI 6–9] vs 8 days [7–11]; log-rank test p=0.007). This is the first published trial with inhaled corticosteroids in COVID-19. Several similar trials are still ongoing.

The PRINCIPLE trial investigated 2x800µg inhaled budesonide added to usual care in (suspected) COVID-19 patients in the community, aged ≥65y or ≥50y with co-morbidities and ≤14d symptoms. The study ran from November 2020 until March 2021 and included 4700 participants; a Bayesian primary analysis model included data of 2530 patients with confirmed COVID-19. This analysis found a shorter time to self-reported recovery (minus 3d; CI: 1-5.4) in the budesonide arm, as well as a lower rate of hospital admission or death (2%, -0.2-4.5%), the latter without however reaching the prespecified threshold of superiority. In prespecified subgroup analyses, the budesonide effect was not modified by symptom duration before randomization, baseline symptom severity, age or comorbidity. The number of serious adverse events was very small and not different between the budesonide group and the usual care group [19].

Results of a phase-III RCT placebo controlled trial on inhaled ciclesonide, including 400 non-hospitalized patients with symptomatic COVID-19 were announced as a press release: no significant differences were found in time to alleviation of COVID-19 related symptoms (primary endpoint) although a reduction in the number of hospitalizations or emergency department visits was observed in one of the secondary endpoints (link). In an advice dated 27/5/2021, EMA considered the evidence published thus far as insufficient to recommend the use of inhaled corticosteroids in COVID-19, as the possibility of harm in patients not requiring additional oxygen as yet cannot be excluded (link).

2.2. Remdesivir

Main message: The WHO issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of the severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients. Moreover, all studies in humans have demonstrated an absence of antiviral effect in hospitalized COVID-19 patients. As dexamethasone is now considered the standard of care for hospitalized patients requiring oxygen or on mechanical ventilation, it is important to highlight that there is almost no data on the impact of combining dexamethasone and remdesivir on clinical outcomes.

Available evidence: Remdesivir (RDV) seemed promising in vitro and in non-human primate models [20]. 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 [21]. 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 specimens, suggesting the absence of antiviral effect.

A final report of the ongoing NIAID-ACTT NCT04280705 trial conducted in the US was published [22] 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 (oxygen 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 [23].

A third RCT sponsored by Gilead (Spinner et al.) assessed the role of remdesivir in hospitalized patients with non-severe COVID-19 (not requiring oxygen supplementation) [24]. 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%). A better clinical status on day 11 after treatment initiation was observed 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 of remdesivir (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 for a significant antiviral effect as was also observed in the Wang et al trial [21].

In December, the results from the SOLIDARITY multicenter worldwide pragmatic trial were published, showing no overall clinical benefit of remdesivir in hospitalized patients with COVID-19. Remdesivir was evaluated in 2743 patients, compared to 2708 controls. In a meta-analysis of the 4 published trials on remdesivir, a weighted average of the results from all trials yielded a rate ratio for death (remdesivir vs. control) of 0.91 (95% CI, 0.79 to 1.05). However, in the subgroup of patients receiving no mechanical ventilation at time of randomization, the rate ratio for death was 0.80 (0.63-1.01) [25]. The WHO issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of the severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients. Nevertheless, WHO continues to endorse including patients in trials with remdesivir to establish with certainty whether remdesivir has a positive effect on survival in mild to moderate, hospitalized COVID-19 patients. The Solidarity and DisCoVeRy trials continued to randomize mild to moderate hospitalized COVID-19 patients to receive remdesivir vs. standard of care until the 27th and 29th of January, respectively. Inclusions into the remdesivir arm were stopped due to futility in severe, but also mild to moderate, hospitalized COVID-19 patients.

In addition, EMA evaluated the full mortality and viral data from NIAID ACTT-1 data upon which EMA recommended to not start remdesivir in COVID-19 patients already on mechanical ventilation and on ECMO. This guidance, that already considers remdesivir as having a modest effect and small window of use, will be further updated when the final data from the DisCoVeRy and Solidarity trials are published. A recent meta-analysis of the 5 published RCTs on remdesivir vs. control has also shown the modest effect of remdesivir in hospitalized patients. Patients in the remdesivir treatment group had a greater likelihood of hospital discharge, and clinical improvement was more rapid than the control group, yet no effect was observed on mortality [26].

Notes on treatment with remdesivir: A post-marketing study based on the World Health Organization pharmacovigilance database identified increased reports of serious bradycardia among patients treated with
remdesivir. Remdesivir was the sole suspected drug among 93% of 88 patients [4]. Following PRAC advice, EMA has recommended to include bradycardia as a possible side-effect of Veklury (link).

2.3. Immunomodulatory agents, anti-interleukin therapy

Main message: Immunomodulatory agents are a varied group of drugs that may prevent or dampen hyper-inflammatory responses which are associated with clinical deterioration and mortality among COVID-19 disease [27,28]. Potential adverse events, immunosuppression and drug interactions have to be carefully taken into consideration if choosing to treat patients.

Available evidence: Several interleukin (IL) and complement 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 (IL-6-receptor antagonist) [29,30], sarilumab (IL-6 receptor antagonist), siltuximab (anti-IL-6) and anakinra (IL-1-receptor antagonist), as well as complement inhibitors such as C3 and C5 inhibitors, C5a receptor inhibitors and C1 esterase inhibitors. Eight randomized trials assessing the use of tocilizumab (TCZ) in hospitalized COVID-19 patients have been recently published [31–33]. These trials were highly heterogeneous regarding the severity of the patients included.

Recently, a WHO-initiated meta-analysis on 27 randomized trials has been published, showing that IL-6 antagonist was associated with lower 28-day all-cause mortality in patients hospitalized for COVID-19 [34]. Importantly, a significant mortality benefit was only found when IL-6 receptor antagonists were coadministered with glucocorticoids, and most evident among patients who received respiratory support with oxygen by nasal cannula, face mask, high-flow nasal oxygen or non-invasive ventilation versus those who required invasive mechanical ventilation [34,35]. There was not a clear benefit associated with anti-IL-6 among patients who already required mechanical ventilation at the time of randomization. Data were strongest for tocilizumab as compared to sarilumab (less available evidence). The accompanying editorial however points out some limitations to this meta-analysis, the most important being the lack of accounting for the baseline risk of death [35]. This might explain the finding that COV-AID, a study carried out in a Belgian setting, showed no added benefit from anti-IL-6 treatment (Declercq J et al., manuscript accepted in Lancet Respiratory Medicine 2021).

Most international guidelines, including those of the European Respiratory Society (ERS), the National Institutes of Health (NIH), and the Infectious Diseases Society of America (IDSA) have now formulated a conditional recommendation, with moderate certainty of evidence, towards the addition of tocilizumab to standard of care (i.e. steroids) rather than standard of care alone, in hospitalized adults with progressive severe (SpO2 <94% on room air, including patients on supplemental oxygen) or critical (mechanic ventilation and ECMO) COVID-19 who have elevated markers of systemic inflammation [36]. In the largest trial on treatment with tocilizumab, the criterion for systemic inflammation was defined as CRP >75 mg/L. Both RECOVERY and REMAP-CAP (the two tocilizumab trials that reported a benefit) initiated treatment early (randomization at median of two days of hospitalization in RECOVERY; <24 hours in the ICU for REMAP-CAP), suggesting tocilizumab may be more beneficial in people with early, rapidly progressive disease.

