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

July 2021; Version 21

Preliminary note

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

This document is periodically revised to provide support to the diverse groups of Belgian clinicians (general practitioners, emergency physicians, infectious disease specialists, pneumologists, intensive care physicians) who have to face suspected/confirmed COVID-19 cases during the epidemic in Belgium. This guideline primarily targets hospital care but refers whenever necessary to other guidelines.

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

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

We have opted for a document with the following structure :

1. Executive Summary, with the current therapeutic recommendations for each category of COVID-19 patients, with indications and precautions (Table 1); the strengths of the recommendations are now provided using the GRADE score [2].
2. The Belgian recommendations for supportive care and adjunctive antiviral/immunomodulatory treatment for suspected/confirmed COVID-19 cases, detailing latest evidence and rationale behind this consensus.
3. A summary of the efficacy data of selected antiviral drugs, clinical evidence for treatment with monoclonal antibodies (Table 2) and *in vitro/in vivo* efficacy of select antiviral drugs (Table 3).
4. An overview of the ongoing clinical trials in Belgium (Table 4).
5. Annexes
6. References

IMPORTANT

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

This document will not describe in detail the generic and supportive management of COVID-19 (except if there are some pathogen-specific interventions). It is also not aimed at providing an extensive review on all potential investigational treatments in the preclinical pipeline.

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

Members of the working group

Koen Blot: Dept. of Epidemiology and Public Health, Sciensano
Emmanuel Bottieau: Dept of Clinical Sciences, Instituut voor Tropische Geneeskunde (ITG)
Nicolas Dauby: Dept. of Internal Medicine and Infectious Diseases, CHU-Saint-Pierre
Julien De Greef: Dept. of Internal Medicine and Infectious Diseases, Clin. Univ. Saint-Luc-UCLouvain
Pieter Depuydt: Dept. of Intensive Care Medicine, UZ Gent
Paul De Munter: Dept. of Internal Medicine, UZ Leuven
Maya Hites: Clinic of Infectious Diseases, Clinique Universitaire de Bruxelles (CUB)-Erasme
Patrick Lacor: Dept. of Internal Medicine, UZ Brussel
Natalie Lorent: Dept. of Pneumologie, UZ Leuven
Jiska Malotaux: Dept. of Internal Medicine, UZ Gent
Fabio Taccone: Dept. of Intensive Care Unit, CUB-Erasme
Caroline Theunissen: Dept. of Clinical Sciences, ITG
Eva Van Braeckel: Dept. of Respiratory Medicine, UZ Gent
Sabrina Van Ierssel: Dept. of Internal Medicine, UZ Antwerpen
Roel Van Loock: DG PRE – Dept. of Assessors, FAGG - AFMPS
Sandrine Milas: Dept Infectious Diseases CHU Charleroi

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

Clinical category	Supportive Care	Additional therapy (Strength of recommendation - GRADE)
Suspicion of COVID-19 ➢ **Mild-to-moderate symptoms** ➢ **No risk group**	Symptomatic treatment	No (Strong recommendation, low-quality or very low quality evidence – 1C)
Confirmed mild or moderate COVID-19 ➢ **Mild disease: symptoms of COVID-19 without lower respiratory tract involvement such as dyspnea or abnormal chest imaging** ➢ **Moderate disease: clinical or radiological evidence of lower respiratory tract disease and SpO2 ≥94% or does not require supplemental oxygen**	Symptomatic treatment	**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** (Annex 5.3) to assess **eligibility criteria** for treatment with mAbs for adult patients with mild or moderate COVID-19 infection.
Confirmed COVID-19 severe disease **≥ 1 of the following:** ➢ **Respiratory rate ≥30/min (adults); ≥40/min (children < 5y)** ➢ **Blood oxygen saturation ≤93% or requires supplemental oxygen** ➢ **PaO2/FiO2 ratio <300** ➢ **Lung infiltrates >50% of the lung field within 24-48 hours**	Optimal supportive care in hospital WARD (or ICU) Provide O_2 Administer prophylactic LMWH if not contra- indicated Consider carefully antibiotics or antifungals according to local epidemiology	**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 < 5 days of symptoms. **Tocilizumab and other interleukin-6 blockers:** consider early administration of IL6-receptor antagonists in addition to corticosteroids in hospitalized patients with rapidly progressive COVID-19 (Conditional recommendation, low quality of evidence)

Clinical category	Supportive Care	Additional therapy (Strength of recommendation - GRADE)
Confirmed COVID-19 critically ill disease **≥ 1 of the following:** ➢ **Acute Respiratory Distress Syndrome** ➢ **Sepsis** ➢ **Altered consciousness** ➢ **Multi-organ failure**	Optimal supportive care in ICU Mechanical ventilation Administer prophylactic LMWH if not contra- indicated Specific prevention & treatment of ARDS Track secondary bacterial and opportunistic (*Aspergillus*) infections Prevention of sub-sequent lung fibrosis	**Dexamethasone** 6 mg IV (or equivalent doses of corticosteroids, see row above) once a day for up 10 days; case by case decision for children and pregnant women pending additional results and with the respective specialists (Strong recommendation, high-quality evidence - 1A). Consider early administration of IL6-receptor antagonists in addition to corticosteroids in hospitalized patients with rapidly progressive COVID-19, (Conditional recommendation, low quality of evidence)

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
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 (Liverpool).
- More information on warnings/precautions of use in Veklury product information .
- 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/.

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

As summarized in the executive summary table, we recommend that dexamethasone (or if not available equivalent doses of corticosteroids) be considered as a standard of care in severe and critical COVID-19 disease (grade 1A). Background data and rationale behind these recommendations are detailed here. Latest results concerning additional antiviral and immunomodulatory treatments are also covered hereunder.

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

2.1. Corticosteroids

2.1.1. Dexamethasone, systemic corticosteroids

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

Available evidence: Although treatment with systemic corticosteroids was initially not recommended [6][7], the availability of new high-quality evidence demonstrates a reduction in mortality among COVID-19 patients with severe disease. Low dose dexamethasone (6 mg/day once daily for 10 days) is a treatment option which has been investigated in one of the UK-RECOVERY study arms. In a publication reporting on preliminary results, dexamethasone significantly reduced the overall 28-day mortality rate (age-adjusted rate ratio, 0.83 [95% CI 0.75 to 0.93]; P=0.001) [8]. In a pre-specified subgroup analysis according to the level of respiratory support that the patients were receiving at randomization, there was a trend showing the greatest absolute and proportional benefit among patients who were receiving invasive mechanical ventilation (11.5 by chi-square test for trend). Compared with standard of care, dexamethasone reduced incidence of death in ventilated patients (29.3% vs. 41.4%, rate ratio 0.64 [95% confidence interval 0.51 to 0.81]) and in other patients receiving oxygen only (23.3% vs. 26.2%, 0.80 [0.70 to 0.92]). No evidence of benefit for patients who did not require oxygen was found, and patients outside the hospital setting were not included in the study. In a 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 in version 12 low-dose dexamethasone for admitted patients requiring oxygen, in particular requiring mechanical ventilation and with a symptom onset > 7 days. Following the publication of the RECOVERY results, three other large RCTs evaluating various doses and types of steroids in critical COVID-19 stopped prematurely patient inclusion before reaching the respective target sample sizes, i.e. REMAP-CAP (multicountry) [9], CoDEX (Brazil) [10], and CAPE COVID (France) [11]. The results of RECOVERY, of the last 3 published ("incomplete") RCTs and of another three ongoing smaller trials were then pooled and 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].

Notes on treatment with systemic corticosteroids: It is currently unknown whether the use of corticosteroids in COVID-19 is independently associated with an increased risk for bacterial or fungal infection. A systematic review with meta-analysis complemented the 7 RCTs analyzed in [5] with 37 retrospective observational studies, covering 20.197 patients [13]. Diverse corticosteroid regimens were investigated, most of which consisted of methylprednisolone; 16/29 and 11/29 studies used respectively high (>1mg/kg prednisolone) and lower (<1mg/kg prednisolone) doses. A trend towards more antibiotic use and more infections (6 studies) was noted; however overall pooled estimate showed a reduced mortality in the corticosteroid-treated patients (OR 0.72; 0.57-87), which is in a range similar to that found in the WHO REACT working group meta-analysis [5].

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) [14]. 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) [15].

Effect of low-dose and short-course corticosteroids on risk of *Strongyloides* reactivation is not well known. Nevertheless, for high-risk patients, such as originating from *Strongyloides* endemic areas, empirical ivermectin treatment should be considered before, or early during, corticosteroid administration treatment [16].

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 [17]. The trial was stopped early because of a reduced number of new cases. Independent statistical review concluded that the study outcome would not change with further participant enrolment. The patients in the budesonide group had a significantly lower probability of an urgent care visit (15% vs 3%). Number needed to treat to avoid an urgent care visit was eight. Self-reported clinical recovery was shortened by 1 day (median 7 days [95% CI 6–9] vs 8 days [7–11]; log-rank test

p=0.007). This is the first published trial with inhaled corticosteroids in COVID-19. Several similar trials are still ongoing.

Preliminary data from two other RCTs on inhaled corticosteroids in COVID-19 are available. The PRINCIPLE trial investigated 2x800µg inhaled budesonide added to standard care in (suspected) COVID-19 patients in the community, aged ≥65y or ≥50y with co-morbidities and ≤14d symptoms and found a shorter time to recovery (minus 3d; CI: 1-5.4) without an effect on hospitalization rate in the budesonide arm [18].

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

2.2. Remdesivir

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

Available evidence: Remdesivir (RDV) seemed promising *in vitro* and in non-human primate models [19]. An initial Chinese trial did not show any survival benefit with remdesivir, but the study could not include enough cases and was discontinued at the end of the local epidemic [20]. 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 [21] confirming a faster recovery in remdesivir-treated hospitalized COVID-19 patients with evidence of pneumonia (n=541) compared to patients given placebo (10 days instead of 15 days; recovery rate ratio 1.29; [95% CI 1.12 to 1.49], p<0.001). The benefit was most apparent in those COVID-19 patients receiving low-flow oxygen, the largest group of patients included in the study, and when remdesivir was given before the 10th day of symptom onset. Results were not conclusive for other groups of patients (those not requiring supplemental oxygen, or in patients requiring mechanical ventilation). No statistical difference was seen for mortality by Day 15 (6.7% mortality versus 11.9%) and by Day 29 (11.4 versus 15.2%), but there was a positive trend compared to placebo (hazard ratio: 0.73 95% CI 0.52 to 1.03).

