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

December 2021; Version 25bis

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 guideline 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 comments, relevant publications, including from the grey literature, and contributions 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.

The following version of this guideline will provide a clear distinction between care in the ambulatory and hospital setting.
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.

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 rapid feedback on safety issues and patient outcomes.

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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>
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<tr>
<td>□ Mild-to-moderate symptoms</td>
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<td>□ No risk group</td>
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<tr>
<td>Confirmed mild or moderate 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>
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<tr>
<td>□ Mild disease: symptoms of COVID-19 without lower respiratory tract involvement such as dyspnea or abnormal chest imaging</td>
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<tr>
<td>□ Moderate disease: clinical or radiological evidence of lower respiratory tract disease and SpO2 ≥94% or does not require supplemental oxygen</td>
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<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. Combination of dexamethasone and remdesivir is no longer to be considered in patients, even those rapidly progressing with &lt; 5 days of symptoms.</td>
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<tr>
<td>≥ 1 of the following:</td>
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<tr>
<td>□ Respiratory rate ≥30/min (adults); ≥40/min (children &lt; 5y)</td>
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<td>□ Blood oxygen saturation ≤93% or requires supplemental oxygen</td>
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<tr>
<td>□ PaO2/FiO2 ratio &lt;300</td>
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<tr>
<td>□ Lung infiltrates &gt;50% of the lung field within 24-48 hours</td>
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<tr>
<td>Tocilizumab and other interleukin-6 blockers: early administration of IL6-receptor antagonists (tocilizumab: 8 mg/kg IV with a maximum of 800 mg, to be repeated one single time with at least an 8 hours interval, if patient continues to progress to further respiratory insufficiency) in addition to corticosteroids in hospitalized patients with rapidly progressive COVID-19 (Strong recommendation, moderate quality of evidence-1B), as long as there is availability of the drug (after prioritizing the drug for patients with cytokine release syndrome caused by chimeric antigen receptors T-cell medicines, giant cell arteritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, and severe rheumatoid arthritis).</td>
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<tr>
<td>Clinical category</td>
<td>Supportive Care</td>
<td>Additional therapy</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
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<tr>
<td>Confirmed COVID-19 critically ill disease</td>
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<td><strong>Dexamethasone</strong> 6 mg IV (or equivalent doses of corticosteroids, see row above) once a day for up to 10 days; case by case decision for children and pregnant women pending additional results and with the respective specialists (Strong recommendation, high-quality evidence - 1A).</td>
</tr>
<tr>
<td>≥ 1 of the following:</td>
<td></td>
<td><strong>Early administration of IL6-receptor antagonists in addition to corticosteroids in hospitalized patients with rapidly progressive COVID-19. 8 mg/kg IV with a maximum of 800 mg, to be repeated one single time with at least an 8 hours interval, if patient continues to progress to further respiratory insufficiency. (Strong recommendation, moderate quality of evidence-1B), as long as there is availability of the drug (after prioritizing the drug for patients with cytokine release syndrome caused by chimeric antigen receptors T-cell medicines, giant cell arteritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, and severe rheumatoid arthritis).</strong></td>
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<tr>
<td>- Acute Respiratory Distress Syndrome</td>
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<td>- Sepsis</td>
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<td>- Altered consciousness</td>
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<tr>
<td>- Multi-organ failure</td>
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</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 infections. 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). **Preliminary data based on in-vitro analyses on the Omicron variant using pseudoviruses shows resistance to both bamlanivimab + etesevimab and casirivimab+imdevimab, and reduced efficacy to tixagevimab+cilgavimab and sotrovimab** [link].
  - 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 be 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 on dialysis) or for geriatric patients.
  - 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.

**Tociluzimab and Anakinra**: 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) may be used to monitor surinfections in patients treated with IL-6 or 1 blockers.

**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://rdvcu.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 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 this study, 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 sub-group analysis, dexamethasone was associated with a reduction in 28-day mortality among those with symptoms for more than 7 days but not among those with more recent symptom onset (12.3 by chi-square test for trend). Based on this survival benefit in the sickest patients, the manageable toxicity of low-dose/short-course dexamethasone in hospitals and the strong biological plausibility of an anti-inflammatory treatment in the second phase of COVID-19 infection, the Belgian Clinical Treatment Guidelines task force has recommended since 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 patient inclusion prematurely 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 meta-analyzed 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].

A living Cochrane Systematic Review and Meta-Analysis on the use of systemic corticosteroids in COVID-19 thus far included 11 RCTs in 8075 participants but restricted outcome analysis to 9 RCTs (up to date until April 2021). The main conclusions were that systemic corticosteroids plus standard care as compared to standard care alone probably reduced all-cause mortality slightly (risk ratio 0.89 (CI 0.80-1.00) and may increase ventilator-free days (mean difference 2.6d , CI 0.7-4.5) [13]. Importantly, 42 ongoing studies and 16 studies reported completed or terminated without yet published results were identified, suggesting that effect estimates and certainty of the evidence may change in the future.

**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 [14]. 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 estimates showed a reduced mortality in the corticosteroid-treated patients (OR 0.72; 0.57-87), 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 [15].

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; 0.60-133) [16]. 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) [17].

Effects of low-dose and short-course corticosteroids on risk of *Strongyloides* reactivation are not well known. Nevertheless, for high-risk patients, such as those originating from *Strongyloides* endemic areas, empirical ivermectin treatment should be considered before, or early during, corticosteroid treatment [18].
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 [19]. 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%). The 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 evaluating 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 from 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 comorbidities. Few serious adverse events were reported, and there was no observed difference between the budesonide group and the usual care group [20].

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 advice dated on 27/5/2021, the EMA considered the evidence published thus far as insufficient to recommend the use of inhaled corticosteroids in COVID-19, as the possibility of causing harm to patients not requiring additional oxygen, cannot as yet be excluded (link).

2.2. REMDESIVIR

Main message: The WHO issued a conditional recommendation against the use of remdesivir (RDV) 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 RDV on clinical outcomes.

Available evidence: RDV seemed promising in vitro and in non-human primate models [21]. An initial Chinese trial did not show any survival benefit with RDV, but the study could not include enough cases and was discontinued at the end of the local epidemic [22]. 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 [23] confirming a faster recovery in RDZ-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 RDZ 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 RDZ 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 endpoints: 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 RDZ treatment. Further evaluation of this subgroup and other high-risk groups, such as immunocompromised persons, is needed to determine the shortest effective duration of therapy in these patients [24].

A third RCT sponsored by Gilead (Spinner et al.) assessed the role of RDZ in hospitalized patients with non-severe COVID-19 (not requiring oxygen supplementation) [25]. 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 RDZ (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 [22].