Notes on treatment with immunomodulatory agents: Caution must be exercised when used in patients with active concomitant (myco-) bacterial and fungal infections and in chronically immunosuppressed patients. Alternative inflammatory markers instead of CRP (such as procalcitonin) could be used for monitoring of surinfection in patients treated with IL-6-blockers.
2.4. Monoclonal antibodies

Main message: Treatment with monoclonal antibodies (mAbs) should be considered in patients with mild or moderate COVID-19 when they are at high risk of developing severe disease and preferably administered within 10 days of symptom onset.

- A summary for all monoclonal antibodies is available below (link).
- An overview of individual study results is provided in chapter 3 (Table 2).
- Please consult the algorithm in Annex 5.3 to assess whether a patient is eligible for treatment with monoclonal antibodies.
- As described in the ministerial decree, the final decision to treat with mAbs should integrate the clinical opinion of the prescribing (hospital-based) physician and a multidisciplinary expert panel, consisting of at least one infectious disease physician and one immunologist.
- Casirivimab + imdevimab (REGEN-COV) can be ordered by the hospital pharmacy using the form available in Annex 5.4.

Resistance of SARS-CoV-2 variants to mAbs and the changing epidemiology must be considered before starting treatment.

- **Delta variant**: intrinsic resistance to bamlanivimab monotherapy
- **Beta and gamma variant**: reduced susceptibility to bamlanivimab + etesevimab bitherapy

As Delta variant is currently the dominant variant in Belgium, bamlanivimab monotherapy should not be administered. Information on genomic SARS-CoV-2 surveillance in Belgium is available via the National Reference Laboratory\(^1\) and Sciensano weekly epidemiological report.\(^2\)

Monoclonal antibodies are not indicated in severe or critical disease. However, they can be considered as salvage therapy among (hospitalized) patients with persistent viral shedding due to an immunocompromised condition. It is important to stress that very early administration might be extremely challenging in the current situation because it necessitates appropriate hospital infrastructure and excellent collaboration with primary care for timely appropriate referral.

Available evidence: Dozens of monoclonal antibodies (mAbs) targeting the Receptor Binding Domain (RBD) of the spike protein (S protein) (with the exception of sotrovimab which does not directly block the ACE2 receptor) have been developed and more than 50 trials are being conducted [37]. Given the long half-life, a single injection (mostly intravenous, or occasionally subcutaneous) is generally used [38].

A summary followed by an overview per molecule is provided below.

2.4.1. Summary

Bitherapy (bamlanivimab + etesevimab, casirivimab + imdevimab) or monotherapy (regdanvimab or sotrovimab) can be considered on a case-by-case basis for COVID-19 patients with mild to moderate disease

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\(^1\) Genomic Surveillance of SARS-CoV-2 in Belgium

\(^2\) COVID-19 Weekly Epidemiological Report, chapter 3.4 Molecular surveillance:
at high risk of clinical deterioration, on the condition that these therapeutics are administered early after infection onset and preferentially among patients with a negative serological test.

**Intrinsic resistance to monoclonal antibodies should also be considered.** Within Belgium, the B.1.617.2 (Delta) variant has become dominant since August 2021 (link). Studies have demonstrated that the B.1.617 (Kappa) and B.1.617.2 (Delta) variant have resistance to bamlanivimab monotherapy [39,40]. Furthermore, based off in-vitro assays demonstrating reduced susceptibility among the beta and gamma variant, distribution of bamlanivimab + etesevimab was temporarily halted in North America’s states where this virus represented >5% of all samples identified through genomic surveillance (link).

These mAbs have been studied less in immunocompromised patients, a group for which such treatment seems attractive, nor in vaccinated individuals or persistent shedders. Furthermore, efficacy studies against new emerging SARS-CoV-2 variants are necessary to understand whether these treatments will remain effective as the genomic landscape evolves.

### 2.4.2. Bamlanivimab

A phase II RCT with bamlanivimab (BLAZE-1, NCT04427501) in mild and moderate COVID-19 outpatients showed promising results on viral decline, symptom resolution and hospitalization [41]. For hospitalized patients with more advanced disease (trial conducted by the ACTIV-3/TICO LY-CoV555 Study Group), bamlanivimab (co-administered with remdesivir) did not demonstrate any clinical benefit [42]. Several US real world case-control studies have shown that bamlanivimab treatment prevents hospitalization among mild to moderate COVID-19 infections. However, these studies were performed between November 2020 and February 2021, when few bamlanivimab resistant variants of concern (VOC) were in circulation [43,44]. Currently, due to the circulation of the delta variant, the prescription of this mAbs is no longer recommended.

### 2.4.3. Bamlanivimab + etesevimab

The phase 2/3 portion of BLAZE-1 outpatients treated with the combination of bamlanivimab and etesevimab, administered together in a single infusion, showed a significant reduction in viral load on day 11, while no significant change was seen on viral load with bamlanivimab alone. Among secondary endpoints, there were no consistent differences between the monotherapy and the combination therapy versus placebo for the other measures of viral load or clinical symptom scores [45]. In the unpublished RCT, phase 3, BLAZE-1 trial, including outpatients with mild or moderate COVID-19, at high risk for progressing to severe COVID-19 who received an intravenous infusion of 2800 mg bamlanivimab + 2800mg etesevimab, a 70% reduction of hospitalization and death by any cause by day 29 was observed [46]. These data are to be confirmed by a publication. According to the unpublished results of the BLAZE-4 phase 2 trial, the only authorized dose of bamlanivimab is 700 mg combined with etesevimab 1400 mg (link). In the US, on June 25, 2021, the distribution of bamlanivimab plus etesevimab was temporarily paused as virologically resistant variants Gamma (P.1) and Beta (B.1.351) constituted >5% of samples identified through genomic surveillance (link).

### 2.4.4. Casirivimab + imdevimab (Ronapreve, REGEN-COV)

Ronapreve (REGEN-COV, REGN-CoV2 or REGEN-CoV2) consists of two antibodies that bind to different regions of the SARS-CoV-2 spike protein receptor. In an interim analysis of a phase 2-3 trial studying the effect of a combination regimen of casirivimab and imdevimab (NCT04425629) on 275 outpatients, a significant decline in viral load on day 7 was observed when compared to placebo, especially in seronegative patients and in patients with high viral load [47]. However, the impact on clinical outcomes (medically attended visit) were less clear. A preprint article elaborated further on the results of the phase 3 portion of this same study in high-
risk outpatients who received various doses of REGEN-COV (2400mg vs 1200mg vs placebo). The results showed that both REGEN-COV dosage regimens significantly reduced hospitalization or death by day 29 (respectively 71.3% reduction [1.3% vs 4.6%] and 70.4% [1.0% vs 3.2%]) [48]. Efficacy of REGEN-COV was consistent across subgroups, including patients that were SARS-CoV-2 seropositive at baseline. The results of a phase 3 trial (part A) on subcutaneous REGEN-COV prophylaxis among uninfected (PCR negative) household contacts exposed to SARS-CoV-2 at home showed 81.4% risk reduction of a symptomatic infection compared with placebo (11/753 [1.5%] vs. 59/752 [7.8%], number needed to treat [NNT]: 15.9) and a shorter time resolution of symptoms (1.2 vs. 3.2 weeks). One third of the subjects (30.5%) had at least one risk factor for severe COVID-19. The main risk factors included: BMI ≥ 35 kg/m2 (13.7%), age ≥ 65 years (8.7%), and diabetes (6.8%). Very few immunosuppressed patients were included in the study (1.5%) [49].