In addition, a randomized, open-label, phase 3 trial, comparing 5-day and 10-day treatment with remdesivir in patients with severe/critical disease (oxygen requirement), did not find a significant difference in efficacy between these two treatment durations. After adjustment for baseline imbalances in disease severity (patients assigned to 10-day course had significantly worse clinical status than those in the 5-day group), outcomes were similar as measured by a number of end points: clinical status at day 14, time to clinical improvement, recovery, and death from any cause. Post-hoc analysis showed that patients receiving

mechanical ventilation or ECMO may benefit from 10 days of remdesivir treatment. Further evaluation of this subgroup and of other high-risk groups, such as immunocompromised persons, is needed to determine the shortest effective duration of therapy in these patients [22].

A third RCT sponsored by Gilead (Spinner et al.) assessed the role of remdesivir in hospitalized patients with non-severe COVID-19 (not requiring oxygen supplementation) [23]. The patients (n=584) were randomized 1:1:1 to 10-day course of RDV, 5-day course of RDV and standard of care. Mortality was low (1%). A better clinical status on day 11 after treatment initiation was observed with the 5-day course but not the 10-day course. The clinical significance of this finding remains uncertain as the patients in the 5-day and 10-day courses received almost the same number of doses of remdesivir (5 and 6, respectively).

It is important to highlight that in both the ACTT-1 and Spinner trials, no impact of RDV on viral shedding was reported. In both trials, the median duration of symptoms before enrollment was 9 days, limiting the potential for a significant antiviral effect as was also observed in the Wang et al trial [20].

In December, the results from the SOLIDARITY multicenter worldwide pragmatic trial were published, showing no overall clinical benefit of remdesivir in hospitalized patients with COVID-19. Remdesivir was evaluated in 2743 patients, compared to 2708 controls. In a meta-analysis of the 4 published trials on remdesivir, a weighted average of the results from all trials yielded a rate ratio for death (remdesivir vs. control) of 0.91 (95% CI, 0.79 to 1.05). However, in the subgroup of patients receiving no mechanical ventilation at time of randomization, the rate ratio for death was 0.80 (0.63-1.01) [24]. The WHO issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of the severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients. Nevertheless, WHO continues to endorse including patients in trials with remdesivir to establish with certainty whether remdesivir has a positive effect on survival in mild to moderate, hospitalized COVID-19 patients. The Solidarity and DisCoVeRy trials continued to randomize mild to moderate hospitalized COVID-19 patients to receive remdesivir vs. standard of care until the 27th and 29th of January, respectively. Inclusions into the remdesivir arm were stopped due to futility in severe, but also mild to moderate, hospitalized COVID-19 patients.

In addition, EMA evaluated the full mortality and viral data from NIAID ACTT-1 data upon which EMA recommended to not start remdesivir in COVID-19 patients already on mechanical ventilation and on ECMO. This guidance, that already considers remdesivir as having a modest effect and small window of use, will be further updated when the final data from the DisCoVeRy and Solidarity trials are published. A recent meta-analysis of the 5 published RCTs on remdesivir vs. control has also shown the modest effect of remdesivir in hospitalized patients. Patients in the remdesivir treatment group had a greater likelihood of hospital discharge, and clinical improvement was more rapid than the control group, yet no effect was observed on mortality [25].

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

2.3. Immunomodulatory agents, anti-interleukin therapy

Main message: Immunomodulatory agents are a varied group of drugs that may prevent or dampen hyper-inflammatory responses which are associated with clinical deterioration and mortality among COVID-19

disease [26,27]. There is currently insufficient RCT evidence yet to recommend their use outside of clinical studies. Potential adverse events, immunosuppression and drug interactions have to be carefully taken into consideration if choosing to treat patients.

Available evidence: Several interleukin (IL) and complement blockers used in inflammatory diseases such as giant cell vasculitis or rheumatoid arthritis have been proposed for repurposing based on limited clinical experience and small observational studies. These drugs include tocilizumab (IL-6-receptor antagonist) [28,29], 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 [30–32]. These trials were highly heterogeneous regarding the severity of the patients included.

In their most recent guidelines, the Infectious Diseases Society of America (IDSA) has formulated a conditional recommendation, with low certainty of evidence, towards the addition of tocilizumab to standard of care (i.e. steroids) rather than standard of care alone, in hospitalized adults with progressive severe (SpO2 ≤94% on room air, including patients on supplemental oxygen) or critical (mechanic ventilation and ECMO) COVID-19 who have elevated markers of systemic inflammation [33]. In the largest trial on treatment with tocilizumab, the criterion for systemic inflammation was defined as CRP >75 mg/L. Both RECOVERY and REMAP-CAP (the two tocilizumab trials that reported a benefit) initiated treatment early (randomization at median of two days of hospitalization in RECOVERY; <24 hours in the ICU for REMAP-CAP), suggesting tocilizumab may be more beneficial in people with early, rapidly progressive disease.

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

These drugs are intensively investigated including in Belgium (see Table 3). Notably, the multicentre COV-AID trial assessing the impact of IL-6 blockade and combined IL-6/IL-1 blockade in our Belgian setting has completed enrollment. Of note, inclusion was based on a combination of biological factors (to better select suitable candidates), in contrast with other trials. Recently, clinical trials using anakinra were temporarily suspended in France; but recruitment is permitted again. Of note, the French trials used higher dosages as compared to those used in Belgium and the Data Safety and Monitoring Board (DSMB) of the COV-AID trial has considered that anakinra could be further evaluated in Belgium.

2.4. Monoclonal antibodies

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

- A summary for all monoclonal antibodies is available below (link).
- An overview of individual study results is provided in chapter 3 (Table 2).
- Please consult the algorithm in Annex 5.3 to assess whether a patient is eligible for treatment with monoclonal antibodies.

- As described in the ministerial decree, the final decision to treat with mAbs should integrate the clinical opinion of the prescribing (hospital-based) physician and a multidisciplinary expert panel, consisting of at least one infectious disease physician and one immunologist.
- Casirivimab + imdevisimab (REGEN-COV) can be ordered by the hospital pharmacy using the form available in Annex 5.4.

Resistance of SARS-CoV-2 variants to mAbs (e.g. bamlanivimab) and the changing epidemiology must be considered before starting treatment. Information on genomic SARS-CoV-2 surveillance in Belgium is available via the National Reference Laboratory[1] and Sciensano weekly epidemiological report.[2]

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

Available evidence: Dozens of monoclonal antibodies (mAbs) targeting the Receptor Binding Domain (RBD) of the spike protein (S protein) have been developed and more than 50 trials are being conducted [34]. Given the long half-life, a single injection (mostly intravenous, subcutaneous and intramuscular routes are under study) is generally used [35].

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 negative serological test. Intrinsic resistance to monoclonal antibodies should be considered.

Preprint studies have demonstrated that the B.1.617 and B.1.617.2 variant has demonstrated resistance to bamlanivimab [45,46]. Bamlavinimab monotherapy emergency use authorization has been revoked in the U.S. due to resistant variants (link). Within Belgium, there has been a rise in the proportion of B.1.617.2 variants since June 2021 (link). **Caution should therefore be exercised before considering treatment with bamlanivimab monotherapy.**

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

[1] Genomic Surveillance of SARS-CoV-2 in Belgium
https://www.uzleuven.be/nl/laboratoriumgeneeskunde/genomic-surveillance-sars-cov-2-belgium

[2] COVID-19 Weekly Epidemiological Report, chapter 3.4 Molecular surveillance:
NL: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Weekly_report_NL.pdf
FR: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Weekly_report_FR.pdf

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 [36]. For hospitalized patients with more advanced disease (trial conducted by the ACTIV-3/TICO LY-CoV555 Study Group), bamlanivimab (co-administered with remdesivir) did not demonstrate any clinical benefit [37]. In a US real-world experience case-control study of 403 high-risk outpatients (including 27% immunosuppressed patients) with mild or moderate COVID-19, fewer number of hospitalizations on day 30 were observed in the group treated with bamlanivimab infusion. However, the reasons for non-administration of bamlanivimab for the majority of patients in the control group are not recorded. No adverse events requiring hospitalization were reported in that study [94].

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 [38]. In the unpublished RCT, phase 3, BLAZE-1 trial, including outpatients with mild or moderate COVID-19, at high risk for progressing to severe COVID-19 who received an intravenous infusion of 2800 mg bamlanivimab + 2800mg etesevimab, a 70% reduction of hospitalization and death by any cause by day 29 was observed [39]. These data are to be confirmed by a publication. According to the unpublished results of the BLAZE-4 phase 2 trial, the only authorized dose of bamlanivimab is 700 mg combined with etesevimab 1400 mg (link).

2.4.4. Casirivimab + imdevimab (REGEN-COV)

Regeneron's REGEN-COV (previously known as REGN-CoV2 or REGEN-CoV2) consists of two antibodies that bind to different regions of the SARS-CoV-2 spike protein receptor. In an interim analysis of a phase 2-3 trial studying the effect of a combination regimen of casirivimab and imdevimab (NCT04425629) on 275 outpatients, a significant decline in viral load on day 7 was observed when compared to placebo, especially in seronegative patients and in patients with high viral load [40]. However, the impact on clinical outcomes (medically attended visit) were less clear. A preprint article elaborated further on the results of the phase 3 portion of this same study in high-risk outpatients who received various doses of REGEN-COV (2400mg vs 1200mg vs placebo). The results showed that both REGEN-COV dosage regimens significantly reduced hospitalization or death by day 29 (respectively 71.3% reduction [1.3% vs 4.6%] and 70.4% [1.0% vs 3.2%]) [41]. Efficacy of REGEN-COV was consistent across subgroups, including patients that were SARS-CoV-2 seropositive at baseline. The preprint results of a phase 3 trial on subcutaneous REGEN-COV prophylaxis among household contacts exposed to SARS-CoV-2 at home (NCT04452318) showed 81.4% risk reduction of a symptomatic infection compared with placebo (11/753 [1.5%] vs. 59/752 [7.8%], number needed to treat [NNT]: 15.9) and a shorter time resolution of symptoms (1.2 vs. 3.2 weeks) [42].