In December 2020, results from the SOLIDARITY multicenter worldwide pragmatic trial were published, showing no overall clinical benefit of RDZ in hospitalized patients with COVID-19. RDZ was evaluated in 2743 patients, compared to 2708 controls. In a meta-analysis of the 4 published trials on RDZ, a weighted average of the results from all trials yielded a rate ratio for death (RDZ 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) [26]. The WHO issued a conditional recommendation against the use of RDZ in hospitalized patients, regardless of the severity, as there was no evidence that RDZ improved survival and other outcomes in these patients. Nevertheless, WHO continued to endorse including patients in trials with RDZ to establish with certainty whether RDZ had a positive effect on survival in mild to moderate, hospitalized COVID-19 patients. The Solidarity trial and its’ European sister trial, DisCoVeRy continued to randomize mild to moderate hospitalized COVID-19 patients to receive RDZ vs. standard of care until the 27th and 29th of January 2021, respectively. Inclusions into the RDZ arm were stopped due to futility in severe, but also mild to moderate, hospitalized COVID-19 patients. The results of the DisCoVeRy trial, with 857 inclusions, were recently published; no significant effect on viral kinetics, clinical progression or outcome was observed in RDZ treated patients compared to those treated with standard of care [27]. In addition, EMA evaluated the full mortality and viral data from NIAID ACTT-1 data upon which EMA recommended to not start RDZ in COVID-19 patients already on mechanical ventilation and on ECMO. This guidance, that already considers RDZ 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 RDZ vs.
control has also shown the modest effect of RDZ in hospitalized patients. Patients in the RDZ 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 [28]. A recently published retrospective, multicenter study published by Gilead, based on the US Premier inpatient database in which 28,855 RDZ-treated patients (within first 48-hours of hospitalization) were matched with 16,687 patients who did not receive RDZ during their hospitalization, showed a statistically significant reduction in mortality by day 14 and day 28 in the overall population and in most baseline oxygen subgroups, except for those who needed high-flow oxygen at baseline [29]. Still another meta-analysis on individual patient data from the 5 big randomized, controlled trials on RDZ is currently being performed.

Although it appeared there was not much place for RDZ in the therapeutic arsenal against COVID-19, unpublished results from the PINETREE trial, a double-blinded, placebo-controlled study just reported an 87% risk reduction for hospitalization or death by a 3-days course of IV remdesivir compared with placebo in 563 non-hospitalized patients at high-risk for disease progression (Hill JA, Paredes Deiros R, Vaca C, et al. Remdesivir for the Treatment of High-Risk Non-Hospitalized Individuals With COVID-19: A Randomized, Double-Blind, Placebo-Controlled Trial. IDWeek 2021 Virtual Conference, Sep 29 – Oct 3, 2021: Oral LB1). These results support the use of antiviral treatments very early on in the course of the disease.

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 patients [30,31]. Potential adverse events, immunosuppression and drug interactions have to be carefully taken into consideration when 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) [32,33], 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 [34–36]. 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 [37]. 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 [37,38]. 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 [38]. 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[39].
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 (mechanical ventilation and ECMO) COVID-19 who have elevated markers of systemic inflammation [40]. 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.

The recommended dosage of tocilizumab is 8mg/kg IV with a maximum dose of 800mg. This dose may be repeated one single time if the patient continues to progress to further respiratory insufficiency, with at least an 8-hours interval after administration of the first dose.

The product RoActemra (tocilizumab) has just been approved on the 17th of December, 2021 for treatment of hospitalised adult patients with severe COVID-19 who are already receiving treatment with corticosteroids and require extra oxygen or mechanical ventilation (link). However, it must be mentioned that there are currently significant drug shortages of this drug, and there are patients who depend on this drug for other indications than COVID-19. It is in this light that the drug must be prioritized. It is recommended to give priority to patients to receive this drug in the following order: patients with cytokine release syndrome caused by chimeric antigen receptors T-cell medicines, giant cell arteritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, and severe rheumatoid arthritis).

A recent double-blinded, RCT study in 1060 patients hospitalized for COVID-19, included across 37 sites in Italy and Greece, also showed a clear outcome benefit in patients with a concentration of soluble urokinase plasminogen activator receptor (suPAR) ≥ 6ng/mL who received anakinra (100 mg QD sub-cutaneously for 7-10 days) compared to those who received standard of care + placebo. 50.4% (204/405) of patients receiving anakinra had fully recovered with no viral RNA detected on day 28 compared to 26.5% (50/189) of patients receiving placebo, and 3.2% (13/405) and 6.9% (13/189) of patients in the anakinra and placebo arms, respectively, died. Therefore, the unadjusted proportional odds of having a worse score on the 11-point WHO-CPS at day 28 with anakinra was 0.36 versus placebo (95% confidence interval (CI) 0.26–0.49, P < 0.0001). Because suPAR measurement is not widely available in the routine laboratory setting, the authors performed a post-hoc analysis to identify other tools to identify patients who might benefit from anakinra treatment. They found that predictors of favorable responses to anakinra are a combination of at least two measures of CRP > 50 mg/L, neutrophil-to-lymphocyte ratio (NLR) > 5.5, ferritin > 700 ng/ml and aspartate aminotransferase (AST) > 44 U/L [41]. Nevertheless, this prediction score remains to be validated in a prospective study.

Kineret (anakinra) has also just been approved on the 16th of December, 2021 for treatment of COVID-19 in adult hospitalized patients with pneumonia who are at risk of developing severe respiratory failure, and who have a measured plasma concentration of suPAR ≥ 6ng/ml (link). Currently, the measurement of suPAR cannot be carried out in a routine fashion in Belgian laboratories.

**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) may be used to monitor surinfections in patients treated with IL-6-blockers.

2.4. MONOCLONAL ANTIBODIES

Main message: Treatment with monoclonal antibodies (mAbs) has consistently demonstrated clinical benefit (reduction of hospital admissions and deaths) provided they are administered within 7-10 days after symptom onset to COVID-19 (out)patients at risk for severe disease progression. A set of criteria and conditions were elaborated in the previous version of the guideline to define patients eligible for this treatment (see ministerial decree).

However, at this moment and still in the near future, available stocks of mAbs in Belgium are extremely limited, while many vulnerable patients can be considered as eligible for this treatment. It is also important to stress that very early administration of this treatment might be extremely challenging in the current situation because it requires appropriate hospital infrastructure and excellent collaboration with primary care for timely appropriate referral.

In order to help clinicians with the difficult selection of patients for whom this intervention would be most beneficial, the working group considers that immunosuppressed patients should get the highest priority for the moment (including patients with end-stage kidney or liver disease). For all other eligible patients, two (quite similar) scoring systems in use in the US (Mayo Clinic [42] and Utah [link]) are provided here below (Annex 5.4); they give some weighted ponderations to the risk factors for adverse outcome. Even if these scores are not entirely evidence-based and have only been internally validated, the working group suggests prioritizing mAb administration to those (out)patients with the highest scores, that reflect in fact cumulative co-morbidities. No rigid cut-off can be however provided for the time being. The cut-off to be used will depend upon availability of mAbs. Of note, mAbs could also be considered as salvage therapy among (hospitalized) patients with persistent viral shedding due to an immunocompromised condition, although this very situation has been poorly studied so far [43]. Careful monitoring of the viral evolution would be key here.