In the RECOVERY, RCT, open-label trial, published in a pre-print, REGEN-COV (casirivimab 4g and imdevimab 4g, IV) plus standard of care was compared with standard of care alone, in hospitalized COVID-19 patients. 3153 patients (32%) were seronegative for SARS-CoV-2, 5272 (54%) seropositive and 1360 (14%) with unknown status at baseline. In the seronegative group, 396 (24%) in the REGEN-COV group and 451 (30%) of standard of care died within 28 days (rate ratio 0.80; 95% CI 0.70-0.91; p=0.001, NNT: 16.7). The proportional effect of REGEN-COV on mortality differed significantly between seropositive and seronegative patients (p-value for heterogeneity = 0.001). The authors conclude that REGN-COV, in hospitalized patients, should only be used in SARS-CoV-2 seronegative patients [50]. This is the first study to have shown efficacy of mAbs in hospitalized patients with COVID-19.

Based off a published study [48], the FDA modified the dosage to casirivimab 600mg plus imdevimab 600mg (June 2021). The same dosage is approved by the MHRA (The UK Medicines and Healthcare products Regulatory Agency (link). Subcutaneous injection could be given when IV administration is not feasible or would lead to delay in treatment (link).

2.4.5. Regdanvimab
A phase 2-3 trial of 325 adult outpatients with COVID-19 (study CT-P59, unpublished) showed a lower proportion of severe COVID-19 (hospitalization, oxygen requirement or death) by day 28 of 4.4% when analysing pooled dosage regimens of CT-P59 (40mg/kg and 80mg/kg) versus 8.7% in the placebo group (link).

2.4.6. Sotrovimab
The interim intent to treat results analysis of the preprint phase 3 COMET-ICE trial (NCT04545060), evaluating a single 500 mg infusion of sotrovimab compared to placebo in 868 high-risk outpatients (most common risks factors: obesity: 63%, >55 years: 47% and diabetes: 23%) demonstrated an 85% (p=0.002) reduction in hospitalization or death at day 29 in the sotrovimab group (1% vs 7%, NNT:16.6) [51].

Notes on treatment with monoclonal antibodies: On February 26, 2021, the EMA’s human medicine committee (CHMP) concluded that casirivimab and imdevimab could be used together to treat COVID-19 patients not requiring supplemental oxygen and at high risk of complication. The same decision was made for bamlanivimab and etesevimab (March 5, 2021), regdanvimab (March 26, 2021) and for sotrovimab (May 21, 2021). On 19 May 2021, the federal government allocated a limited stock of mAbs REGN-COV2 (casirivimab + imdevimab) to hospitals. The use of these mAbs is subject to specific conditions, described by the ministerial decree in the Moniteur Belge/Belgisch Staatsblad (link).

The algorithm for treatment with mAbs (Annex 5.3) is based on published literature (mostly of low quality of evidence) and on expert opinion. The expert opinion was formed after concertation with a delegation of
Belgian immunologists and transplant physicians. This mAbs treatment algorithm is liable to change over time, depending on developing evidence in the literature and the availability of mAbs in Belgium.

Up to now, no studies on treatment with mAbs in vaccinated individuals have been published. Although vaccination prevents severe disease and mortality in a large majority of patients, breakthrough infections have been reported (link). Therefore, we included the serological status rather than the vaccination status in the decision tree. The final decision on mAbs treatment should integrate the clinical opinion of the prescribing (hospital-based) physician and a multidisciplinary expert panel, consisting of at least an infectious disease physician and an immunologist (cfr. ministerial decree). A monthly follow-up report entitled « REGN-COV2 Rapport de suivi mensuel / Maandelijk opvolgingrapport » should be sent to FAGG (umn@fagg-ammps.be).

Viral genomic monitoring during mAbs therapy is suggested to monitor the risk of developing resistance during treatment. Patients treated with mAbs should be under quarantine and a SARS-CoV-2 nasopharyngeal PCR test should be performed 7-10 days after treatment. If the test is positive, virus sequencing should be performed. SARS-CoV-2 variant classifications and definitions are available via the CDC. **Monoclonal antibodies bind to epitopes on spike protein, which is used as an immunogen in all COVID-19 vaccines. Therefore it is possible they may interfere with the development of an effective immune responses to COVID-19 vaccines.** Based on the estimated half-life of mAbs and evidence suggesting that reinfection is uncommon within the 90 days after initial infection, the CDC recommends deferring vaccination for at least 90 days after receiving mAbs (link).

### 2.5. Convalescent plasma

**Main message:** Current high-quality evidence does not demonstrate that convalescent plasma improved clinical outcomes among hospitalized patients with COVID-19 disease. There is currently insufficient evidence on the early administration of convalescent plasma to prevent severe disease among high-risk patients.

**Available evidence:** Animal studies with SARS-CoV-1 and SARS-CoV-2 infections indicate a protective role of neutralizing antibodies. In addition to marked antiviral activity, plasma administration has been associated with decreased inflammatory markers in a trial in India [52]. Several observational studies, non-controlled and controlled non-randomized trials, and four RCT’s have been published [53]. Observational studies show survival benefit of transfusing COVID-19 convalescent plasma (CCP) with high antibody titers [54]. 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 and the plasma was administrated late in the course of the disease (median time from symptom onset to randomization: 30 days) [55].

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 day 28 (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 [56]. This concurs with the Dutch RCT that was stopped early due to the finding of comparable amounts of neutralizing antibodies in patients as in the administered convalescent plasma, as early as median 10 days after symptom onset [57]. A large placebo-controlled randomized trial from Argentina did not find an impact on mortality of administration of CCP containing high titers of neutralizing antibodies. However, 29% of the patients in the plasma arm were critically ill [58]. The RECOVERY trial randomized 11,558 patients to convalescent plasma or usual care. They did not
find any difference in 28-day mortality between the two groups (both 24%). There was also no difference in secondary outcomes such as discharge at day 28 or progression to mechanical ventilation or death in those not mechanically ventilated at randomization [59]. A Cochrane review including some republished data including those of the RECOVERY trial, and a meta-analysis performed by the RECOVERY group, did not find a difference in mortality [59,60]. In three additional published RCTs exploring early in-hospital and high-dose convalescent plasma, among which the DAWn-plasma trial, no clinical effect of convalescent plasma was found [61–63]. The REMAP-CAP study also halted recruitment in the convalescent arm due to futility. Until now the data have not yet been published.