In the RECOVERY, RCT, open-label trial, published in a pre-print, REGEN-COV (casirivimab 4g and imdevimab 4g, IV) plus standard of care was compared with standard of care alone, in hospitalized COVID-19 patients. 3153 patients (32%) were seronegative for SARS-CoV-2, 5272 (54%) seropositive and 1360 (14%) with unknown status at baseline. In the seronegative group, 396 (24%) in the REGEN-COV group and 451 (30%) of standard of care died within 28 days (rate ratio 0.80; 95% CI 0.70-0.91; p=0.001, NNT: 16.7). The proportional effect of REGEN-COV on mortality differed significantly between seropositive and seronegative patients (p-

value for heterogeneity = 0.001). The authors conclude that REGN-COV, in hospitalized patients, should only be used in SARS-CoV-2 seronegative patients [43]. This is the first study to have shown efficacy of mAbs in hospitalized patients with COVID-19.
On June 3, the FDA modified the dosage to casirivimab 600mg plus imdevimab 600mg. Subcutaneous injection could be given when IV administration is not feasible or would lead to delay in treatment (link).

2.4.5. Regdanvimab

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

2.4.6. Sotrovimab

The interim results analysis of the unpublished phase 3 COMET-ICE trial (NCT04545060), evaluating a single 500 mg infusion of sotrovimab compared to placebo in 868 high-risk outpatients (most common risks factors: obesity: 63%, >55 years: 47% and diabetes: 23%) demonstrated an 85% (p=0.002) reduction in hospitalization or death at day 29 in the sotrovimab group (link). In addition, results from in-vitro and animal model in a pre-print study seem to demonstrate that VIR-7831 maintains activity against currently circulating variants of concern, including the India variant (B.1.617) [44].

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

The algorithm for treatment with mAbs (Annex 5.3) is based on published literature up to June 2021 (mostly of low quality of evidence) and on expert opinion. The expert opinion was formed after concertation with a delegation of Belgian immunologists and transplant physicians. This mAbs treatment algorithm is liable to change over time, depending on developing evidence in the literature and the availability of mAbs in Belgium.

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

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 [47]. Several observational studies, non-controlled and controlled non-randomized trials, and four RCT's have been published [48]. Observational studies show survival benefit of transfusing COVID-19 convalescent plasma (CCP) with high antibody titers [49]. In contrast, the prematurely terminated randomized controlled trial in severely ill COVID-19 patients in Wuhan didn't show faster clinical improvement nor decreased mortality in patients receiving convalescent plasma. This study was however underpowered and the plasma was administrated late in the course of the disease (median time from symptom onset to randomization: 30 days) [50].

An Indian multicenter open label RCT in severe non critically ill COVID-19 patients (P/F 200-300mmHg or RR>24 + SatO2 ≤ 93% with FiO_2 21%) did not show any reduction in disease progression and all-cause mortality at day 28 (19% vs 18%). However, an antiviral effect was demonstrated as well as a faster resolution of dyspnea. In this study post-hoc analysis showed low levels of neutralizing antibodies in the administered plasma and detected neutralizing antibodies in 79% of patients at baseline [51]. This concurs with the Dutch RCT that was stopped early due to the finding of comparable amounts of neutralizing antibodies in patients as in the administered convalescent plasma, as early as median 10 days after symptom onset [52]. A large placebo-controlled randomized trial from Argentina did not find an impact on mortality of administration of CCP containing high titers of neutralizing antibodies. However, 29% of the patients in the plasma arm were critically ill [53]. 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 [54]. A Cochrane review including some republished data including those of the RECOVERY trial, and a meta-analysis performed by the RECOVERY group, did not find a difference in mortality [54,55]. The REMAP-CAP study also halted recruitment in the convalescent arm due to futility. Until now the data have not yet been published.

An Argentinian blinded RCT evaluated early (i.e. within 3d of symptom onset) administration of convalescent plasma in older COVID-19 patients, i.e. >75y or >64 -75y with comorbidities [56]. They found a RR reduction of 0,52 (95% CI 0,29-0,94). The study was terminated early due to a fall in the COVID-19 incidence in Argentina, including 76% percent of the provided inclusion number. On the other hand, the NIH trial C3PO evaluating convalescent plasma for treatment of early-onset (<7 days) non-hospitalized COVID-19 patients was halted as interim analysis of 511 participants (of the 900 planned) found no clinical benefit (link).

Notes on treatment with convalescent plasma: We only recommend the administration of convalescent plasma within clinical trials in Belgium such as the CONFIDENT study that is currently ongoing (of note recruitment is closed for the DAWN-plasma trial). At this moment there are no clinical trials in Belgium on early administration of COVID-19 convalescent plasma in risk groups. Both Rode Kruis and Croix Rouge are collecting plasma from patients who have experienced COVID-19. Whenever possible, patients should be informed at discharge on the possibility to donate plasma and to contact their local RKV/CR center. AFMPS/FAGG has recommended that donation should only take place more than 28 days after symptoms

have ended. Of note, administration of CCP could be considered in case of persistent viral shedding (> 1 month) in severe COVID-19 patients with B cell-related immunosuppression (including patients on Rituximab and other B-cell depleting agents) unable to mount an antibody response, as shown in a French case series by Heuso et al [57] and other case series. The volume and antibody titer used in different reports varies [58].

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 [59]. 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 [60,61].

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.

2.6.1. Baricitinib

Baricitinib is an orally administered, selective inhibitor of Janus kinase (JAK) 1 and 2. In a randomized placebo-controlled trial in patients with moderate and severe COVID-19, treatment with baricitinib 4mg qd and remdesivir was shown to reduce recovery time and to accelerate improvement in clinical status when compared to remdesivir alone [62]. Corticosteroids were not considered standard of care in this study. It's currently unclear whether the benefit of baricitinib with remdesivir would reach the benefit of steroids alone. Prices of baricitinib and remdesivir are significantly higher than steroids, so this treatment should not be used as standard of care pending further evaluation: including use without remdesivir, use on top of steroids or use in comparison with steroids. One large double blind randomized placebo-controlled trial (SOC included systemic corticosteroids in 80% of patients) showed no influence of baricitinib on combined primary endpoints (progression to requiring high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation or death by day 28), but there was a significant reduction of mortality at day 28 and day 60 [63]. According to a press release (Feb 2021: link), baricitinib is to be investigated as a possible treatment for COVID-19 in the RECOVERY trial. On the 29th of April, the EMA has begun the evaluation of an application to extend the use of Olumiant (baricitinib) to include treatment of COVID-19 in hospitalized patients from 10 years of age who require supplemental oxygen.

2.6.2. Tofacitinib

Tofacitinib is an oral JAK inhibitor already approved for the treatment of rheumatoid arthritis (Xeljanz). A placebo controlled randomized trial treated hospitalized COVID-19 patients not requiring ventilation with tofacitinib 10mg twice daily in addition to standard of care. This led to a significant reduction in incidence of

death or respiratory failure (18.1% vs 29.0%, risk ratio 0.63, P=0.04). This effect was consistent across the different levels of oxygen supplementation at baseline. Corticosteroid use was high in both groups (78.5%). The study showed no increased risk of secondary infection associated with the use of tofacitinib.

2.6.3. Roxulitinib

Only preliminary data are available for roxulitinib. None of it is sufficient to support its use outside of studies [64].

2.7. Interferon

Main message: Interferons (IFN) have antiviral effects and modulate the immune response [65]. 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 [66]. 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 [67]. 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 [68]. 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, resp 1412 and 651 patients, did not provide any survival benefit vs control, HR 1.16 (0,96-1,39) in hospitalized patients [24]. The results of the DisCoVeRy trial have been published, including a lopinavir/ritonavir interferon ß-1a arm [69]. There was no impact on clinical outcomes. Inclusion in the study arm was stopped prematurely due to futilty.

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 [70,71]. A few studies have looked at IFN administration by spray or atomization, to improve local effects and avoid systemic adverse reactions [72,73].

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 [74]. Another pilot double-blind placebo RCT found that hospitalized COVID-19 patients treated with 14 days of nebulized interferon β-1a had a greater odds for clinical improvement [75]. 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 [76].

The role of hydroxychloroquine for treatment of hospitalized COVID-19 patients was assessed in the RECOVERY, SOLIDARITY and DisCoVeRy trials. None of these studies found improved clinical outcomes among treated patients. The prospective randomized controlled trial (RCT) RECOVERY in UK has stopped enrolling patients on the 5th of June after finding no beneficial effect of high dose hydroxychloroquine (9600 mg in total over 10 days) in patients hospitalized with COVID-19. For the same reason (absence of efficacy in hospitalized patients), the SOLIDARITY trial communicated the suspension of recruitment in the HCQ arm (9600 mg over 10 days) on 18th of June (link). Similarly, the DisCoVeRy trial stopped enrolling participants in the HCQ arm (5600 mg in total over 10 days) at the same period. The results of the large RECOVERY trial on HCQ efficacy in hospitalized COVID-19 patients have demonstrated that mortality at Day 28 was similar in HCQ recipients compared to standard of care (421/1561, 27% versus 790/3155, 25%; p=0.15). No benefit was observed for all secondary outcomes and subgroups of patients [77]. Another smaller RCT in Brazil conducted in mild-to-moderate hospitalized patients did not find any improvement of the clinical status (seven-level ordinal scale) in participants having received HCQ (total dosage: 5600 mg), alone or with azithromycin (500 mg/day for 7 days) [78].

The role of hydroxychloroquine as post-exposure prophylaxis or as early treatment for mild COVID-19 disease was also assessed through additional RCTs, yet they found no clinical benefit. One RCT using HCQ (low-dose) as post-exposure prophylaxis (PEP), showed no prevention of "illness compatible with COVID-19" [40]. This trial had however several limitations such as undocumented treatment adherence and no laboratory confirmation of SARS-CoV-2 infection in 85% of the participants. Another RCT by the same group studied early administration of HCQ in mild/ambulatory patients with laboratory-confirmed or symptomatic contacts (n=423), and no substantial symptom reduction was observed in the HCQ arm compared to masked placebo [79]. Here again, many participants (about 40%) were not tested. In a well-designed Spanish RCT evaluating early treatment with HCQ in adults with mild disease (n=293), no clinical (shortening of symptoms) nor viral (reduction of shedding) benefits were observed [80]. 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 [81].