- 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.
- Please consult the scoring system in Annex 5.4 to assess how to prioritize mAbs, when availability is limited.
- 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-Ronapreve) / sotrovimab (Xevudy) can be ordered by the hospital pharmacy using the form available in Annex 5.5.

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 biotherapy
- **Omicron variant**: preliminary data suggest resistance to both bamlanivimab + etesevimab, and casirivimab+imdevimab, and reduced activity to tixagevimab+cilgavimab and sotrovimab (link). These data will need to be confirmed by publications.

Information on genomic SARS-CoV-2 surveillance in Belgium is available via the National Reference Laboratory¹ and Sciensano’s weekly epidemiological report.²

**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 [44]. Given the long half-life, a single injection (mostly intravenous, or occasionally subcutaneous) is generally used [45].

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 at high risk of clinical deterioration, on the condition that these therapeutics are administered early after infection onset and preferentially among patients with a high predictive score of progression to a severe disease.

**Intrinsic resistance to monoclonal antibodies should also be considered.** Within Belgium, the B.1.617.2 (Delta) variant is dominant since August 2021 (link), but B.1.1.529 (Omicron) is increasing since the beginning of December and is expected to become the dominant circulating lineage in the coming weeks (link). Preliminary data for Omicron suggest resistance to bamlanivimab+etesevimab, and casirivimab+imdevimab and reduced efficacy for tixagevimab+cilgavimab and sotrovimab (link). These data will need to be confirmed by publications.

These mAbs have been less studied 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.

The Cochrane review on the efficacy of neutralising monoclonal antibodies for COVID-19 infection concluded that the certainty in the evidence for all non-hospitalised people is low, and for hospitalised people is very low to moderate, and that this current evidence is insufficient to currently draw any meaningful conclusions regarding treatment with SARS-CoV-2 neutralising mAbs [46].

### 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 [47]. For hospitalized patients with more advanced disease (trial conducted by the ACTIV-3/TICO LY-CoV555 Study Group),

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¹ Genomic Surveillance of SARS-CoV-2 in Belgium

² COVID-19 Weekly Epidemiological Report, chapter 3.4 Molecular surveillance:
bamlanivimab (co-administered with remdesivir) did not demonstrate any clinical benefit [48]. 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 [49,50]. 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 [51]. In the RCT, phase 3, BLAZE-1 trial, including 1035 outpatients with mild or moderate COVID-19, at high risk for progressing to severe COVID-19 (including 6.4% of immunosuppressed patients) 2.1% patients in the bamlanivimab 2800 mg + etesevimab 2800 mg group had a hospitalization or died by Day 29 versus 7.0% in the placebo group (relative risk difference, 70%; P<0.001, NNT=20.4) [52]. No deaths occurred in the bamlanivimab–etesevimab group compared to 10 deaths in the placebo group. 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).

On the 2nd of November 2021, EMA ended the rolling review of bamlanivimab and etesevimab after Eli Lilly decided to withdraw from the process.

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

Ronapreve (REGEN-COV, REGN-CoV2 or REGN-CoV2) consists of two antibodies that bind to different regions of the SARS-CoV-2 spike protein receptor.

**Treatment of mild or moderate COVID-19 outpatients:**

In an interim analysis of a phase 2-3 trial studying the effect of a combination regimen of casirivimab and imdevimab (NCT04425629) in 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 [53]. However, the impact on clinical outcomes (medically attended visit) were less clear.

In 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; p<0.001[18/1355, 1.3% vs 62/1341, 4.6%, NNT 30.3], and 70.4%; p=0.002 [7/736, 1.0% vs 24/748, 3.2%, NNT=45.45]) [48]. Efficacy of REGEN-COV (hospitalization or death, resolution of symptoms and viral load reduction) was consistent across subgroups, including patients that were SARS-CoV-2 seropositive at baseline. Based on that study, [54], 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) and since the 12th of November by the EMA (link). Subcutaneous injection can be given when IV administration is not feasible or would lead to treatment delay (link).
**Post-exposure prophylaxis:**
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 to 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%) [55].

In Part B of the same study (available as a preprint), which compared REGEN-COV SC to placebo for preventing the progression of early SARS-CoV-2 infection in asymptomatic close contacts (PCR SARS-CoV-2 positive, primary analysis focused on seronegative participants), a 31.5% relative risk reduction of developing symptomatic infection in the REGN-COV group (29/100 [29.0%] vs 44/104 [42.3%]; p=.038), was observed.

**Treatment of hospitalized patients with severe COVID-19**
In the RECOVERY, RCT, open-label trial, published in a pre-print, REGEN-COV (casirivimab 4g and imdevimab 4g, IV) plus standard of care (including corticosteroids) 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 with severe COVID-19, should only be used in SARS-CoV-2 seronegative patients [56]. This is the first study to have shown efficacy of mAbs in hospitalized patients with COVID-19.

A preprint retrospective study including 85 US patients with immunodeficiency-associated antibody disorders (8.1% primary deficiencies and 91.9% secondary acquired, mostly rituximab or hemopathies), showed that REGEN-COV was associated with rapid viral clearance and clinical improvement among 37 patients with symptoms ≥21 days [43].

On the 12th of November 2021, the EMA gave a marketing authorisation for Ronapreve (casirivimab / imdevimab) to prevent and treat COVID-19 (within 7 days of symptom onset) in adults and adolescents as of age 12, ≥40 kg, who do not require supplemental oxygen and are at increased risk for progressing to severe COVID-19. The dosage regimen for treatment and post-exposure prophylaxis is a single 600+600mg iv infusion or sc injection. For pre-exposure prophylaxis, dosage regimen is initially a 600+600mg infusion/injection followed by 300+300mg infusion/injection every 4 weeks (no data on repeat dosing beyond 24w).

**2.4.5. Regdanvimab**
A phase 2-3 trial of 325 adult outpatients with COVID-19 (study CT-P59, unpublished) showed a smaller 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).

On the 12th of November 2021, EMA gave a marketing authorisation for Regkirona (regdanvimab, CT-P59) for treating adult patients with COVID-19 who do not require supplemental oxygen and are at increased risk for progression to severe COVID-19. The posology is one single iv infusion 40mg/kg.
A main study involving 1,315 patients with COVID-19 showed that Regkirona led to fewer patients requiring hospitalisation or oxygen therapy, or death, when compared with placebo. Among the patients at increased risk of developing severe illness, 3.1% of patients treated with Regkirona (14 out 446) were hospitalised, required supplemental oxygen or died within 28 days of treatment compared with 11.1% of patients on placebo (48 out of 434). The majority of patients in the study were infected with the original SARS-CoV-2 virus or the Alpha variant; data on the efficacy of Regkirona against new circulating SARS-CoV-2 variants is currently limited.

A present, there is no availability of this product in Belgium.