An Argentinian blinded RCT evaluated early (i.e. within 3d of symptom onset) administration of convalescent plasma in older COVID-19 patients, i.e. >75y or >64 -75y with comorbidities [64]. They found a RR reduction of 0,52 (95% CI 0,29-0,94). The study was terminated early due to a fall in the COVID-19 incidence in Argentina, including 76% percent of the provided inclusion number. On the other hand, the NIH trial C3PO evaluating convalescent plasma for treatment of early-onset (<7 days) non-hospitalized COVID-19 patients (≥50 years old or with a risk factor) was halted as interim analysis of 511 participants (of the 900 planned) found no difference in disease progression [65].

Notes on treatment with convalescent plasma: We only recommend the administration of convalescent plasma within clinical trials in Belgium such as the CONFIDENT study that is currently ongoing (of note recruitment is closed for the DAWN-plasma trial). At this moment there are no clinical trials in Belgium on early administration of COVID-19 convalescent plasma in risk groups. 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 CCP 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 Heuso et al [66] and other case series. The volume and antibody titer used in different reports varies [67].

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-plasma) is not possible. CCP is a standard fresh frozen plasma from convalescent voluntary donors with SARS-CoV-2 neutralizing 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 blood bank laboratory or RKV/CR. Of note, emergence of viral populations with significant mutations in the spike protein has been reported during treatment of immunocompromised patients with convalescent plasma [68]. Furthermore, the genomic differences between SARS-CoV-2 variants globally and regionally affect response to convalescent plasma treatment. Formal studies evaluating the value of convalescent plasma in this setting are needed [69,70].
2.6. Janus kinase inhibitors

Main message: Baricitinib (and other Janus kinase inhibitors) are promising anti-inflammatory drugs targeting multiple cytokines that have shown a survival benefit when administered in addition to standard of care (i.e. systemic corticosteroids). The EMA is currently reviewing Baricitinib as a possible COVID-19 treatment. NIH recommends baricitinib in addition to dexamethasone in severe patients as an alternative to tocilizumab. **Tofacitinib is also proposed as an alternative to baricitinib when unavailable (link).**

2.6.1. Baricitinib

Baricitinib is an orally administered, selective inhibitor of Janus kinase (JAK) 1 and 2. In a randomized placebo-controlled trial in patients with moderate and severe COVID-19, treatment with baricitinib 4mg qd and remdesivir was shown to reduce recovery time and to accelerate improvement in clinical status when compared to remdesivir alone [71]. Corticosteroids were not considered standard of care in this study. It’s currently unclear whether the benefit of baricitinib with remdesivir would reach the benefit of steroids alone. Prices of baricitinib and remdesivir are significantly higher than steroids, so this treatment should not be used as standard of care pending further evaluation: including use without remdesivir, use on top of steroids or use in comparison with steroids. One large double blind randomized placebo-controlled trial (SOC included systemic corticosteroids in 80% of patients) showed no influence of baricitinib on combined primary endpoints (progression to requiring high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation or death by day 28), but there was a significant reduction of mortality at day 28 and day 60 [72]. According to a press release (Feb 2021: link), baricitinib is to be investigated as a possible treatment for COVID-19 in the RECOVERY trial. On the 29th of April, the EMA has begun the evaluation of an application to extend the use of Olumiant (baricitinib) to include treatment of COVID-19 in hospitalized patients from 10 years of age who require supplemental oxygen.

2.6.2. Tofacitinib

Tofacitinib is an oral JAK inhibitor already approved for the treatment of rheumatoid arthritis (Xeljanz). A placebo controlled randomized trial treated hospitalized COVID-19 patients not requiring ventilation with tofacitinib 10mg twice daily in addition to standard of care. This led to a significant reduction in incidence of death or respiratory failure (18.1% vs 29.0%, risk ratio 0.63, P=0.04). This effect was consistent across the different levels of oxygen supplementation at baseline. Corticosteroid use was high in both groups (78.5%). The study showed no increased risk of secondary infection associated with the use of tofacitinib.

2.6.3. Roxulitinib

Only preliminary data are available for roxulitinib. None of it is sufficient to support its use outside of studies [73].

2.7. Interferon

Main message: Interferons (IFN) have antiviral effects and modulate the immune response [74]. At this moment there is insufficient evidence to support the use of interferon treatment in early or severe COVID-19 disease.

Available evidence: There are several case series, case-control trials, small RCT’s and the interim results of the WHO-solidarity trial that have been published so far. Hung et al compared combination therapy including IFN ß-1b, ribavirin and lopinavir/ritonavir (n=86) vs lopinavir/ritonavir alone (n= 41) in an open label RCT [75]. 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 β-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 [76]. The same group also evaluated IFN β-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 [77]. 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. Results from the WHO-SOLIDARITY trial show that Interferon IFN β-1a given with or without lopinavir/ritonavir, resp 1412 and 651 patients, did not provide any survival benefit vs control, HR 1.16 (0.96-1.39) in hospitalized patients [25]. The results of the DisCoVeRy trial have been published, including a lopinavir/ritonavir interferon β-1a arm [78]. There was no impact on clinical outcomes. Inclusion in the study arm was stopped prematurely due to futility.

Several smaller RCTs have looked at IFN β-1a, in addition to SOC including lopinavir/ritonavir, in severe COVID-19 and could not find a clinical benefit [77,79,80]. A recent Indian multicenter open label RCT evaluated a single dose Pegylated interferon α2b in moderate COVID-19 with only modest results, faster clinical improvement and viral clearance [81].

Recently two small studies have looked at the effect of early single dose administration of peginterferon-lambda in outpatients with COVID-19 and found opposing results [82,83]. A few studies have looked at IFN administration by spray or atomization, to improve local effects and avoid systemic adverse reactions [84,85].

At this moment one small, underpowered RCT looked at the effect of combination of inhaled interferon β-1b and Favipiravir vs standard of care with hydroxychloroquine in severe COVID-19, finding no effect [86]. Another pilot double-blind placebo RCT found that hospitalized COVID-19 patients treated with 14 days of nebulized interferon β-1a had a greater odds for clinical improvement [87]. No data were available on additional therapies used in these patients. Further studies are needed to clarify the role of Interferons in the treatment of COVID-19.

2.8. Chloroquine and hydroxychloroquine

Main message: Current high-quality evidence demonstrates that hydroxychloroquine (HQC) does not improve clinical outcomes among COVID-19 infected patients. It has been decided since the beginning of June 2020 (version 10) not to recommend its off-label use for COVID-19 in Belgium anymore. In December 2020, the WHO recommended against the use of (hydroxy-)chloroquine in clinical care regardless of COVID-19 severity.

Available evidence: Chloroquine and hydroxychloroquine initially appeared promising because it could inhibit replication of SARS-CoV-2 in vitro [88].

The role of hydroxychloroquine for treatment of hospitalized COVID-19 patients was assessed in the RECOVERY, SOLIDARITY and DisCoVeRy trials. None of these studies found improved clinical outcomes among treated patients. 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 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 [89]. 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) [90].

The role of hydroxychloroquine as post-exposure prophylaxis or as early treatment for mild COVID-19 disease was also assessed through additional RCTs, yet they found no clinical benefit. One 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. 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 [91]. 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 [92]. 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 [93].

2.9. Lopinavir/ritonavir

Main message: Due to lack of evidence for clinical benefit in the SOLIDARITY, RECOVER and DisCoVeRy trials, lopinavir/ritonavir (LPV/r) is not recommended as a treatment in COVID-19 disease. In December 2020, WHO recommended against the use of LPV/r in clinical care regardless of COVID-19 severity.