2.9. Lopinavir/ritonavir

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

Available evidence: In an RCT, lopinavir/ritonavir (LPV/r 400 mg/100 mg twice daily), initiated more than 12 days after symptom onset (median, IQR 11–17 days), did not show significant clinical benefits in hospitalized patients with COVID-19 [82]. Another small RCT conducted in China did not show any viral or clinical benefit

however (or at best very marginal) [82]. On the 4th of July 2020, the WHO announced that the lopinavir/ritonavir arm was discontinued in the SOLIDARITY trial because of lack of benefit (link). This arm was also stopped in RECOVERY and DisCoVeRy for the same reason. Finally, a benefit risk-assessment performed by the BRAT (Benefit-Risk Action Team) network and published on the 23 June 2020, concluded that the benefit-risk profile for lopinavir/ritonavir in severe COVID-19 cannot be considered positive until further efficacy and effectiveness data become available [83]. 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) [84]. Specific communication regarding ongoing clinical trials is still awaited.

2.10. Favipiravir

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

Available evidence: Favipiravir has a half-cytotoxic concentration (CC50) > 400 µM and the EC50 of favipiravir against SARS-CoV-2 in Vero E6 cells was 61.88 µM/L (much higher than the EC50 of favipiravir for influenza), resulting in a selectivity index (SI) > 6.46 [85]. The half-life is approximately 5 hours. Therefore, higher dosing ranges are considered for the treatment of COVID-19 than for influenza (loading dose of 2400mg to 3000mg BID followed by a maintenance dose 1200mg to 1800mg BID) [86]. An antiviral effect has been observed in animal models (hamsters) at high dosage [87]. This observation has been confirmed in another experiment in Syrian hamsters [88].

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 [89].

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 [90]. A multicentric RCT in Iran did not show any clinical benefit in hospitalized COVID-19 patients treated with favipiravir when compared to LPV/r [91]. Larger trials are still ongoing.

2.11. Molnupiravir

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

2.12. Camostat mesylate

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

Camostat mesylate is a serine protease inhibitor used in Japan, which is being evaluated as repurposed drug after it has been shown to reduce SARS-CoV-2 infection of primary human lung cells (Calu-3 cell line) in vitro [92]. Camostat mesylate is under investigation in monotherapy or in combination with either hydroxychloroquine or azithromycin (eg. NCT04355052 (Israel), NCT04321096 (Denmark)).

The first results of the Danish RCT among 205 hospitalized patients (137 treated with camostat mesylate, 200 mg t.i.d. for 5 days, vs 68 treated with placebo) shows that this drug was safe, but had no viral nor clinical added benefit compared to standard of care [93].

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

2.13. Azithromycin

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

Azithromycin, shown to have some antiviral and immunomodulatory effect, has been promoted by some groups based on observational viral and clinical data [94]. 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 [78] and severe hospitalized patients [16], 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 [95]. The results of DAWN-AZITHRO are also expected soon (Table 3).

2.14. Ivermectin

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

Available evidence: *In vitro* inhibition of SARS-CoV-2 replication in Vero/hSLAM 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) [96].

Until now, eight (5 double-blind) randomized controlled trials studying the effect of ivermectin at different dosages on viral clearance and/or clinical recovery and/or survival have been published in peer-reviewed journals [97–105]. Seven out of eight trials excluded severe and critical COVID-19 patients and dosages of

ivermectin varied between 100 µg and 400 µg/kg. Four of them showed a more rapid decline in viral load. None of these studies demonstrated any differences in resolution of symptoms or in mortality, except one (non-blinded) RCT which demonstrated significantly less development of symptoms in asymptomatic patients when treated with a single dose of ivermectin [106]. 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 [107]. 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 [108]. More robust data and evidence from ongoing clinical trials are expected.

2.15. Colchicine

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

This well-known drug used in several inflammatory diseases has also gained much attention recently. No antiviral activity against SARS-CoV-2 has been demonstrated so far, but its inhibitory action against neutrophil chemotaxis/adhesion and against the inflammasome appears interesting [109]. 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) [110]. 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 [111]. For in-hospital patients, evidence remains scarce. A few observational studies using variable drug dosages have been published, suggesting a possible clinical benefit [112]. 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) [113]. 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 [114]. Two systematic reviews of eight studies (some of them pre-print) with heterogeneous design and varied "control" arms both in out- and inpatients suggested some survival benefit and concluded that large RCTs

were still needed. The current evidence does not permit to recommend for or against use of colchicine in the treatment of COVID-19 until data of larger RCTs are published. Of note, the RECOVERY consortium has announced by press release on the 5th of March 2021 that they have closed recruitment in the colchicine arm because it did not demonstrate mortality benefit in addition to corticosteroids in patients hospitalized with COVID-19. Peer-review publication is awaited.

2.16. Aspirin

Main message: Aspirin has demonstrated no clinical benefit in two large trials among hospitalized patients across different forms of disease severity and should not be used in the management of COVID-19.

Aspirin (ASA) is a non-selective inhibitor of COX-1 and COX-2 enzymes leading to a decreased production of prostaglandins, thromboxane A2 by platelets. Low dose ASA is associated with antithrombotic effect. In animal models ASA inhibits disseminated intravascular coagulation (DIC) during *Staphylococcus aureus* sepsis through inhibition of platelet activation. Patients with septic shock have decreased risk of DIC when using ASA [115]. One retrospective study found a decreased risk of mechanical ventilation, ICU admission and in-hospital mortality among patients admitted with COVID-19 [116]. Different cohort studies have shown a decreased risk of acute lung injury/ARDS in patients on chronic ASA-treatment.

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

2.17. General notes

Note - ACE inhibitors or ARBs:

There is currently no evidence from clinical or epidemiological studies that establishes a link between their use and severe COVID 19 [117,118]. An RCT found no impact of ACEi/ARB switch in COVID-19 [119]. The same type of concerns were raised for non-steroidal anti-inflammatory drugs (NSAIDs), with also no evidence so far to advise for or against these drugs in COVID-19 patients. A nationwide cohort study in Denmark found no difference in COVID-19 outcome in patients with recent use of NSAID [120]. However, to be safe, and while waiting pending results, paracetamol may be preferred as first-line symptomatic treatment of pain and fever (at usual dosage), while NSAIDs should be used with caution (as in common practice) and according to common practice (contra-indicated in case of renal failure for example).

Note - pregnant women:

Specialized care and close monitoring for complications is absolutely necessary in COVID-19 pregnant women. A COVID positive patient, if maternal condition allows it, can deliver vaginally. Large organizations like WHO, RCOG and ACOG support the practice of breastfeeding even in the context of active SARS-CoV-2 disease, but with application of necessary preventive measures (mask, nipple cleaning, frequent handwashing). See additional guidance on newborns of COVID-19 positive mothers via the following link. Antiviral treatment of COVID19 confirmed pregnant women should be considered depending on the safety profile, maternal risk factors (diabetes, hypertension, asthma) and pregnancy outcome (possible risk of premature delivery in the setting of viral infection) [121]. Remdesivir is available for compassionate use in pregnant women with severe disease and the first observational data provide reassurance about safety [122]. 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):

FR: https://covid-19.sciensano.be/sites/default/files/Covid19/Guideline%20traitement%20COVID%20enfants.pdf

NL: https://covid-19.sciensano.be/sites/default/files/Covid19/Guideline%20behandeling%20COVID%20kinderen_0.pdf

Note – anticoagulation in COVID-19 patients:

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

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

Note – Oxygen therapy in COVID-19 patients:

A working group coordinated by AFMPS/FAGG has prepared guidelines for oxygen therapy in:

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

Note – Ambulatory care:

- **Treatment of COVID-19 patients in nursing homes :** Collège de Médecine Générale : Mise à jour du protocole thérapeutique des résidents d'institutions âgés de plus de 75 ans atteints de Covid-19 :

  https://www.le-gbo.be/wp-content/uploads/2020/10/20201025_Revision_Protocole_therapeutique_COVID_institution.pdf
- **Superior Health Council advice on Vitamine D, Zinc and COVID-19**

  https://www.health.belgium.be/fr/avis-9620-vitamine-d-zinc-et-covid-19
- **Outpatient care for Covid-19 patients in the context of saturation in Belgian hospitals**

  FR : https://kce.fgov.be/fr/soins-ambulatoires-aux-patients-covid-19-dans-le-contexte-d%E2%80%99une-saturation-des-h%C3%B4pitaux-belges

  NL : https://kce.fgov.be/nl/ambulante-zorg-voor-covid-19-pati%C3%ABnten-in-het-kader-van-de-verzadiging-in-belgische-ziekenhuizen

3. Summary of efficacy data of selected antiviral drugs

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

mAb, Company	Clinical Trial		Study group	Main results	NNT	EMA approval	Available in Belgium
Bamlanivimab (LY CoV555/LY3819253) Eli Lilly and Company	Monotherapy (IV)	BLAZE-1 phase 2 NCT04427501 [36]	Mild to moderate COVID-19, outpatients	Statistically reducing of VL on Day 11 for Ly CoV555 at 2800 mg dose (-0.53 log, p=0.02)	NA	No CHMP review 05/03/21 for IV use	No
	Combined with Remdesivir (IV)	ACTIV-3/TICO NCT04501978 [37]	Hospitalised patients without end-organ failure	Efficacy outcomes at Day 5 not statistically significant in the LyCoV555+ remdesivir vs placebo group	NA	Since April bamlavinimab monotherapy is **no longer recommended** in the U.S due to resistant variants (link)	
Bamlanivimab (LY CoV555/LY3819253) + **Etesevimab** (LY CoV016/LY3832479) Eli Lilly and Company	Combination therapy (IV)	BLAZE-1 phase 3. NCT04427501 [38] BLAZE-1 phase 3 High Risk patients Unpublished: [39]	Mild to moderate COVID-19, outpatients Mild to moderate COVID-19, outpatients at high risk group	Statistically reducing of VL on Day 11 for combination treatment (-0.57 log p=0.01) Unpublished	NA	No CHMP review 05/03/21 for IV use	No
Casirivimab (REGN10933) + **imdevimab (REGN10987)**	Combination therapy (IV)	Phase 2/3 NCT04425629 [40]	Mild to moderate COVID-19, outpatients	Interim analysis: proportion of MAV in REGN-COV2 group through Day 29 (3% vs 6% in the placebo group) and MAV proportion for baseline seronegative	33 11 (seroneg. patients)	No CHMP review 26/02/21 for IV use	Since 19 May 2021, via government for IV use in

Regeneron Pharmaceuticals, Roche		Phase 3 portion NCT04425629 Preprint: [41]	Mild to moderate COVID-19, high risk outpatients	patients (6% vs 15% in the placebo group) 71.3% (2400mg) and 70.4% (1200mg) reduction in hospitalization and all-cause death by day 29	45.5		mild to moderate COVID-19 (conditional use) (link)
	Combination therapy (SC)	Phase 3 NCT04452318 (SC) Preprint: [42]	Prevention in household contact positive SARS-CoV-2 (SC)	81.4% risk reduction of a symptomatic infection in the REGN-COV2 (casirivimab 600 mg/imdevimab 600 mg) group compared with placebo (1.5% vs 7.8%) and a shorter time of resolution of symptoms (1.2 vs 3.2 weeks	15.9		
	Combination therapy (IV)	Phase 3 RECOVERY trial NCT04381936 Preprint [43]	Hospitalised patients	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	16.7		
Sotrovimab (VIR 7831/GSK4182136) GlaxoSmithKline and Vir Biotechnology	Monotherapy (IV)	Phase 2-3 COMET-ICE NCT04545060 Preprint: [123]	Mild to moderate COVID-19 at high risk group	85% of reduction of hospitalization or death through Day 29 (1% vs 7%)	16.7	No CHMP review 21/05/21 for IV use	No
	Combined with bamlanivimab (IV)	BLAZE-4 NCT04634409 Unpublished	Mild to moderate COVID-19	Unpublished			
Regdanvimab Regkirona (CT-P59) Celltrion	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	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.