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 risk 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 vs. placebo (1% vs 7%, NNT:16.6) [57]. Preprint of the final trial confirmed the interim analysis with a 79% (95% CI, 50% to 91%; p<.001) relative reduction of hospitalization or death in the sotrovimab group (6/528 [1%]) vs placebo (30/529 [6%], NNT 20).

On the 16th of December 2021, the EMA issued a positive opinion on Xevudy, thus resulting in a grant for marketing authorization for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age of weighing at least 40 kg) (link).

2.4.7. Tixagevimab and cilgavimab (AZD7442)

AZD7442 is a combination of two fully human, long-acting SARS-CoV-2-neutralizing antibodies, AZD8895 (tixagevimab) and AZD1061 (cilgavimab). The half-life extension more than triples the durability of its action compared to conventional mAbs [58].

AstraZeneca, through a press release, has communicated the results of the PROVENT trial (NCT04625725) (link) and the TACKLE trial (NCT04723394) (link).

The PROVENT Phase III pre-exposure prophylaxis trial showed that AZD7442 (300mg administered intramuscularly -IM) in unvaccinated and seronegative adult patients who were expected to have an inadequate response to SARS-Co-V2 vaccination achieved a statistically significant reduction in the incidence of symptomatic COVID-19.

The TACKLE Phase III trial, evaluated the AZD7442 600mg (IM) in non-hospitalised patients (of which 90% were of high risk for severe COVID-19) with mild-to-moderate symptomatic COVID-19. The results showed a statistically significant reduction in severe COVID-19 or deaths compared to placebo.

The EMA started the rolling review of Evusheld (tixagevimab and cilgavimab) on 14 October 2021.

PROVENT trial: PROVENT
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. Since mid November, 2021, sotrovimab is available in Belgian hospitals for outpatient treatments. The use of these mAbs is subject to specific conditions, described by the ministerial decree in the Moniteur Belge/Belgisch Staatsblad (link, AR SOTROVIMAB).

The algorithm for treatment with mAbs (Annex 5.3) is based on published literature (mostly of low quality 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 RCT 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 or Sotrovimab Rapport de suivi mensuel / Maandelijk opvolgingrapport » should be sent to FAGG (umn@fagg.afmps.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 the 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 response 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 [59]. Several observational studies, non-controlled and
controlled non-randomized trials, RCT’s, and part of several meta-analyses and living reviews have been published [60][61]. Several observational studies show survival benefit of transfusing COVID-19 convalescent plasma (CPP) with high antibody titers [62]. In contrast, RCT’s could not demonstrate a benefit on mortality of CPP in hospitalized patients with COVID-19, among which the RECOVERY trial is the largest one published until now [63][64][65][66]. 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 [67]. The REMAP-CAP study, carried out in critically ill patients also halted recruitment in the convalescent arm due to futility. Until now, the data have not yet been published. A Cochrane review including some unpublished data (including those from the RECOVERY trial at that time), and a meta-analysis performed by the RECOVERY group, did not find a difference in mortality between convalescent plasma and usual care [61,67] [68–71].

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 [72]. 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 previewed inclusion number. On the other hand, the NIH trial C3PO evaluating convalescent plasma compared to standard of care for treatment of early-onset (<7 days), non-hospitalized COVID-19 patients (≥50 years old or with a risk factor) was halted after interim analysis of 511 participants (of the 900 planned) found no difference in disease progression between the two groups [73]. More results from RCT’s evaluating early administration of CPP are still expected.

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. 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. The 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 [74] and other case series [75]. The volume and antibody titer used in different reports varies [76].

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 [77]. 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 [78,79].
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 RDZ alone [80]. Corticosteroids were not considered standard of care in this study, so the comparison of baricitinib versus baricitinib in association with corticoids was not evaluated. Prices of baricitinib and RDZ 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 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 (hazard ratio [HR] 0·57 [95% CI 0·41–0·78]; nominal p=0·0018) and day 60 (HR 0·62 [95% CI 0·47–0·83]; p=0·0050) [81]. In an addendum cohort of critically ill patients (baseline IMV/ECM, with 86% corticosteroid treated), the COV-BARRIER study demonstrated (preprint) a reduction in 28-day all-cause mortality compared to placebo (39·2% vs 58·0%; hazard ratio [HR]=0·54 [95%CI 0·31–0·96]; p=0·030). This reduction persisted through day 60 (mortality 45·1% vs 62·0%; HR=0·56 [95%CI 0·33–0·97]; p=0·027) [82]. According to a press release (Feb 2021: link), baricitinib is being 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 RCT 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 infections associated with the use of tofacitinib [83].

2.6.3. Ruxolitinib

Only preliminary data are available for ruxolitinib;the data is not sufficient to support its use outside of studies [84].
2.7. INTERFERON

Main message: Interferons (IFN) have antiviral effects and modulate the immune response [85]. 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 [86]. Only 52 patients starting therapy <7d of symptom onset received at least one dose of interferon, as by study protocol. They found a shortened viral shedding and faster clinical improvement in the IFN-containing arm. Another RCT evaluated IFN ß-1b with or without standard of care including hydroxychloroquine plus lopinavir/ritonavir or atazanavir/ritonavir (both groups n=33). They found a faster clinical improvement, in primary outcome; and a decreased ICU admission, although the study was probably underpowered for this [87]. The same group also evaluated IFN ß-1a in addition to the same standard of care (n=42) vs standard of care alone (n=39), and could not find any difference in clinical response [88]. 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 ß-1a given with or without lopinavir/ritonavir, respectively 1412 and 651 patients, did not provide any survival benefit vs control in hospitalized patients (HR 1.16 (0.96-1.39)) [26]. The results of the DisCoVeRy trial have been published, including a lopinavir/ritonavir interferon ß-1a arm [89]. 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 ß-1a, in addition to SOC including lopinavir/ritonavir, in severe COVID-19 and could not find a clinical benefit [88,90,91]. A recent indian multicenter open label RCT evaluated a single dose of Pegylated interferon α2b in moderate COVID-19 with only modest clinical improvement and viral clearance [92].

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 [93,94]. A few studies have looked at IFN administration by spray or atomization, to improve local effects and avoid systemic adverse reactions [95,96].

At this moment one small, underpowered RCT looked at the effect of combination of inhaled interferon ß-1b and Favipiravir vs standard of care with hydroxychloroquine in severe COVID-19, finding no effect [97]. Another pilot double-blind placebo RCT found that hospitalized COVID-19 patients treated with 14 days of nebulized interferon ß-1a had a greater odds for clinical improvement [98]. 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 (HCQ) 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 [99].

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 RCT RECOVERY in UK 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 the 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 shown 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 [100]. Another smaller RCT in Brazil conducted in mild-to-moderate hospitalized patients did not find any improvement in the clinical status (seven-level ordinal scale) of participants who received HCQ (total dosage: 5600 mg), alone or with azithromycin (500 mg/day for 7 days) [101].