Available evidence: In an RCT, lopinavir/ritonavir (LPV/r 400 mg/100 mg twice daily), initiated more than 12 days after symptom onset (median, IQR 11–17 days), did not show significant clinical benefits in hospitalized patients with COVID-19 [94]. Another small RCT conducted in China did not show any viral or clinical benefit however (or at best very marginal) [94]. 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 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 [95]. 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) [96]. Specific communication regarding ongoing clinical trials is still awaited.

2.10. Favipiravir

Main message: Although some encouraging pre-clinical data (mainly in hamster models) have been published, there is currently no evidence from clinical trials concerning the potential utility of this drug for in- or out-
patients with COVID-19 infection. This drug is currently unavailable for treatment outside of clinical trials in Belgium.

**Available evidence:** 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 [97]. 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 to 1800mg BID) [98]. An antiviral effect has been observed in animal models (hamsters) at high dosage [99]. This observation has been confirmed in another experiment in Syrian hamsters [100].

In a 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 [101].

An interim analysis of a small phase 2 RCT showed a lower rate of PCR positivity at day 5 post-favipiravir initiation but with no difference at day 10 [102]. A multicentric RCT in Iran did not show any clinical benefit in hospitalized COVID-19 patients treated with favipiravir when compared to LPV/r [103]. Larger trials are still ongoing.

### 2.11. Molnupiravir

Molnupiravir is a new antiviral with demonstrated activity against SARS-CoV-2 in ferret and mouse models (as prophylaxis and treatment). After preliminary phase 1 and phase 2 data suggest the drug is safe and has antiviral activity in humans as well, a phase 3 trial has been initiated in non-hospitalized patients at risk of severe disease progression (PHASE OUT trial). Results will not be known before the end of the year 2021.

### 2.12. Camostat mesylate

**Main message:** There is no published evidence of clinical efficacy of this drug for COVID-19. This drug is currently unavailable for treatment outside of clinical trials in Belgium.

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 [104]. Camostat mesylate is under investigation in monotherapy or in combination with either hydroxychloroquine or azithromycin (eg. NCT04355052 (Israel), NCT04321096 (Denmark)).

The first results of the Danish RCT among 205 hospitalized patients (137 treated with camostat mesylate, 200 mg t.i.d. for 5 days, vs 68 treated with placebo) shows that this drug was safe, but had no viral nor clinical added benefit compared to standard of care [105].

The results of early treatment in ambulatory patients are still awaited. A phase 2 trial in ambulatory patients looking for antiviral activity is ongoing in UZ Gent (Table 3). Large multi-country trials with clinical endpoints are ongoing and a trial is approved in the ambulatory setting in the KUL.
2.13. Azithromycin

**Main message:** Despite some initial interest based on in vitro data, large clinical trials (e.g. RECOVERY) have not demonstrate improved clinical outcomes among COVID-19 patients.

Azithromycin, shown to have some antiviral and immunomodulatory effect, has been promoted by some groups based on observational viral and clinical data [106]. The potential benefit of using AZM alone or with other drugs has not been demonstrated so far. Two large RCTs in Brazil have explored the usefulness of this drug in association with HCQ, both in mild/moderate [90] and severe hospitalized patients [17], and did not find any added value compared to HCQ alone. The azithromycin arm of RECOVERY was closed on November 27, 2020 for futility, after 2582 patients were randomized to azithromycin and compared to 5182 patients receiving standard of care. No effect was observed on 28-day mortality, nor on the risk of progression to mechanical ventilation or on length of hospital stay [107]. The results of DAWN-AZITHRO are also expected soon (Table 3).

2.14. Ivermectin

**Main message:** Currently there is insufficient high-quality evidence to justify the use of ivermectin. In line with WHO and EMA, we recommend against the use of ivermectin in clinical care.

**Available evidence:** *In vitro* inhibition of SARS-CoV-2 replication in Vero/hSLAM cells [9] 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). Preliminary evidence based on compilation of observational studies suggested survival benefit in ivermectin recipients (OR, 0.27; 95% CI, 0.09-0.80; P< 0.03) [108].

Until now, 11 (5 double-blind) randomized controlled trials studying the effect of ivermectin at different dosages on viral clearance and/or clinical recovery and/or survival have been published in peer-reviewed journals [109–120]. All but one excluded severe and critical COVID-19 patients and dosages of ivermectin varied between 100 µg and 400 µg/kg (single doses up to 5 consecutive days). One trial studied the efficacy of an ivermectin nanosuspension nasal spray [120]. Seven of these studies showed a more rapid decline in viral load. None of these studies demonstrated any differences in resolution of symptoms or mortality, except three (two of which non-blinded) RCTs demonstrating significantly less development of symptoms in asymptomatic patients when treated with a single dose of ivermectin [121], less progression to severe illness [122], and more rapid clinical improvement [120,122]. A recently published systematic review and meta-analysis of RCT’s concluded that ivermectin did not reduce all-cause mortality, length of stay or viral clearance in COVID-19 patients with mostly mild disease [123]. Many of the available RCTs show several methodological issues such as small sample size, lack of blinding, various drugs in the control arms, different clinical scenarios (as prophylaxis, early outpatient administration and later treatment in admitted patients) and/or incomplete data on outcomes, as summarized in a Commentary in British Medical Journal (BMJ) Evidence-Based Medicine [124]. More robust data and evidence from ongoing clinical trials are expected.
2.15. Colchicine

Main message: Preliminary evidence from large trials (RECOVERY) did not find any clinical benefit of this drug for hospitalized COVID-19 patients. Earlier administration in PCR-diagnosed ambulatory patients seemed to provide a marginal benefit in preventing hospital admission in a large randomized controlled trial (COLCORONA). This must be balanced with the well-known adverse events (diarrhea), the number to treat (70) to prevent one admission and the rather long duration (one month) of the evaluated regimen.