3.2. Table 3: *In vitro / in vivo* efficacy of antiviral drugs selected for treatment of confirmed COVID-19 infection

Note: all ongoing clinical treatment trials/studies over COVID-19 (> 300) are compiled in a real-time dashboard at LitCovid website, see The Lancet [124]*; we try to summarize the relevant information for selected drugs*

Drug	*In vitro* activity			*In vivo* activity (animal models)			Clinical studies SARS-CoV-2 (non-exhaustive)	Mechanism of action
	SARS-CoV-1	MERS-CoV	SARS-CoV-2	SARS-CoV-1	MERS-CoV	SARS-CoV-2		
Favipiravir Used in Japan against influenza	Not studied	Not studied	++ * [76] *at higher dosage than for influenza)	-	-	+ [87]	ChiCTR2000029600: Shorter viral clearance time and improved radiological evolution compared to lopinavir/ritonavir (non-randomized) [89] NCT04373733 (PIONEER): recruiting NCT04349241: Completed, no yet published	Inhibition of the activity of RNA dependent RNA polymerase (RdRp)[125,126]
Camostat Used in Japan for reflux esophagitis and pancreatitis	++ [92]	++ [92]	++ [92]	++ [127]	-	-	NCT04355052 : recruiting NCT04321096 : recruiting NCT04353284 : recruiting NCT04374019 : recruiting	Inhibition of TMPRSS2, a cellular serine protease, that primes SARS-CoV-2 Spike (S) protein for cell-entry [92]
Interferons	+ [128]	+ [128]	++ [65,129]	+ [130]	+ [131]	- [24]	3 RCT's with small number of patients (see text). Further studies needed	

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

PROTOCOL CODE / EudraCT n°	STUDY TYPE	INVESTIGATED PRODUCTS	PATIENT PROFILE	PRINCIPAL INVESTIGATOR/ COORDINATING CENTER
COV-AID 2020-001500-41 (completed)	Multicentric, randomized, factorial design, interventional study	Six arms: Anakinra (anti-IL1), Siltuximab (anti-IL6), Tocilizumab (anti-IL6) in monotherapy, double or single combinations; standard of care (SoC)	COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome	B. Lambrecht / UZ Gent
SARPAC 2020-001254-22 (completed)	Multicentric, randomized, open-label, interventional study	2 arms: Sargramostim (recombinant GM-CSF)) vs SoC	Acute hypoxic respiratory failure of COVID-19 patients	B. Lambrecht / UZ Gent
DAWN – azithro 2020-001614-38 (completed)	Multicentric, randomized, open-label, adaptive, proof-of-concept clinical trial	2 arms: Azithromycin vs SoC (other arms can be included later)	COVID-19 PCR confirmed hospitalized patients	UZ Leuven
DisCoVeRy 2020-000936-23 Remdesivir arm stopped	Multicentric, randomized, open-label, adaptive clinical trial	2 arms: ~~Remdesivir~~ vs SoC	COVID-19 PCR confirmed hospitalized patients	M. Hites / Hôpital Erasme UCL St-Luc
DAWN-plasma (No IMP, therefore no EudraCT number) Recruitment is finished	Open-label randomized Multicenter Adaptive design	2arms: convalescent plasma vs SoC	COVID-19 PCR confirmed hospitalized patients	G. Meyfroidt/ UZ Leuven
REMAP-CAP 2015-002340-14	Randomized, embedded, multifactorial, adaptive platform trial	Antiviral therapy: No vs Kaletra Corticosteroid therapy:	COVID-19 PCR confirmed hospitalized patients	AZ Sint-Jan (Brugge), CHU Charleroi, UZ Gent

	for community acquired pneumonia, amended for COVID-19	No vs hydrocortisone 7d vs shock dependent hydrocortisone <u>Immune modulation:</u> No vs interferon-beta-1a vs anakinra (anti-IL1)		
DAWN-antico 2020-001739-28A (completed)	Randomized, open-label, adaptive, proof-of-concept clinical trial	3 arms: High prophylactic LMWH +/- anakinra*; Apronin (antifibrinolytic) +/- anakinra*; standard dose of LMWH * anakinra only for patients in hyper-inflammatory stage	COVID-19 PCR confirmed hospitalized patients	UZ Leuven
Biophytis – BIO101 2020-001498-63	Adaptive design phase 2 to 3, randomized, double- blind, multicentre clinical trial	2 arms: BIO101 (activator of Mas-receptor of the renin-angiotensin system) vs SoC	COVID-19 PCR confirmed hospitalized patients	UCL Namur St elisabeth AZ St Maarten (Mechelen)
ZILU-COV 2020-002130-33 (completed)	prospective, randomized, open-label, interventional clinical trial	2 arms: Zilucoplan (inhibitor of complement protein C5) vs SoC	COVID-19 PCR confirmed hospitalized patients	B. Lambrecht/UZ Gent
OSCAR (GSK) 2020-001759-42	Randomized, double-blind, placebo-controlled clinical trial	2 arms Otilimab (anti-GM-CSF) vs SoC	Patients with severe pulmonary COVID-19 related disease	GSK
MOT-C-204 (Inotrem) 2020-001504-24	Randomized, double-blind, placebo controlled, adaptive, exploratory clinical study	2 arms: Nangibotide iv (TREM1 inhibitor) vs placebo	Mechanically ventilated patients due to COVID-19 and with features of systemic inflammation	UCL St-Luc, ZOL
TJT2012 2020-002102-58	Prospective open-label P1/2 clinical trial	Mesenchymal stromal cells	Patients with severe COVID-19 requiring	CHU Liège

			supplemental O2	
ARGX-117-2001 (ArgenX) 2020-001546-19 (completed)	First-in-human, open-label P1 clinical study	ARGX-117 iv (Humanized antibody that blocks C2b)	COVID-19 hospitalized patients	UZ Gent
AT-527 (ATEA pharmaceuticals) 2020-002869-34	Randomized, double blind, placebo controlled, P2 trial	AT-527 (guanosine nucleotide prodrug) Vs placebo	Moderate COVID-19 patients with risk factors for poor outcomes	CHU St-Pierre, AZ St-Maarten (Mechelen)
ABX464-401 (Abivax) 2020-001673-75 Halted for futility	Randomized, double blind, placebo controlled,, P2/3 trial	ABX464 (antiviral) Vs Placebo	Mild-moderate COVID-19 patients with risk factors	UZ Gent, Erasme and CHU Saint-Pierre
COV-AAT 2020-003475-18	Randomized, placebo controlled, double blind Phase 2 study	2-arm: Camostat (antiviral, serine protease inhibitor) vs placebo	Ambulatory COVID-19 patients	UZ Gent
ETHIC trial 2020-003125-39	Open label, randomized, P3b trial	2-arm: Enoxaparin vs SoC	Ambulatory COVID-19 patients	F. Cools / Thrombosis Research Institute
AZD7442 2020-004356-16	Randomized, double blind, placebo controlled, Phase 3 trial	2-arm: AZD 7442 (cocktail of 2 mAb against SARS-CoV-2) Vs Placebo As pre-exposure prohlyaxis	Healthy adults	Astra Zeneca
CONVINCE 2020-002234-32	Open-label, randomized, Phase 4 trial	factorial 2x2 design: Edoxaban and/or colchicine VS No intervention	Ambulatory COVID-19 patients	P Vranckx (Jessaziekenhuis hasselt)
TRISTARDS (Boehringer Ingelheim) 2020-002913-16	Open label, randomized, sequential, parallel-group, adaptive PIIb/III trial	Alteplase (thrombolyticum) High or low dose + SoC vs SoC alone	Hospitalized patients with ARDS	ULB Erasme / HOSP St-Pierre
FITE19 (PTC therapeutics) 2020-001872-13	randomized, double-blind, placebo-controlled, PII/III study	PTC299 (antiviral) Vs placebo	Hospitalized COVID-19 patients	CHU St Pierre / Clinique St Pierre (Ottignies)