The role of hydroxychloroquine as post-exposure prophylaxis or as early treatment for mild COVID-19 disease was also assessed through additional RCTs, yet no clinical benefit was found. 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 infections 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 [102]. Here again, many participants (about 40%) were not tested for SARS-CoV2 infection. 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 [103]. 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 [104].

2.9. LOPINAVIR/RITONAVIR

Main message: Due to lack of evidence for clinical benefit in the SOLIDARITY, RECOVERY 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 [105]. Another small RCT conducted in China did not show any viral or clinical benefit either (or at best very marginal) [105]. 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 23rd of 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 [106]. 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) [107]. Results from ongoing clinical trials are 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 [108]. The half-life is approximately 5 hours. Therefore, higher dosing ranges are considered necessary 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) [109]. An antiviral effect has been observed in animal models (hamsters) at high dosage [110]. This observation has been confirmed in another experiment in Syrian hamsters [111]. The combination of favipiravir with molnupiravir (see below) demonstrated a synergistic benefit in the hamster infection model [112].

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 [113].

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 [114]. Another small RCT in India in mild/moderate patients did not find any significant effect on the duration of viral shedding compared to placebo (but a slight reduction in time to clinical cure) [115]. A multicentric RCT in Iran did not show any clinical benefit in hospitalized COVID-19 patients treated with favipiravir when compared to LPV/r [116]. Also, early administration of favipiravir (1800 mg BID D1 and 800 mg BID till D5) was not associated with any clinical benefit in a large RCT (n=500) among high-risk mild/moderate Malaysian patients [117]. Large trials are still ongoing.

2.11. MOLNUPIRAVIR

Main message: Very preliminary studies suggest that this new antiviral drug could be beneficial in early treatment of COVID-19, but no data from RCTs have yet been published.

Available evidence: Molnupiravir is a ribonucleoside analogue with broad antiviral activity including against SARS-CoV-2 in different animal models (ferret, guinea pigs and mouse models) both as prophylaxis and treatment. 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 concluded (stopped before finishing recruitment, based on the recommendation of the independent Data Monitoring Committee, and in consultation with the U.S. Food and Drug Administration (FDA), due to positive results observed at the interim analysis) in which orally administered 800 mg molnupiravir bd vs placebo was given to non-hospitalized patients at risk of severe
disease progression within 5 days of symptom onset (MOVe-OUT trial: NCT04575597). Updated results of the trial showed only a 30% relative risk reduction of hospitalisation and death through 30 days since treatment initiation among 1433 participants. There were 9 deaths in the placebo group and 1 in the group that received molnupiravir. Furthermore, in the pre-specified sub-group of patients with SARS-CoV2 nucleocapsid antibodies, low viral load, those with diabetes at baseline, several ethnic minorities such as Black, Asian and Native American, and patients enrolled in the Asia-Pacific region showed no positive effect with Molnupiravir treatment, possibly due to small sample sizes [118]. Theoretical concerns about long-term mutagenicity, increased risk of inducing SARS-COV-2 variants need to be addressed.

Since the 23rd of November, Lagevrio (molnupiravir) is under evaluation for marketing authorization at EMA. EMA will assess the benefits and risks of Lagevrio in a reduced timeline and could issue an opinion within weeks if the data submitted are sufficiently robust and complete to show the efficacy, safety and quality of the drug.

Of note, the Phase 3 trial (MOVE-IN) for hospitalized patients was not initiated for possible futility.

2.12. PF-07321332/RITONAVIR (PAXLOVID)

PF-07321332 is a SARS-CoV-2 protease inhibitor, which blocks the activity of the SARS-CoV-2-3CL protease (Mpro) and has in-vitro pan-human coronavirus activity [119]. Co-administration with ritonavir slows the metabolism of PF-07321332. In a preprint animal study, in Syrian Golden hamsters, PF-332 (PF-07321332) protected against infection with the beta (B.1.351) and delta (B.1.617.2) SARS-CoV-2 variants [120].

On 5 November, Pfizer announced via a press release the interim results of the Phase 2/3 RCT EPIC-HR (NCT04960202), that showed an 89% reduction in risk of hospitalization or death in (unvaccinated) high-risk outpatients treated within three days of symptom onset with PF-07321332/ritonavir vs placebo (3/389, 0.8%; no deaths vs 27/385, 7%; 7 deaths, p<0.0001).

The product is currently (since the 19th of November, 2021) subject of an art 5.3 scientific review at EMA. EMA is starting this review to support national authorities who may decide on its early use for COVID-19, for example in emergency use settings, prior to marketing authorisation.

2.13. CAMOSTAT MESYLATE

Main message: There is no published evidence for 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 a repurposed drug after it has shown to reduce SARS-CoV-2 infection of primary human lung cells (Calu-3 cell line) in-vitro [121]. 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 is safe, but it had no viral nor clinical added benefit compared to standard of care [122].

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.

2.14. FLUVOXAMINE

Main message: Two independent RCTs (one large and one small) and two observational studies have shown that fluvoxamine early treatment is associated with prevention of clinical deterioration in outpatient, at-risk subjects [123,124]. The effect on robust clinical endpoints such as hospitalizations or deaths is not fully established, and it is unclear whether it could be beneficial in a fully vaccinated population (with lower baseline risk of complications). For the moment, no strong recommendation can be made for early administration of fluvoxamine or similar drugs in high-risk outpatients.

Fluvoxamine is a SSRI antidepressant drug but also a strong S1R agonist associated with reduction of inflammation during sepsis. It also has possible anti-platelet activation properties [125].

A small pilot placebo-controlled trial (n= 80 and n=72 subjects in the fluvoxamine and placebo groups respectively) found a significant difference in the rate of clinical deterioration (0% vs 8%; p=0.009). Dosage used in this pilot trial was 50 mg day 1, then 100 mg BID for 2 days then 100 mg TID until day 15) [126]. A larger placebo-controlled trial (TOGETHER) in Brazil (n= 741 and n= 756 in the fluvoxamine and placebo groups, respectively, the vast majority of participants not being vaccinated) found a significant decrease of a composite primary outcome event (hospitalization OR stay > 6h in the emergency room) (10.7% vs 15.7%). In secondary analysis, mortality was also decreased in the per-protocol fluvoxamine group vs placebo (1 vs 12 deaths), but the difference was not significant in the intent-to-treat population. Dose used was 100 mg BID for 10 days [127].

2.15. AZITHROMYCIN

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

Azithromycin, shown to have some antiviral and immunomodulatory effect, has been promoted by some groups based on observational viral and clinical data [128]. 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 [101] and severe hospitalized patients [18], 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 [129]. The results of DAWN-AZITHRO are also expected soon (Table 3).
2.16. 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 cells9 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) [130].