This well-known drug used in several inflammatory diseases has also gained much attention recently. No antiviral activity against SARS-CoV-2 has been demonstrated so far, but its inhibitory action against neutrophil chemotaxis/adhesion and against the inflammasome appears interesting [125]. A large multicenter placebo-controlled RCT evaluated colchicine (2 x 0.5 mg for 3 days followed by 0.5 mg/day for one month) in > 4000 PCR-confirmed COVID-19 ambulatory patients with risk factors for severe covid (being age, main comorbidities, fever or a set of full blood count abnormalities) [126]. The trial showed no significant effect of colchicine on the combined primary outcome (death or hospitalization) when considering all included cases (4,7% vs 5,8%, OR 0,79, p=0,081) but showed a reduction of this outcome when considering the prespecified group of PCR-proven cases (4,6% vs 6%, OR 0,75, p=0,042). There were two times more diarrhea in the colchicine group than in the placebo group (13.7 vs 7.3%; p<0.001). The trial was stopped at 75% of planned recruitment, due to organizational constraints. As discussed in the accompanying editorial, these findings do not imply that colchicine will likely become the first-line community treatment for early COVID-19, because the effect size was small, and the number needed to treat large (70). It adds however some evidence that anti-inflammatory drugs administered early in the course of the disease may be beneficial [127]. For in-hospital patients, evidence remains scarce. A few observational studies using variable drug dosages have been published, suggesting a possible clinical benefit [128]. One small open-label RCT has evaluated the efficacy of colchicine for hospitalized patients (one third of the patients however did not require oxygen at inclusion) [129]. No patient received corticosteroids as part of SOC treatment. The trial showed a significant reduction in clinical deterioration and an improvement in terms of time to clinical deterioration in the colchicine group. It should be noted that recruitment was terminated prematurely due to slow patient accrual, with 105 of 180 planned inclusions. A second RCT including 75 moderately to severely ill patients (a majority of them also treated with corticosteroids) showed a reduction of the duration of both oxygen supplementation and hospitalization among colchicine-treated patients. ICU admission and death were rare in both groups [130]. Two systematic reviews of eight studies (some of them pre-print) with heterogeneous design and varied “control” arms both in out- and inpatients suggested some survival benefit and concluded that large RCTs were still needed. The current evidence does not permit to recommend for or against use of colchicine in the treatment of COVID-19 until data of larger RCTs are published. Of note, the RECOVERY consortium has announced by press release on the 5th of March 2021 that they have closed recruitment in the colchicine arm because it did not demonstrate mortality benefit in addition to corticosteroids in patients hospitalized with COVID-19. Peer-review publication is awaited.

2.16. Aspirin

Main message: Aspirin has demonstrated no clinical benefit in two large trials among hospitalized patients across different forms of disease severity and should not be used in the management of COVID-19.
Aspirin (ASA) is a non-selective inhibitor of COX-1 and COX-2 enzymes leading to a decreased production of prostaglandins, thromboxane A2 by platelets. Low dose ASA is associated with antithrombotic effect. In animal models ASA inhibits disseminated intravascular coagulation (DIC) during *Staphylococcus aureus* sepsis through inhibition of platelet activation. Patients with septic shock have decreased risk of DIC when using ASA [131]. One retrospective study found a decreased risk of mechanical ventilation, ICU admission and in-hospital mortality among patients admitted with COVID-19 [132]. Different cohort studies have shown a decreased risk of acute lung injury/ARDS in patients on chronic ASA-treatment.

Dozens of RCTs are evaluating ASA in COVID-19 in addition to standard of care. By press release, RECOVERY trial announced that Aspirin (150 mg daily) has no impact on mortality as compared to standard of care in hospitalized patients (link). Similar findings were announced for critically ill patients in the REMAP-CAP trials.
2.17. General notes

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 [133,134]. An RCT found no impact of ACEi/ARB switch in COVID-19 [135]. The same type of concerns were raised for non-steroidal anti-inflammatory drugs (NSAIDs), with also no evidence so far to advise for or against these drugs in COVID-19 patients. A nationwide cohort study in Denmark found no difference in COVID-19 outcome in patients with recent use of NSAID [136]. 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. Monoclonal antibody 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) [137]. International guidelines are available, including from NIH, RCOG and WHO guidance.

Note – children:
Specific guidelines are available: Traitement et prise en charge de l’enfant atteint de la COVID-19: Particularités pédiatrique/Opvang en behandeling van kinderen met COVID-19 gerelateerde ziekte (online on 1 December 2020):

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 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 thromboprophylaxis 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 – Ambulatory care:

• 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:

• Superior Health Council advice on Vitamine D, Zinc and COVID-19

• Outpatient care for Covid-19 patients in the context of saturation in Belgian hospitals
### 3. Summary of efficacy data of selected antiviral drugs

#### 3.1. Table 2: Summary of available clinical evidence for treatment with neutralizing monoclonal antibodies (mAb) against SARS-CoV-2 spike protein

<table>
<thead>
<tr>
<th>mAb, Company</th>
<th>Clinical Trial</th>
<th>Study group</th>
<th>Main results</th>
<th>NNT</th>
<th>EMA approval</th>
<th>Available in Belgium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bamlanivimab</strong></td>
<td>Monotherapy (IV)</td>
<td>Mild to moderate COVID-19, outpatients</td>
<td>Statistically reducing of VL on Day 11 for LyCoV555 at 2800 mg dose (-0.53 log, p=0.02)</td>
<td>NA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Eli Lilly and Company</td>
<td>BLAZE-1 phase 2 NCT04427501[41]</td>
<td><strong>Combined with Remdesivir (IV)</strong></td>
<td>Hospitalised patients without end-organ failure</td>
<td>NA</td>
<td>CHMP review 05/03/21 for IV use</td>
<td>Delta variant resistant to bamlanivimab monotherapy (link)</td>
</tr>
<tr>
<td></td>
<td>ACTIV-3/TICO NCT04501978[42]</td>
<td>Hospitalised patients without end-organ failure</td>
<td>Efficacy outcomes at Day 5 not statistically significant in the LyCoV555+remdesivir vs placebo group</td>
<td>NA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Bamlanivimab + Etesevimab</strong></td>
<td>Combination therapy (IV)</td>
<td>Mild to moderate COVID-19, outpatients</td>
<td>Statistically reducing of VL on Day 11 for combination treatment (-0.57 log, p=0.01)</td>
<td>NA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Eli Lilly and Company</td>
<td>BLAZE-1 phase 3 NCT04427501[45]</td>
<td>Mild to moderate COVID-19, outpatients</td>
<td></td>
<td>NA</td>
<td>CHMP review 05/03/21 for IV use</td>
<td>Beta and gamma variant resistant to bamlanivimab + etesevimab (link)</td>
</tr>
<tr>
<td></td>
<td>BLAZE-1 phase 3 High Risk patients Unpublished: [46]</td>
<td>Mild to moderate COVID-19, outpatients at high risk group</td>
<td></td>
<td>NA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Casirivimab + imdevimab</strong></td>
<td>Combination therapy (IV)</td>
<td>Mild to moderate COVID-19, outpatients</td>
<td>Interim analysis: proportion of MAV in REGN-COV2 group through Day 29 (3% vs 6% in the placebo group) and MAV proportion for baseline seronegative patients (6% vs 15% in the placebo group)</td>
<td>33</td>
<td>No</td>
<td>Since 19 May 2021 via government for IV use in mild to moderate COVID-19</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Phase</td>
<td>NCT Number</td>
<td>Preprint</td>
<td>Description</td>
<td>Effect</td>
</tr>
<tr>
<td>-------</td>
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<td>-------------</td>
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</tr>
<tr>
<td><strong>Combination therapy (SC)</strong></td>
<td>Phase 3</td>
<td>NCT04425629</td>
<td>Preprint: [48]</td>
<td>Mild to moderate COVID-19, high risk outpatients</td>
<td>71.3% (2400mg) and 70.4% (1200mg) reduction in hospitalization and all-cause death by day 29</td>
<td>45.5</td>
</tr>
<tr>
<td><strong>Combination therapy (IV)</strong></td>
<td>Phase 3 RECOVERY trial</td>
<td>NCT04452318 (SC) [49]</td>
<td>Prevention in household contact positive SARS-CoV-2 (SC)</td>
<td>81.4% risk reduction of a symptomatic infection in the REGN-COV2 (casirivimab 600 mg/imdevimab 600 mg) group compared with placebo (1.5% vs 7.8%) and a shorter time of resolution of symptoms (1.2 vs 3.2 weeks)</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td><strong>Sotrovimab</strong></td>
<td>Monotherapy (IV)</td>
<td>Phase 2-3 COMET-ICE</td>
<td>NCT04545060 Preprint: [51]</td>
<td>Mild to moderate COVID-19 at high risk group</td>
<td>85% of reduction of hospitalization or death through Day 29 (1% vs 7%)</td>
<td>16.7</td>
</tr>
<tr>
<td><strong>Regdanvimab</strong></td>
<td>Monotherapy (IV)</td>
<td>Unpublished:</td>
<td>Adult with mild to moderate COVID-19</td>
<td>Proportion of hospitalization, oxygen requirement or death by day 28: CT-P59 40 mg/kg: 4.0% vs 8.7% in the placebo group; CT-P59 80mg/kg: 4.9%, pooled CT-P59: 4.4% vs 8.7% in the placebo group</td>
<td>21.3</td>
<td>No</td>
</tr>
</tbody>
</table>