MIT-Co001-C101 2020-003403-33	Randomized, double-blind, placebo-controlled, phase 2 trial	Estetrol (E4) + SoC vs placebo + SoC	Hospitalized moderate COVID-19 patients	Erasme Hospital CHR de la Citadelle
C4611001 (Pfizer) 2020-003905-73 (completed)	Phase 1b, 2-part, double blind, placebo controlled	PF07304814 (antiviral) iv vs placebo	Hospitalized moderate COVID-19 patients	Hôpital Erasme CHU Brugmann Institut Jules Bordet CHU UCL Namur C.H.R. de la Citadelle
PANAMO 2020-001335-28	adaptive randomized double blind placebo controlled Phase II/III	IFX-1 (immnomodulator: C5a blocker) + SoC vs placebo + SoC	Hospitalized Patients with severe COVID-19 pneumonia	UZA CHU Dinant Godinne UCL Namur Erasme
DAWN-camostat 2020-005911-27	Randomized double blind controlled trial phase III	camostat mesylate vs placebo	ambulatory COVID-19 patients	UZ Leuven
COVID-RESCAP 2020-001714-38	Randomized, placebo controlled, double blind, phase II	RESCAP (bovine alkaline phosphatase) vs placebo	Severe COVID-19 patients with acute respiratory insufficiency	Jesssa Ziekenhuis Hasselt / B. Stessels
SG018 2020-004743-83	Randomized, double-blind, placebo-controlled, phase III	SNG001 (IFN-β1a) vs placebo	Hospitalised moderate COVID-19 patients	CHU Liège – Sart Tilman AZ Groeninge Kortrijk CHR Citadelle Liège CHU Brugmann Brussels
CV43043 (Roche) 2020-005759-18	Randomized, double-blind, placebo-controlled phase III	RO7496998 (AT-527) vs placebo	Mild to moderate ambulatory COVID-19 patients	3 primary care physicians in BE (Roche: global.rochegenentechtrials@roche.com)
HOPECOVID-19 2021-000492-36	Randomized, double-blind, placebo controlled, phase II	Lactavir vs placebo	Ambulatory COVID-19 patients	UCL
EXEVIR0101 2020-005299-36	FIH, open label, SAD (part 1) Randomised, double blind, placebo controlled (part 2)	XVR011 (bivalent single domain antibody fragment) vs placebo	Hospitalised mild to moderate COVID-19 patients	UZ Gent CHU de Liège UZ Brussel AZ Sint-Maarten, Mechelen CHU Saint-Pierre
1487-0003 (BI 767551) 2021-000408-309	Phase III randomized, double-blind,	BI 767551 (antiviral) Vs placebo	Household contacts to a confirmed	Boehringer Ingelheim Pharma

	placebo-controlled, parallel-group, group-sequential	SARS-CoV-2 infected individual	
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.

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

For pregnant women and children <12y. Request on https://rdvcu.gilead.com/

When using Remdesivir for compassionate use, a notification to umn@fagg-afmps.be and to the ethics committee of the concerned site is to be made. The notification should include the following information:

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

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

5.2. Safety profiles

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

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

Any suspected adverse events related to these drugs should be reported through the usual channels, as part of regular pharmacovigilance activities: www.notifieruneffetindesirable.be or https://www.fagg.be/nl/melden_van_een_bijwerking_als_gezondheidszorgbeoefenaar

5.3. Eligibility criteria for treatment with monoclonal antibodies*

Screening for criteria 1: Laboratory-confirmed, non-severe COVID-19 infection

- SARS-CoV-2 RT-PCR or antigen positive test
- Mild or moderate COVID-19 disease severity**
- Symptom onset <10 days and SARS-CoV-2 positive test <5 days
- Age ≥12 years old
- Informed consent documented in patient's medical dossier

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

If yes to all bullet points, proceed to next step

Screening for criteria 2: Risk factors for severe COVID-19 disease

- **Immunocompromised**, defined as:
  - Hematological malignancy
  - Solid cancer undergoing treatment
  - Solid organ or hematopoetic stem cell transplantation
  - Primary immune deficiency
  - HIV with CD4 <200/mm^3 and/or detectable viral load
  - Prednisolone ≥20mg ≥14 days, or other immunosuppressive drugs: see Superior Health Council list of (potentially) immunosuppressive drugs (link)
  - Sickle-cell anemia
  - Major thalassemia

OR

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

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

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

***Monoclonal antibodies**

- Bamlanivimab + etesivimab
- Casirivimab + imdevimab
- Regdanvimab
- Sotrovimab

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

****Disease severity**

Mild: symptoms of COVID-19 without lower respiratory tract involvement such as dyspnea or abnormal chest imaging

Moderate: clinical or radiological evidence of lower respiratory tract disease and SpO2 ≥ 94% (or no supplemental oxygen required for patients with chronic hypoxia)

Severe: ≥1 of the following:

- Respiratory rate ≥30/min; ≥40/min (children < 5y)
- Blood oxygen saturation ≤93% or need supplemental oxygen
- PaO2/FiO2 ratio <300
- Lung infiltrates >50% of the lung field within 24-48 hours

Immunocompromised patient:

- Patient is eligible for treatment with mAbs regardless of SARS-CoV-2 serology.
- Refer quickly to a multidisciplinary expert panel for approval to start treatment

Patient with at least one comorbidity but not immunocompromised:

- Test SARS-CoV-2 spike protein IgG serology
- If <u>IgG seropositive</u>:
  Not eligible for treatment with mAbs
- If <u>IgG seronegative</u>:
  Patient is eligible for treatment with mAbs
  Refer quickly to a multidisciplinary expert panel for approval to start treatment

5.4. REGEN-COV order form

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

Acrobat Document

6. References

1 Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, *et al.* **Endothelial cell infection and endotheliitis in COVID-19**. *The Lancet* 2020; **395**:1417–1418.

2 Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, *et al.* **Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force**. *Chest* 2006; **129**:174–181.

3 Adamsick ML, Gandhi RG, Bidell MR, Elshaboury RH, Bhattacharyya RP, Kim AY, *et al.* **Remdesivir in Patients with Acute or Chronic Kidney Disease and COVID-19**. *JASN* 2020; **31**:1384–1386.

4 Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns - Clinical Microbiology and Infection. https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00094-X/fulltext (accessed 8 Mar2021).

5 Group TWREA for C-19 T (REACT) W, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, *et al.* **Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis**. *JAMA* Published Online First: 2 September 2020. doi:10.1001/jama.2020.17023

6 Organization WH. **Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020**. Published Online First: 2020.https://apps.who.int/iris/handle/10665/331446 (accessed 16 Mar2020).

7 Russell CD, Millar JE, Baillie JK. **Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury**. *Lancet* 2020; **395**:473–475.

8 The RECOVERY Collaborative Group. **Dexamethasone in Hospitalized Patients with Covid-19**. *N Engl J Med* 2020; :NEJMoa2021436.

9 Investigators TWC for the R-C, Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, *et al.* **Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial**. *JAMA* Published Online First: 2 September 2020. doi:10.1001/jama.2020.17022

10 Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, *et al.* **Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial**. *JAMA* Published Online First: 2 September 2020. doi:10.1001/jama.2020.17021

11 Dequin P-F, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, *et al.* **Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial**. *JAMA* Published Online First: 2 September 2020. doi:10.1001/jama.2020.16761

12 Prescott HC, Rice TW. **Corticosteroids in COVID-19 ARDS: Evidence and Hope During the Pandemic**. *JAMA* Published Online First: 2 September 2020. doi:10.1001/jama.2020.16747

13 van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. **Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes**. *Critical Care* 2020; **24**:696.

14 Mongardon N, Piagnerelli M, Grimaldi D, Perrot B, Lascarrou J-B, Aissaoui N, *et al.* **Impact of late administration of corticosteroids in COVID-19 ARDS**. *Intensive Care Med* 2021; **47**:110–112.

15 Chaudhuri D, Sasaki K, Karkar A, Sharif S, Lewis K, Mammen MJ, *et al.* **Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis**. *Intensive Care Med* 2021; **47**:521–537.

16 Stauffer WM, Alpern JD, Walker PF. **COVID-19 and Dexamethasone: A Potential Strategy to Avoid Steroid-Related Strongyloides Hyperinfection**. *JAMA* 2020; **324**:623–624.

17 Ramakrishnan S, Nicolau DV, Langford B, Mahdi M, Jeffers H, Mwasuku C, *et al.* **Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial**. *The Lancet Respiratory Medicine* 2021; **0**. doi:10.1016/S2213-2600(21)00160-0

18 Group PC, Yu L-M, Bafadhel M, Dorward J, Hayward G, Saville BR, *et al.* **Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial**. *medRxiv* 2021; :2021.04.10.21254672.

19 Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, Schulz J, *et al.* **Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2**. *Nature* 2020; :1–7.

20 Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, *et al.* **Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial**. *The Lancet* 2020; **0**. doi:10.1016/S0140-6736(20)31022-9

21 Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, *et al.* **Remdesivir for the Treatment of Covid-19 — Final Report**. *N Engl J Med* 2020; :NEJMoa2007764.

22 Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, *et al.* **Remdesivir for 5 or 10 Days in Patients with Severe Covid-19**. *New England Journal of Medicine* 2020; **0**:null.

23 Spinner CD, Gottlieb RL, Criner GJ, López JRA, Cattelan AM, Viladomiu AS, *et al.* **Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial**. *JAMA* 2020; **324**:1048–1057.

24 WHO Solidarity Trial Consortium. **Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results**. *New England Journal of Medicine* 2020; **0**:null.

25 Lai C-C, Chen C-H, Wang C-Y, Chen K-H, Wang Y-H, Hsueh P-R. **Clinical efficacy and safety of remdesivir in patients with COVID-19: a systematic review and network meta-analysis of randomized controlled trials**. *J Antimicrob Chemother* Published Online First: 24 March 2021. doi:10.1093/jac/dkab093

26 Del Valle DM, Kim-Schulze S, Huang H-H, Beckmann ND, Nirenberg S, Wang B, *et al.* **An inflammatory cytokine signature predicts COVID-19 severity and survival**. *Nature Medicine* 2020; **26**:1636–1643.

27 Webb BJ, Peltan ID, Jensen P, Hoda D, Hunter B, Silver A, *et al.* **Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study**. *The Lancet Rheumatology* 2020; **2**:e754–e763.

28 Alzghari SK, Acuña VS. **Supportive Treatment with Tocilizumab for COVID-19: A Systematic Review**. *J Clin Virol* 2020; **127**:104380.

29 Xu X, Han M, Li T, Sun W, Wang D, Fu B, *et al.* **Effective treatment of severe COVID-19 patients with tocilizumab**. *PNAS* Published Online First: 29 April 2020. doi:10.1073/pnas.2005615117

30 Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, *et al.* **Efficacy of Tocilizumab in Patients Hospitalized with Covid-19**. *New England Journal of Medicine* Published Online First: 21 October 2020. doi:10.1056/NEJMoa2028836

31 Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, *et al.* **Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial**. *JAMA Intern Med* Published Online First: 20 October 2020. doi:10.1001/jamainternmed.2020.6615

32 Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P, *et al.* **Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial**. *JAMA Intern Med* Published Online First: 20 October 2020. doi:10.1001/jamainternmed.2020.6820

33 Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC-C, *et al.* **Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19**. *Clin Infect Dis* Published Online First: 27 April 2020. doi:10.1093/cid/ciaa478

34 Renn A, Fu Y, Hu X, Hall MD, Simeonov A. **Fruitful Neutralizing Antibody Pipeline Brings Hope To Defeat SARS-Cov-2**. *Trends in Pharmacological Sciences* 2020; **0**. doi:10.1016/j.tips.2020.07.004

35 Marovich M, Mascola JR, Cohen MS. **Monoclonal Antibodies for Prevention and Treatment of COVID-19**. *JAMA* 2020; **324**:131–132.