Until now, 18 (10 double-blinded) RCTs studying the effect of ivermectin at different dosages on viral clearance, prevention, clinical recovery and survival have been published in peer-reviewed journals [131–145]. All but two 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 [142]. 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 five (two of which non-blinded) RCTs demonstrating significantly less development of symptoms in asymptomatic patients when treated with a single dose of ivermectin [146], more rapid resolution of anosmia [111], less progression to severe illness [147], and more rapid clinical improvement [142,145,147]. 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 [148]. 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 [149]. Based on the current low to very low evidence, a Cochrane systematic review on ivermectin as treatment or prevention of COVID-19 in in- and outpatients failed to demonstrate its efficacy or safety and does not support its use outside of well-designed RCTs [150]. More robust data and evidence from ongoing clinical trials are expected.

Of note, a recent correspondence in the N Engl J Med warns about the risks of severe ivermectin toxicity (including ataxia, visual disturbances, convulsions,...leading to hospital admission) when misused at high dosages for treatment or prevention of COVID-19 [151].

2.16. 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 RCT (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 [152]. 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) [153]. 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 [154]. For in-hospital patients, evidence remains scarce. A few observational studies using variable drug dosages have been published, suggesting a possible clinical benefit [155]. 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) [156]. 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 [157]. 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 from larger RCTs are published. However, according to the results of an arm of the RECOVERY trial, there was no demonstrated benefit of colchicine in addition to steroids (in terms of mortality at Day 28, duration of hospital stay or progression to mechanical ventilation) in patients hospitalized with COVID-19 [158]. A smaller RCT (n=103) evaluating colchicine in hospital patients reached the same conclusions. These observations strongly suggest that colchicine has no place in patients admitted for severe/critical COVID-19 [159].

2.17. 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. One retrospective study found a decreased risk of mechanical ventilation, ICU admission and in-hospital mortality among patients admitted with COVID-19 [160]. 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.
2.18. 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 [161,162]. An RCT found no impact of ACEi/ARB switch in COVID-19 [163]. The same types 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 [164]. 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) [165]. 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](https://www.health.belgium.be). 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:


**Note – Ambulatory care:**


- **Outpatient care for Covid-19 patients in the context of saturation in Belgian hospitals**


3. Summary of efficacy data of selected antiviral drugs

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>
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<tbody>
<tr>
<td><strong>Bamlanivimab</strong></td>
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<td>Eli Lilly and Company</td>
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<tr>
<td>Monotherapy (IV)</td>
<td>BLAZE-1 phase 2</td>
<td>Mild to moderate COVID-19, outpatients</td>
<td>Statistically reducing of VL on Day 11 for Ly CoV555 at 2800 mg dose (-0.53 log, p=0.02)</td>
<td>NA</td>
<td>No</td>
<td>No</td>
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<td>NCT04427501</td>
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<td>CHMP review 05/03/21 for IV use</td>
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<tr>
<td>Combined with Remdesivir (IV)</td>
<td>ACTIV-3/TICO</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>Delta variant resistant to bamlanivimab monotherapy (link)</td>
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<td>NCT04501978 [48]</td>
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<td><strong>Bamlanivimab + Etesevimab</strong></td>
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<tr>
<td>Combination therapy (IV)</td>
<td>BLAZE-1 phase 3</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>
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<td>NCT04427501</td>
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<td>CHMP review 05/03/21 for IV use</td>
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<tr>
<td></td>
<td>BLAZE-1 phase 3</td>
<td>Mild to moderate COVID-19, outpatients in high-risk groups</td>
<td>Statistically reduction of hospitalization or death by Day 29 for bamlanivimab 2800 mg + etesevimab 2800 mg group vs placebo Day (relative risk difference, 70%; P&lt;0.001), NNT=20.4)</td>
<td>NA</td>
<td>Beta and gamma variant resistant to bamlanivimab + etesevimab (link)</td>
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<td></td>
<td>High Risk patients [52]</td>
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<tr>
<td><strong>Casirivimab + imdevimab</strong></td>
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<td>Interim analysis: proportion of MAV in REGN-COV2 group through Day 29 (3% vs 6% in the placebo group) and</td>
<td></td>
<td>No</td>
<td>Since 19 May 2021, via</td>
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<tr>
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<td>Phase 2/3</td>
<td>Mild to moderate COVID-19, outpatients</td>
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<td>Regeneron Pharmaceuticals, Roche, Ronapreve</td>
<td>Phase 3 portion NCT04425629</td>
<td>Mild to moderate COVID-19, high risk outpatients</td>
<td>MAV proportion for baseline seronegative patients (6% vs 15% in the placebo group)</td>
<td>71.3% (2400mg) and 70.4% (1200mg) reduction in hospitalization and all-cause death by day 29</td>
<td>(sero-neg. patients)</td>
<td>45.5</td>
</tr>
<tr>
<td>Combination therapy (SC)</td>
<td>Phase 3 NCT04452318 (SC)</td>
<td>Prevention in household contact positive SARS-CoV-2 (SC)</td>
<td>81.4% risk reduction of a symptomatic infection in the REGEN-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>71.3% (2400mg) and 70.4% (1200mg) reduction in hospitalization and all-cause death by day 29</td>
<td>(sero-neg. patients)</td>
<td>15.9</td>
</tr>
<tr>
<td>Combination therapy (IV)</td>
<td>Phase 3 RECOVERY trial NCT04381936 Preprint [56]</td>
<td>Hospitalised patients</td>
<td>casirivimab 4g and imdevimab 4g, IV + usual care. In seronegative SARS-CoV2, 396 (24%) in the REGEN-COV group and 451 (30%) of usual care died within 28 days (rate ratio 0.80; 95% CI 0.70-0.91; p=0.0010)</td>
<td>81.3% (2400mg) and 70.4% (1200mg) reduction in hospitalization and all-cause death by day 29</td>
<td>(sero-neg. patients)</td>
<td>16.7</td>
</tr>
<tr>
<td>Sotrovimab GlaxoSmithKline and Vir Biotechnology</td>
<td>Monotherapy (IV) Phase 2-3 COMET-ICE NCT04545060 Preprint: [57] REF NEJM</td>
<td>Mild to moderate COVID-19 in high-risk groups</td>
<td>85% of reduction of hospitalization or death through Day 29 (1% vs 7%)</td>
<td>71.3% (2400mg) and 70.4% (1200mg) reduction in hospitalization and all-cause death by day 29</td>
<td>(sero-neg. patients)</td>
<td>16.7</td>
</tr>
<tr>
<td>Combined with bamlanivimab (IV)</td>
<td>BLAZE-4 NCT04634409 Unpublished</td>
<td>Mild to moderate COVID-19</td>
<td>Unpublished</td>
<td>71.3% (2400mg) and 70.4% (1200mg) reduction in hospitalization and all-cause death by day 29</td>
<td>(sero-neg. patients)</td>
<td>16.7</td>
</tr>
</tbody>
</table>
| Regdanvimab | Monotherapy (IV) | Unpublished: [link](#) | Adult with mild to moderate COVID-19 | Proportion of hospitalization, oxygen requirement or death by day 28:  
CT-P59 40 mg/kg: 4.0%  
CT-P59 80mg/kg: 4.9%,  
pooled CT-P59: 4.4%  
vs  
8.7% in the placebo group | 21.3 | No  
CHMP review 26/03/21  
EMA authorization 12/11/21 for treatment in adults | No |