mAb: monoclonal antibody; NNT: number needed to treat; EMA: European Medicines Agency; IV: intravenous; VL: viral load; NA: not applicable; CHMP: Committee for Medicinal Products for Human use; MAV: medically attended visit; SC: subcutaneous.
3.2. Table 3: *In vitro / in vivo* efficacy of antiviral drugs selected for treatment of confirmed COVID-19 infection

*Note: all ongoing clinical treatment trials/studies over COVID-19 (> 300) are compiled in a real-time dashboard at LitCovid website, see The Lancet [138]; we try to summarize the relevant information for selected drugs*

<table>
<thead>
<tr>
<th>Drug</th>
<th><em>In vitro activity</em></th>
<th><em>In vivo activity</em> (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>Favipiravir</td>
<td>Not studied</td>
<td>Not studied</td>
<td>++ *</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td><em>at higher dosage than for influenza</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Camostat</td>
<td>++ [104]</td>
<td>++ [104]</td>
<td>++ [104]</td>
<td>++ [141]</td>
</tr>
<tr>
<td>Interferons</td>
<td>+ [142]</td>
<td>+ [142]</td>
<td>++ [74,143]</td>
<td>+ [144]</td>
</tr>
</tbody>
</table>

*Note: Many other antiviral/immunological treatments have been/are being investigated, including (list not exhaustive) ribavirin, favipiravir, 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.*
### 4. Clinical trials in Belgium

For an overview of all currently running clinical trials in Belgium, you can search on 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>
<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><strong>COV-AID 2020-001500-41 (completed)</strong></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>B. Lambrecht / UZ Gent</td>
</tr>
<tr>
<td><strong>SARPAC 2020-001254-22 (completed)</strong></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 / UZ Gent</td>
</tr>
<tr>
<td><strong>DAWN – azithro 2020-001614-38 (completed)</strong></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><strong>DisCoVeRy 2020-000936-23</strong> Remdesivir arm stopped</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 UCL St-Luc</td>
</tr>
<tr>
<td><strong>DAWN-plasma (No IMP, therefore no EudraCT number)</strong> Recruitment is finished</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><strong>REMAP-CAP 2015-002340-14</strong></td>
<td>Randomized, embedded, multifactorial, adaptive platform trial</td>
<td>Antiviral therapy: No vs Kaletra Corticosteroid therapy</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>AZ Sint-Jan (Brugge), CHU Charleroi, UZ Gent</td>
</tr>
<tr>
<td>Study</td>
<td>Design Details</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Log Numbers</td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
<td>---------------</td>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>for community acquired pneumonia, amended for COVID-19</td>
<td>No vs hydrocortisone 7d vs shock dependent hydrocortisone</td>
<td>Immune modulation: No vs interferon-beta-1a vs anakinra (anti-IL1)</td>
<td>UZ Leuven</td>
<td></td>
</tr>
<tr>
<td><strong>DAWN-antico</strong> 2020-001739-28A (completed)</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</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td><strong>Biophytis – BIO101</strong> 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><strong>ZILU-COV</strong> 2020-002130-33 (completed)</td>
<td>Prospective, open-label, intervention 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><strong>OSCAR (GSK)</strong> 2020-001759-42 (completed)</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><strong>MOT-C-204</strong> (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><strong>TJT2012</strong> 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</td>
<td>CHU Liège</td>
</tr>
<tr>
<td>Study Name</td>
<td>Design</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Stage</td>
</tr>
<tr>
<td>------------</td>
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</tr>
<tr>
<td>ARGX-117-2001 (ArgenX 2020-001546-19 (prematurely ended))</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, placebo controlled, P2 trial</td>
<td>AT-527 (guanosine nucleotide prodrug) Vs placebo</td>
<td>Moderate COVID-19 patients with risk factors for poor outcomes</td>
<td>CHU St-Pierre, AZ St-Maarten (Mechelen)</td>
</tr>
<tr>
<td>ABX464-401 (Abivax 2020-001673-75 Halted for futility)</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>COV-AAT 2020-003475-18</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 2020-003125-39</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 2020-004356-16</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 As pre-exposure prophylaxis</td>
<td>Healthy adults</td>
<td>Astra Zeneca</td>
</tr>
<tr>
<td>CONVINCE 2020-002234-32</td>
<td>Open-label, randomized, Phase 4 trial</td>
<td>factorial 2x2 design: Edoxaban and/or colchicine VS No intervention</td>
<td>Ambulatory COVID-19 patients</td>
<td>P Vranckx (Jessaziekenhuis hasselt)</td>
</tr>
<tr>
<td>TRISTARDS (Boehringer Ingelheim 2020-002913-16)</td>
<td>Open label, randomized, sequential, parallel-group, adaptive PIIIb/III trial</td>
<td>Alteplase (thrombolyticum) High or low dose + SoC vs SoC alone</td>
<td>Hospitalized patients with ARDS</td>
<td>ULB Erasme / HOSP St-Pierre</td>
</tr>
<tr>
<td>FITE19 (PTC therapeutics 2020-001872-13)</td>
<td>randomized, double-blind, placebo-</td>
<td>PTC299 (antiviral) Vs placebo</td>
<td>Hospitalized COVID-19 patients</td>
<td>CHU St Pierre / Clinique St Pierre (Ottignies)</td>
</tr>
<tr>
<td>Study ID</td>
<td>Study Design</td>
<td>Intervention</td>
<td>Comparison</td>
<td>Primary Endpoint</td>
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<tr>
<td>----------</td>
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</tr>
<tr>
<td>MIT-Co001-C101 2020-003403-33</td>
<td>Randomized, double-blind, placebo-controlled, phase 2 trial</td>
<td>Estetrol (E4) + SoC vs placebo + SoC</td>
<td>Hospitalized moderate COVID-19 patients</td>
<td>Erasme Hospital CHR de la Citadelle</td>
</tr>
<tr>
<td>C4611001 (Pfizer) 2020-003905-73 (completed)</td>
<td>Phase 1b, 2-part, double blind, placebo controlled</td>
<td>PF07304814 (antiviral) iv vs placebo</td>
<td>Hospitalized moderate COVID-19 patients</td>
<td>Hôpital Erasme CHU Brugmann Institut Jules Bordet CHU UCL Namur C.H.R. de la Citadelle</td>
</tr>
<tr>
<td>PANAMO 2020-001335-28</td>
<td>adaptive randomized double blind placebo controlled Phase II/III</td>
<td>IFX-1 (immunomodulator: C5a blocker) + SoC vs placebo + SoC</td>
<td>Hospitalized Patients with severe COVID-19 pneumonia</td>
<td>UZA CHU Dinant Godinne UCL Namur Erasme</td>
</tr>
<tr>
<td>DAWN-camostat 2020-005911-27</td>
<td>Randomized double blind controlled trial phase III</td>
<td>camostat mesylate vs placebo</td>
<td>ambulatory COVID-19 patients</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td>COVID-RESCAP 2020-001714-38</td>
<td>Randomized, placebo controlled, double blind, phase II</td>
<td>RESCAP (bovine alkaline phosphatase) vs placebo</td>
<td>Severe COVID-19 patients with acute respiratory insufficiency</td>
<td>Jesssa Ziekenhuis Hasselt / B. Stessels</td>
</tr>
<tr>
<td>SG018 2020-004743-83</td>
<td>Randomized, double-blind, placebo-controlled, phase III</td>
<td>SNG001 (IFN-β1a) vs placebo</td>
<td>Hospitalised moderate COVID-19 patients</td>
<td>CHU Liège – Sart Tilman AZ Groeninge Kortrijk CHR Citadelle Liège CHU Brugmann Brussels</td>
</tr>
<tr>
<td>CV43043 (Roche) 2020-005759-18</td>
<td>Randomized, double-blind, placebo-controlled, phase III</td>
<td>RO7496998 (AT-527) vs placebo</td>
<td>Mild to moderate ambulatory COVID-19 patients</td>
<td>3 primary care physicians in BE (Roche: global.rochegenentechtrials @roche.com)</td>
</tr>
<tr>
<td>HOPECOVID-19 2021-000492-36</td>
<td>Randomized, double-blind, placebo controlled, phase II</td>
<td>Lactavir vs placebo</td>
<td>Ambulatory COVID-19 patients</td>
<td>UCL</td>
</tr>
<tr>
<td>EXEVIR0101 2020-005299-36</td>
<td>FIH, open label, SAD (part 1) Randomised, double blind, placebo controlled (part 2)</td>
<td>XVR011 (bivalent single domain antibody fragment) vs placebo</td>
<td>Hospitalised mild to moderate COVID-19 patients</td>
<td>UZ Gent CHU de Liège UZ Brussels AZ Sint-Maarten, Mechelen CHU Saint-Pierre</td>
</tr>
<tr>
<td>Trial ID</td>
<td>Design</td>
<td>Status</td>
<td>Sponsor</td>
<td></td>
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</tr>
<tr>
<td>1487-0003 (BI 767551) 2021-000408-309 (prematurely ended)</td>
<td>Phase III randomized, double-blind, placebo-controlled, parallel-group, group-sequential</td>
<td>BI 767551 (antiviral) Vs placebo</td>
<td>Household contacts to a confirmed SARS-CoV-2 infected individual</td>
<td>Boehringer Ingelheim Pharma</td>
</tr>
</tbody>
</table>