36 Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, *et al.* **SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19**. *New England Journal of Medicine* 2020; **0**:null.

37 Lundgren J. **A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19**. *New England Journal of Medicine* 2020; **0**:null.

38 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:doi:10.1001/jama.2021.0202

39 BAMLANIVIMAB+ETESEVIMAB FOR TREATMENT OF COVID-19 IN HIGH-RISK AMBULATORY PATIENTS. CROI Conference. https://www.croiconference.org/abstract/bamlanivimabetesevimab-for-treatment-of-covid-19-in-high-risk-ambulatory-patients/ (accessed 10 May2021).

40 Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, *et al.* **REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19**. *New England Journal of Medicine* 2021; **384**:238–251.

41 Weinreich D, Sivapalasingam S, Norton TD, Ali S, Gao H, Bhore R, *et al.* **REGEN-COV Antibody Cocktail Clinical Outcomes Study in Covid-19 Outpatients**. *medRxiv* 2021; :2021.05.19.21257469.

42 O'Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan K-C, Sarkar N, *et al.* **Subcutaneous REGEN-COV Antibody Combination for Covid-19 Prevention**. *medRxiv* 2021; :2021.06.14.21258567.

43 Group RC, Horby PW, Mafham M, Peto L, Campbell M, Pessoa-Amorim G, *et al.* **Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial**. *medRxiv* 2021; :2021.06.15.21258542.

44 Cathcart AL, Havenar-Daughton C, Lempp FA, Ma D, Schmid MA, Agostini ML, *et al.* **The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2**. *bioRxiv* 2021; :2021.03.09.434607.

45 Hoffmann M, Hofmann-Winkler H, Krüger N, Kempf A, Nehlmeier I, Graichen L, *et al.* **SARS-CoV-2 variant B.1.617 is resistant to Bamlanivimab and evades antibodies induced by infection and vaccination**. *bioRxiv* 2021; :2021.05.04.442663.

46 Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, *et al.* **Reduced sensitivity of infectious SARS-CoV-2 variant B.1.617.2 to monoclonal antibodies and sera from convalescent and vaccinated individuals**. *bioRxiv* 2021; :2021.05.26.445838.

47 Bandopadhyay P, Rozario RD, Lahiri A, Sarif J, Ray Y, Paul SR, *et al.* **Nature and dimensions of the systemic hyper-inflammation and its attenuation by convalescent plasma in severe COVID-19**. *The Journal of Infectious Diseases* Published Online First: 12 January 2021. doi:10.1093/infdis/jiab010

48 Valk SJ, Piechotta V, Chai KL, Doree C, Monsef I, Wood EM, *et al.* **Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review**. *Cochrane Database of Systematic Reviews* Published Online First: 2020. doi:10.1002/14651858.CD013600

49 Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, *et al.* **Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma**. *JAMA* Published Online First: 27 March 2020. doi:10.1001/jama.2020.4783

50 Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, *et al.* **Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial**. *JAMA* Published Online First: 3 June 2020. doi:10.1001/jama.2020.10044

51 Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P, *et al.* **Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial)**. *BMJ* 2020; **371**:m3939.

52 Gharbharan A, Jordans CCE, GeurtsvanKessel C, den Hollander JG, Karim F, Mollema FPN, *et al.* **Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection**. *Nat Commun* 2021; **12**:3189.

53 Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, *et al.* **A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia**. *New England Journal of Medicine* 2020; **0**:null.

54 Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, *et al.* **Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial**. *The Lancet* 2021; **397**:2049–2059.

55 Piechotta V, Iannizzi C, Chai KL, Valk SJ, Kimber C, Dorando E, *et al.* **Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review**. *Cochrane Database Syst Rev* 2021; **5**:CD013600.

56 Libster R, Marc GP, Wappner D, Coviello S, Bianchi A, Braem V, *et al.* **Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults**. *New England Journal of Medicine* Published Online First: 6 January 2021. doi:10.1056/NEJMoa2033700

57 Hueso T. **Convalescent plasma therapy for B-cell–depleted patients with protracted COVID-19**. ; :6.

58 Betrains A, Godinas L, Woei-A-Jin FJSH, Rosseels W, Herck YV, Lorent N, *et al.* **Convalescent plasma treatment of persistent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in patients with lymphoma with impaired humoral immunity and lack of neutralising antibodies**. *British Journal of Haematology* 2021; **192**:1100–1105.

59 Kemp SA, Collier DA, Datir RP, Ferreira IATM, Gayed S, Jahun A, *et al.* **SARS-CoV-2 evolution during treatment of chronic infection**. *Nature* 2021; :1–10.

60 Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, *et al.* **Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7**. *Nature* 2021; **593**:130–135.

61 Kunze KL, Johnson PW, Helmond N van, Senefeld JW, Petersen MM, Klassen SA, *et al.* **Mortality in individuals treated with COVID-19 convalescent plasma varies with the geographic provenance of donors**. *medRxiv* 2021; :2021.03.19.21253975.

62 Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, *et al.* **Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19**. *New England Journal of Medicine* Published Online First: 11 December 2020. doi:10.1056/NEJMoa2031994

63 Marconi VC, Ramanan AV, Bono S de, Kartman CE, Krishnan V, Liao R, *et al.* **Efficacy and safety of baricitinib in patients with COVID-19 infection: Results from the randomised, double-blind, placebo-controlled, parallel-group COV-BARRIER phase 3 trial**. *medRxiv* 2021; :2021.04.30.21255934.

64 Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, *et al.* **Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial**. *J Allergy Clin Immunol* 2020; **146**:137-146.e3.

65 Yuan S, Chan CC-Y, Chik KK-H, Tsang JO-L, Liang R, Cao J, *et al.* **Broad-Spectrum Host-Based Antivirals Targeting the Interferon and Lipogenesis Pathways as Potential Treatment Options for the Pandemic Coronavirus Disease 2019 (COVID-19)**. *Viruses* 2020; **12**. doi:10.3390/v12060628

66 Hung IF-N, Lung K-C, Tso EY-K, Liu R, Chung TW-H, Chu M-Y, *et al.* **Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial**. *Lancet* 2020; **395**:1695–1704.

67 Rahmani H, Davoudi-Monfared E, Nourian A, Khalili H, Hajizadeh N, Jalalabadi NZ, *et al.* **Interferon β-1b in treatment of severe COVID-19: A randomized clinical trial**. *Int Immunopharmacol* 2020; **88**:106903.

68 Davoudi-Monfared E, Rahmani H, Khalili H, Hajiabdolbaghi M, Salehi M, Abbasian L, *et al.* **A Randomized Clinical Trial of the Efficacy and Safety of Interferon β-1a in Treatment of Severe COVID-19**. *Antimicrobial Agents and Chemotherapy* 2020; **64**. doi:10.1128/AAC.01061-20

69 Ader F, Peiffer-Smadja N, Poissy J, Bouscambert-Duchamp M, Belhadi D, Diallo A, *et al.* **An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with COVID-19**. *Clinical Microbiology and Infection* 2021; **0**. doi:10.1016/j.cmi.2021.05.020

70 Feld J, Kandel C, Biondi M. Peginterferon-lambda for the treatment of COVID-19 in outpatients | medRxiv. https://www.medrxiv.org/content/10.1101/2020.11.09.20228098v1 (accessed 6 Apr2021).

71 Jagannathan P, Andrews JR, Bonilla H, Hedlin H, Jacobson KB, Balasubramanian V, *et al.* **Peginterferon Lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial**. *Nat Commun* 2021; **12**:1967.

72 Huang Y-Q, Tang S-Q, Xu X-L, Zeng Y-M, He X-Q, Li Y, *et al.* **No Statistically Apparent Difference in Antiviral Effectiveness Observed Among Ribavirin Plus Interferon-Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon-Alpha in Patients With Mild to Moderate Coronavirus Disease 2019: Results of a Randomized, Open-Labeled Prospective Study**. *Front Pharmacol* 2020; **11**. doi:10.3389/fphar.2020.01071

73 Zhou Q, Chen V, Shannon CP, Wei X-S, Xiang X, Wang X, *et al.* **Interferon-α2b Treatment for COVID-19**. *Front Immunol* 2020; **11**. doi:10.3389/fimmu.2020.01061

74 Khamis F, Naabi HA, Lawati AA, Ambusaidi Z, Sharji MA, Barwani UA, *et al.* **Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia**. *International Journal of Infectious Diseases* 2021; **102**:538–543.

75 Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, *et al.* **Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial**. *The Lancet Respiratory Medicine* 2021; **9**:196–206.

76 Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, *et al.* **Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro**. *Cell Research* 2020; :1–3.

77 Group TRC. **Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19**. *New England Journal of Medicine* Published Online First: 8 October 2020. doi:10.1056/NEJMoa2022926

78 Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, *et al.* **Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19**. *New England Journal of Medicine* 2020; **0**:null.

79 Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, *et al.* **Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19**. *Annals of Internal Medicine* Published Online First: 16 July 2020. doi:10.7326/M20-4207

80 Mitjà O, Corbacho-Monné M, Ubals M, Tebe C, Peñafiel J, Tobias A, *et al.* **Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial**. *Clin Infect Dis* Published Online First: 16 July 2020. doi:10.1093/cid/ciaa1009

81 Mitjà O, Corbacho-Monné M, Ubals M, Alemany A, Suñer C, Tebé C, *et al.* **A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19**. *New England Journal of Medicine* 2020; **0**:null.

82 Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, *et al.* **A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19**. *N Engl J Med* 2020; :NEJMoa2001282.

83 Osborne V, Davies M, Lane S, Evans A, Denyer J, Dhanda S, *et al.* **Lopinavir-Ritonavir in the Treatment of COVID-19: A Dynamic Systematic Benefit-Risk Assessment**. *Drug Saf* Published Online First: 23 June 2020. doi:10.1007/s40264-020-00966-9

84 Horby PW, Mafham M, Bell JL, Linsell L, Staplin N, Emberson J, *et al.* **Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial**. *The Lancet* 2020; **0**. doi:10.1016/S0140-6736(20)32013-4

85 Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, *et al.* **Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro**. *Cell Research* 2020; :2019–2021.