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.
**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 [166]; we try to summarize the relevant information for selected drugs*

<table>
<thead>
<tr>
<th>Drug</th>
<th>In vitro activity</th>
<th>In vivo activity (animal models)</th>
<th>Clinical studies SARS-CoV-2 (non-exhaustive)</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SARS-CoV-1</td>
<td>MERS-CoV</td>
<td>SARS-CoV-2</td>
<td>SARS-CoV-1</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>Used in Japan against influenza</td>
<td>Not studied</td>
<td>Not studied</td>
<td>++ * [99]</td>
</tr>
<tr>
<td>Camostat</td>
<td>Used in Japan for reflux esophagitis and pancreatitis</td>
<td>++ [121]</td>
<td>++ [121]</td>
<td>++ [121]</td>
</tr>
<tr>
<td>Interferons</td>
<td></td>
<td>+ [170]</td>
<td>+ [170]</td>
<td>++ [85,171]</td>
</tr>
</tbody>
</table>

*Note: Many other antiviral/immunological treatments have been/are being investigated, including (list not exhaustive) ribavirin, fabiravir, convalescent plasma, monoclonal antibodies, complement inhibitors etc. see Landscape analysis of therapeutics WHO 17/02/2020, link. At this moment, any of these drug candidates should ONLY be evaluated in clinical trials and in Belgium, these trials should ideally be coordinated centrally.*
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 4: Belgian COVID-19 Clinical Trials

<table>
<thead>
<tr>
<th>PROTOCOL CODE / EudraCT n°</th>
<th>STUDY TYPE</th>
<th>INVESTIGATED PRODUCTS</th>
<th>PATIENT PROFILE</th>
<th>PRINCIPAL INVESTIGATOR/ COORDINATING CENTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>COV-AID 2020-001500-41</td>
<td>Multicentric, randomized, factorial design,</td>
<td>Six arms: Anakinra (anti-IL1), Siltuximab (anti-IL6),</td>
<td>COVID-19 patients with acute hypoxic respiratory</td>
<td>B. Lambrecht / UZ Gent</td>
</tr>
<tr>
<td>(completed)</td>
<td>interventional study</td>
<td>Tocilizumab (anti-IL6) in monotherapy, double or single</td>
<td>failure and systemic cytokine release syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>combinations; standard of care</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>SARPAC 2020-001254-22</td>
<td>Multicentric, randomized, open-label,</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>(completed)</td>
<td>interventional study</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
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</tr>
<tr>
<td>DAWN – azithro 2020-001614-38</td>
<td>Multicentric, randomized, open-label,</td>
<td>2 arms: Azithromycin vs SoC (other arms can be included</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td>(completed)</td>
<td>adaptive, proof-of-concept clinical trial</td>
<td>later)</td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>DisCoVeRy 2020-000936-23</td>
<td>Multicentric, randomized, open-label,</td>
<td>2 arms: Remdesivir AZD7442 vs SoC</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>M. Hites / Hôpital Erasme UCL St-Luc</td>
</tr>
<tr>
<td>Remdesivir arm stopped</td>
<td>adaptive clinical trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAWN-plasma (No IMP,</td>
<td>Open-label randomized Multicenter Adaptive</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>therefore no EudraCT</td>
<td>design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>number) Recruitment is</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>finished</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Name</td>
<td>Design</td>
<td>Description</td>
<td>Interventions</td>
<td>Outcomes</td>
</tr>
<tr>
<td>------------</td>
<td>--------</td>
<td>-------------</td>
<td>---------------</td>
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</tr>
<tr>
<td>REMAP-CAP 2015-002340-14</td>
<td>Randomized, embedded, multifactorial, adaptive platform trial for community acquired pneumonia, amended for COVID-19</td>
<td><strong>Antiviral therapy:</strong> No vs Kaletra</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>AZ Sint-Jan (Brugge), CHU Charleroi, UZ Gent</td>
</tr>
<tr>
<td><strong>DAWN-antico 2020-001739-28A (completed)</strong></td>
<td>Randomized, open-label, adaptive, proof-of-concept clinical trial</td>
<td>3 arms: High prophylactic LMWH +/- anakinra*; Apronin (antifibrinolytic) +/- anakinra*; standard dose of LMWH * anakinra only for patients in hyper-inflammatory stage</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td><strong>Biophytis – BIO101 2020-001498-63</strong></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 2020-002130-33 (completed)</strong></td>
<td>Prospective, randomized, open-label, interventional clinical trial</td>
<td>2 arms: Zilucoplan (inhibitor of complement protein C5) vs SoC</td>
<td>COVID-19 PCR confirmed hospitalized patients</td>
<td>B. Lambrecht/UZ Gent</td>
</tr>
<tr>
<td><strong>OSCAR (GSK) 2020-001759-42 (completed)</strong></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 (Inotrem) 2020-001504-24</strong></td>
<td>Randomized, double-blind, placebo controlled,</td>
<td>2 arms: Nangibotide iv (TREM1 inhibitor) vs placebo</td>
<td>Mechanically ventilated patients due to COVID-19</td>
<td>UCL St-Luc, ZOL</td>
</tr>
<tr>
<td>Study ID</td>
<td>Trial Type</td>
<td>Intervention</td>
<td>Population</td>
<td>Site</td>
</tr>
<tr>
<td>----------</td>
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</tr>
<tr>
<td>TJT2012 2020-002102-58</td>
<td>Prospective, open-label P1/2 clinical trial</td>
<td>Mesenchymal stromal cells</td>
<td>Patients with severe COVID-19 requiring supplemental O2</td>
<td>CHU Liège</td>
</tr>
<tr>
<td>ARGX-117-2001 (ArgenX) 2020-001546-19 (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>Trial Code</td>
<td>Designation</td>
<td>Design/Details</td>
<td>Primary Outcome</td>
<td>Study Location</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>TRISTARDS</td>
<td>Open label, randomized,</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>(Boehringer Ingelheim)</td>
<td>sequential, parallel-group,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2020-002913-16</td>
<td>adaptive PIIb/III trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FITE19 (PTC therapeutics)</td>
<td>randomized, double-blind,</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>2020-001872-13</td>
<td>placebo-controlled, PII/III study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIT-Co001-C101 (Pfizer)</td>
<td>Randomized, double-blind,</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>2020-003403-33 (completed)</td>
<td>placebo-controlled, phase 2 trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4611001</td>
<td>Phase 1b, 2-part, double blind,</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>(Pfizer)</td>
<td>placebo controlled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANAMO</td>
<td>adaptive randomized, double-blind,</td>
<td>IFX-1 (immunomodulator: C5a blocker) + SoC vs placebo + SoC</td>
<td>Hospitalized Patients with severe COVID-19 pneumonia</td>
<td>UZA</td>
</tr>
<tr>
<td>2020-001335-28</td>
<td>placebo controlled, Phase II/III</td>
<td></td>
<td></td>
<td>CHU Dinant Godinne UCL Namur Erasme</td>
</tr>
<tr>
<td>DAWN-camostat</td>
<td>Randomized double blind controlled</td>
<td>camostat mesylate vs placebo</td>
<td>ambulatory COVID-19 patients</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td>2020-005911-27</td>
<td>trial Phase III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-RESCAP</td>
<td>Randomized, placebo controlled,</td>
<td>RESCAP (bovine alkaline phosphatase) vs placebo</td>
<td>Severe COVID-19 patients with acute respiratory insufficiency</td>
<td>Jessa Ziekenhuis Hasselt / B. Stessels</td>
</tr>
<tr>
<td>2020-001714-38</td>
<td>double blind, phase II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SG018</td>
<td>Randomized, double-blind,</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>2020-004743-83</td>
<td>placebo-controlled, phase III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV43043 (Roche)</td>
<td>Randomized, double-blind,</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: <a href="mailto:global.rochegeotenctrials@roche.com">global.rochegeotenctrials@roche.com</a>)</td>
</tr>
<tr>
<td>2020-005759-18</td>
<td>placebo-controlled, phase III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOPECovid-19</td>
<td>Randomized, double-blind,</td>
<td>Lactavir vs placebo</td>
<td>Ambulatory COVID-19 patients</td>
<td>UCL</td>
</tr>
<tr>
<td>2021-000492-36</td>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### EXEVIR0101