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

5.1. Availability of remdesivir

This annex explains how to access remdesivir. However, since version 21 (July 2021), remdesivir is no longer recommended for the treatment of COVID-19 patients.

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 (as stated in art 107/1).

A request for compassionate use can be sent to 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.

If you have problems obtaining the medicinal products in this guideline, please contact supply-problems@fagg-afmps.be

5.2. Safety profiles

Safety profiles can be found at www.BCFI.be (SKPs), www.CBIP.be (RCPs) or via https://geneesmiddelendatabank.fagg-afmps.be/

More information via www.ema.europe.eu (European Medicines Agency)

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
5.3. Eligibility criteria for treatment with monoclonal antibodies*

Screening for criteria 1: Laboratory-confirmed, non-severe COVID-19 infection
- SARS-CoV-2 RT-PCR or antigen positive test
- Mild or moderate COVID-19 disease severity**
- Symptom onset <10 days and SARS-CoV-2 positive test <5 days
- Age ≥12 years old
- Informed consent documented in patient’s medical dossier

If no to any of the following bullet points: not eligible for mAb treatment

If yes to all bullet points, proceed to next step

Screening for criteria 2: Risk factors for severe COVID-19 disease
- Immunocompromised, defined as:
  - Hematological malignancy
  - Solid cancer undergoing treatment
  - Solid organ or hematopoietic stem cell transplantation
  - Primary immune deficiency
  - HIV with CD4 <200/mm³ and/or detectable viral load
  - Prednisolone ≥20mg ≥14 days, or other immunosuppressive drugs: see Superior Health Council list of (potentially) immunosuppressive drugs (link)
  - Sickle-cell anemia
  - Major thalassemia

OR
- At least one comorbidity, defined as:
  - Age ≥65 years old
  - Obesity with BMI ≥30 kg/m²
  - Cardiovascular disease, including uncontrolled hypertension
  - Chronic lung disease, including asthma
  - Type 1 or type 2 diabetes mellitus
  - Chronic kidney disease (eGFR <30 ml/min), including hemodialysis
  - Chronic liver disease (Child Pugh B or C)
  - Chronic neurological disease

If patient has no listed comorbidity: not eligible for mAb treatment

If patient has a risk factor (immunosuppression or ≥1 comorbidity), proceed to next step

**Monoclonal antibodies
- Bamlanivimab + etesivimab
- Casirivimab + imdevimab
- Regdanvimab
- Sotrovimab

Bamlanivimab monotherapy is not recommended due to documented resistance to B.1.617 and B.1.617.2 variants

**Disease severity
Mild: symptoms of COVID-19 without lower respiratory tract involvement such as dyspnea or abnormal chest imaging
Moderate: clinical or radiological evidence of lower respiratory tract disease and SpO₂ ≥ 94% (or no supplemental oxygen required for patients with chronic hypoxia)
Severe: ≥1 of the following:
- Respiratory rate ≥30/min;
  ≥40/min (children < 5y)
- Blood oxygen saturation ≤93% or need supplemental oxygen
- PaO₂/FiO₂ ratio <300
- Lung infiltrates >50% of the lung field within 24-48 hours

If patient has no listed comorbidity: not eligible for mAb treatment
Immunocompromised patient:
- Patient is eligible for treatment with mAbs regardless of SARS-CoV-2 serology.
- Refer quickly to a multidisciplinary expert panel for approval to start treatment

Patient with at least one comorbidity but not immunocompromised:
- Test SARS-CoV-2 spike protein IgG serology
- If IgG seropositive:
  Not eligible for treatment with mAbs
- If IgG seronegative:
  Patient is eligible for treatment with mAbs
  Refer quickly to a multidisciplinary expert panel for approval to start treatment
5.4. REGEN-COV order form

Imbedded in this document is the REGEN-COV order form. This form can be filled in and sent to strategicstock@medista.be to order stock from Medista.
6. References


45 Gottlieb RL, Nirula A, Chen P. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19 A Randomized Clinical Trial. *NEJM* Published Online First: 21 January 2021. doi:10.1001/jama.2021.0202