86 Shiraki K, Daikoku T. **Favipiravir, an anti-influenza drug against life-threatening RNA virus infections**. *Pharmacology & Therapeutics* 2020; **209**:107512.

87 Kaptein SJF, Jacobs S, Langendries L, Seldeslachts L, Horst S ter, Liesenborghs L, *et al.* **Favipiravir at high doses has potent antiviral activity in SARS-CoV-2−infected hamsters, whereas hydroxychloroquine lacks activity**. *PNAS* Published Online First: 9 October 2020. doi:10.1073/pnas.2014441117

88 Driouich J, Cochin M, Lingas G. **Favipiravir antiviral efficacy against SARS-CoV-2 in a hamster model.** *Nat Commun* 2021; **12**:1735–1735.

89 Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, *et al.* **Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study**. *Engineering* Published Online First: 2020. doi:10.1016/j.eng.2020.03.007

90 Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, *et al.* **AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase II/III Multicenter Randomized Clinical Trial**. *Clin Infect Dis* Published Online First: 9 August 2020. doi:10.1093/cid/ciaa1176

91 Solaymani-Dodaran M, Ghanei M, Bagheri M, Qazvini A, Vahedi E, Hassan Saadat S, *et al.* **Safety and efficacy of Favipiravir in moderate to severe SARS-CoV-2 pneumonia**. *Int Immunopharmacol* 2021; **95**:107522.

92 Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, *et al.* **SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor**. *Cell* 2020; **181**:271-280.e8.

93 Gunst JD, Staerke NB, Pahus MH, Kristensen LH, Bodilsen J, Lohse N, *et al.* **Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial.** *EClinicalMedicine* 2021; :100849.

94 Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Sevestre J, *et al.* **Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study**. *Travel Medicine and Infectious Disease* 2020; :101663.

95 Abaleke E, Abbas M, Abbasi S, Abbott A, Abdelaziz A, Abdelbadiee S, *et al.* **Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial**. *The Lancet* 2021; **0**. doi:10.1016/S0140-6736(21)00149-5

96 Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter J-J. **Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019**. *Chest* Published Online First: 13 October 2020. doi:10.1016/j.chest.2020.10.009

97 Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, *et al.* **A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness**. *Int J Infect Dis* 2020; **103**:214–216.

98 Podder C, Chowdhury N, Sina M, Haque W. **Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study**. *IMC Journal of Medical Science* 2020; **14**.

99 Chaccour C, Casellas A, Matteo AB-D, Pineda I, Fernandez-Montero A, Ruiz-Castillo P, *et al.* **The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial**. *EClinicalMedicine* 2021; **0**. doi:10.1016/j.eclinm.2020.100720

100 Babalola OE, Bode CO, Ajayi AA, Alakaloko FM, Akase IE, Otrofanowei E, *et al.* **Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double-blind, dose-response study in Lagos**. *QJM: An International Journal of Medicine* Published Online First: 18 February 2021. doi:10.1093/qjmed/hcab035

101 Pott-Junior H, Bastos Paoliello MM, Miguel A de QC, da Cunha AF, de Melo Freire CC, Neves FF, *et al.* **Use of ivermectin in the treatment of Covid-19: A pilot trial**. *Toxicol Rep* 2021; **8**:505–510.

102 Seet RCS, Quek AML, Ooi DSQ, Sengupta S, Lakshminarasappa SR, Koo CY, *et al.* **Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: An open-label randomized trial**. *Int J Infect Dis* 2021; **106**:314–322.

103 Okumuş N, Demirtürk N, Çetinkaya RA, Güner R, Avcı İY, Orhan S, *et al.* **Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients**. *BMC Infectious Diseases* 2021; **21**:411.

104 Galan LEB, Santos NMD, Asato MS, Araújo JV, de Lima Moreira A, Araújo AMM, *et al.* **Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection**. *Pathog Glob Health* 2021; :1–8.

105 López-Medina E, López P, Hurtado IC, Dávalos DM, Ramirez O, Martínez E, *et al.* **Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial**. *JAMA* Published Online First: 4 March 2021. doi:10.1001/jama.2021.3071

106 Samaha AA, Mouawia H, Fawaz M, Hassan H, Salami A, Bazzal AA, *et al.* **Effects of a Single Dose of Ivermectin on Viral and Clinical Outcomes in Asymptomatic SARS-CoV-2 Infected Subjects: A Pilot Clinical Trial in Lebanon**. *Viruses* 2021; **13**:989.

107 Roman YM, Burela PA, Pasupuleti V, Piscoya A, Vidal JE, Hernandez AV. **Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials**. *Clinical Infectious Diseases* Published Online First: 28 June 2021. doi:10.1093/cid/ciab591

108 Garegnani LI, Madrid E, Meza N. **Misleading clinical evidence and systematic reviews on ivermectin for COVID-19**. *BMJ Evidence-Based Medicine* Published Online First: 22 April 2021. doi:10.1136/bmjebm-2021-111678

109 Schlesinger N, Firestein BL, Brunetti L. **Colchicine in COVID-19: an Old Drug, New Use**. *Curr Pharmacol Rep* 2020; :1–9.

110 Tardif J-C, Bouabdallaoui N, L'Allier PL, Gaudet D, Shah B, Pillinger MH, *et al.* **Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial**. *The Lancet Respiratory Medicine* 2021; **0**. doi:10.1016/S2213-2600(21)00222-8

111 Russell CD. **Exploiting an early immunological window of opportunity in COVID-19**. *The Lancet Respiratory Medicine* 2021; **0**. doi:10.1016/S2213-2600(21)00225-3

112 Vrachatis DA, Giannopoulos GV, Giotaki SG, Raisakis K, Kossyvakis C, Iliodromitis KE, *et al.* **Impact of colchicine on mortality in patients with COVID-19: A meta-analysis**. *Hellenic Journal of Cardiology* Published Online First: 6 January 2021. doi:10.1016/j.hjc.2020.11.012

113 Deftereos SG, Siasos G, Giannopoulos G, Vrachatis DA, Angelidis C, Giotaki SG, *et al.* **The GReek study in the Effects of Colchicine in COvid-19 complications prevention (GRECCO-19 study): rationale and study design**. *Hellenic Journal of Cardiology* Published Online First: 3 April 2020. doi:10.1016/j.hjc.2020.03.002

114 Lopes MI, Bonjorno LP, Giannini MC, Amaral NB, Benatti MN, Rezek UC, *et al.* **Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomized, double-blinded, placebo controlled clinical trial**. *medRxiv* 2020; :2020.08.06.20169573.

115 Bianconi V, Violi F, Fallarino F, Pignatelli P, Sahebkar A, Pirro M. **Is Acetylsalicylic Acid a Safe and Potentially Useful Choice for Adult Patients with COVID-19 ?** *Drugs* 2020; :1–14.

116 Chow JH, Khanna AK, Kethireddy S, Yamane D, Levine A, Jackson AM, *et al.* **Aspirin Use is Associated with Decreased Mechanical Ventilation, ICU Admission, and In-Hospital Mortality in Hospitalized Patients with COVID-19**. *Anesthesia & Analgesia* 2020; **Publish Ahead of Print**. doi:10.1213/ANE.0000000000005292

117 Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. **Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19**. *New England Journal of Medicine* 2020; **382**:2431–2440.

118 Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, *et al.* **Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19**. *New England Journal of Medicine* 2020; **382**:2441–2448.

119 Cohen JB, Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, *et al.* **Continuation versus discontinuation of renin–angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial**. *The Lancet Respiratory Medicine* 2021; **0**. doi:10.1016/S2213-2600(20)30558-0

120 Lund LC, Kristensen KB, Reilev M, Christensen S, Thomsen RW, Christiansen CF, *et al.* **Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: A Danish nationwide cohort study**. *PLOS Medicine* 2020; **17**:e1003308.

121 Qiao J. **What are the risks of COVID-19 infection in pregnant women?** *The Lancet* 2020; **395**:760–762.

122 Burwick RM, Yawetz S, Stephenson KE, Collier A-RY, Sen P, Blackburn BG, *et al.* **Compassionate Use of Remdesivir in Pregnant Women with Severe Covid-19**. *Clin Infect Dis* doi:10.1093/cid/ciaa1466

123 Gupta A, Gonzalez-Rojas Y, Juarez E, Casal MC, Moya J, Falci DR, *et al.* **Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab**. *medRxiv* 2021; :2021.05.27.21257096.

124 Thorlund K, Dron L, Park J, Hsu G, Forrest JI, Mills EJ. **A real-time dashboard of clinical trials for COVID-19**. *The Lancet Digital Health* Published Online First: 24 April 2020. doi:10.1016/S2589-7500(20)30086-8

125 Delang L, Abdelnabi R, Neyts J. **Favipiravir as a potential countermeasure against neglected and emerging RNA viruses**. *Antiviral Research* 2018; **153**:85–94.

126 Furuta Y, Komeno T, Nakamura T. **Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase**. *Proceedings of the Japan Academy, Series B* 2017; **93**:449–463.

127 Zhou Y, Vedantham P, Lu K, Agudelo J, Carrion R, Nunneley JW, *et al.* **Protease inhibitors targeting coronavirus and filovirus entry**. *Antiviral Research* 2015; **116**:76–84.

128 Zumla A, Chan JFW, Azhar EI, Hui DSC, Yuen K-Y. **Coronaviruses — drug discovery and therapeutic options**. *Nature Reviews Drug Discovery* 2016; **15**:327–347.

129 Clementi N, Ferrarese R, Criscuolo E, Diotti RA, Castelli M, Scagnolari C, *et al.* **Interferon-β-1a Inhibition of Severe Acute Respiratory Syndrome–Coronavirus 2 In Vitro When Administered After Virus Infection**. *J Infect Dis* 2020; **222**:722–725.

130 Haagmans BL, Kuiken T, Martina BE, Fouchier RAM, Rimmelzwaan GF, van Amerongen G, *et al.* **Pegylated interferon-alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques**. *Nat Med* 2004; **10**:290–293.

131 Falzarano D, de Wit E, Rasmussen AL, Feldmann F, Okumura A, Scott DP, *et al.* **Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques**. *Nat Med* 2013; **19**:1313–1317.