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Design</th>
<th>Intervention</th>
<th>Population</th>
<th>Site(s)</th>
</tr>
</thead>
<tbody>
<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, AZ Sint-Maarten, Mechelen, CHU Saint-Pierre</td>
</tr>
</tbody>
</table>

### 1487-0003 (BI 767551) 2021-000408-309 (prematurely ended)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Design</th>
<th>Intervention</th>
<th>Population</th>
<th>Site(s)</th>
</tr>
</thead>
<tbody>
<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>

### COV-BARRIER-PEDS 2021-001338-21

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Design</th>
<th>Intervention</th>
<th>Population</th>
<th>Site(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COV-BARRIER-PEDS 2021-001338-21</td>
<td>Multicenter, Open-Label, Pharmacokinetic and Safety Study</td>
<td>Baricitinib</td>
<td>Pediatric patients from 1 to less than 18 years old hospitalized with COVID-19</td>
<td>Centre Hospitalier Régional de la Citadelle / Eli Lilly (<a href="mailto:EU_Lilly_Clinical_Trials@lilly.com">EU_Lilly_Clinical_Trials@lilly.com</a>)</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 (link)).

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.europa.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

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

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 hematopoetic 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
  - Pregnancy

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

**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 a risk factor (immunosuppression or ≥1 comorbidity), proceed to next step
**Immunocompromised patient:**
- Patient is eligible for treatment with mAbs regardless of SARS-CoV-2 MASS or UTAH score.
- Refer quickly to a multidisciplinary expert panel for approval to start treatment

**Patient with at least one comorbidity but not immunocompromised:**
- Determine the MASS score and/or Utah score (see synoptic table page 44)
- Refer quickly to a multidisciplinary expert panel for approval to start treatment
- Patient will be eligible according to the prioritization framework (see page 44)
5.4. PROPOSAL FOR A PRIORITISATION FRAMEWORK REGARDING THE USE OF MONOCLONAL ANTIBODIES (MABS) IN AT-RISK PATIENTS WITH MILD/MODERATE COVID-19 IN BELGIUM

Since May 2021, through a ministerial decree, the mAb therapies are authorized in Belgium for early administration in mild to moderate COVID-19 patients at high risk of complication, but availability is extremely limited for the moment.

The first mAbs available, casirivimab/imdevimab (REGN-COV2) are currently no longer available and have been replaced by a limited stock of Sotrovimab 500 mg (GlaxoSmithKline) since November 17.

The current eligibility criteria are rather large (see Annex 5.3), resulting in a risk that availability of mAbs or resources to administer them are insufficient. For this reason, the task force has reflected on a prioritization strategy for both vaccinated and unvaccinated patients at high risk of progression to severe COVID-19. The proposal relies on two scores established in academic reference centers in the US based on emerging observational evidence. Both scores have similarities and slight differences. Since evidence remains very limited, this synoptic Table should only be considered as a guidance to support the decisions of the hospital multidisciplinary committees.

In general, patients reaching the highest scores are those who should benefit most from these therapies (taking also in consideration the short-term prognosis in case of terminal underlying diseases). Cut-offs are provided by the respective research groups for selecting the patients most in need, if resources are limited. The task force feels however that no rigid scoring threshold can be recommended at this stage. As availability and administration capacities are expected to increase, selection of patients will become more liberal to provide access to a larger group of high-risk patients.
### Synoptic Table summarizing both scoring systems (Mayo Clinic [42] & Utah [link])

<table>
<thead>
<tr>
<th>Criteria/Comorbidities*</th>
<th>Score Mayo Clinic (MASS)</th>
<th>Score Utah</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total = 18</td>
<td>Total = 24.5</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>Age 50-60 years</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m²</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>BMI ≥35 kg/m²</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>End-stage liver disease</td>
<td>(not mentioned)</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Immunosuppression (of any type)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Genetic/congenital disorder</td>
<td>Case by case discussion</td>
<td>1</td>
</tr>
<tr>
<td>Chronic neurologic disease</td>
<td>(not mentioned)</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Case by case discussion</td>
<td>No score attributed</td>
</tr>
<tr>
<td>Non White/Hispanic</td>
<td>(not mentioned)</td>
<td>2</td>
</tr>
<tr>
<td>Male</td>
<td>(not mentioned)</td>
<td>1</td>
</tr>
<tr>
<td>Not fully vaccinated</td>
<td>(not mentioned)</td>
<td>3</td>
</tr>
<tr>
<td>Negative serology</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

* Interpretation:

- For the Mayo Clinic guideline, in case of scarce resources, mAbs should be given in priority to patients with MASS ≥ 4 (admission rate was significantly lower in the local experience, for a number to treat between 3 and 8).
  Limitations: there is no clear distinction between vaccinated and unvaccinated patients, and no guidance is provided for pregnant women.

- For the Utah guideline, in case of scarce resources, mAbs should be given in priority to patients with a score ≥ 7 (note that unvaccinated status gets 3 points here)
  Limitation: no internal validation data have been published so far
5.5. MABS 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.

Imbedded in this document is the Xevufy (sotrovimab) order form. This form can be filled in and sent to strategicstock@medista.be to order stock from Medista.
6. References


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


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


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Seftel D, Boulware DR. Prospective Cohort of Fluvoxamine for Early Treatment of Coronavirus Disease 19. *Open Forum Infectious Diseases* 2021; 8:ofab050.


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