22 October 2021

Report of the COVID-19 therapeutics sub-group

COVID-19 therapeutics portfolio – list of ten most promising candidates

Contents

The opinions of the COVID-19 therapeutics sub-group present the views of the independent scientists who are members of the sub-group. They do not necessarily reflect the views of the European Commission nor its services. The opinions are published by the European Union in their original language only.

Executive Summary

The COVID-19 therapeutics sub-group of the European expert group on SARS-CoV-2 variants has been requested to establish a broad and diverse portfolio of COVID-19 therapeutic candidates in the development pipeline, and identify the most promising ten. Since different stage and severity of the disease, as well as different individual risks require different therapeutic approaches, experts first identified product categories of interest and then populated the categories with actual therapeutic candidates following objective and science-based criteria.

In selecting the 10 most promising candidates, experts focused on the products with the highest potential impact on the pandemic but also with a high likelihood to reach European patients soon. Three types of products emerged from the criteria-based screening: antiviral monoclonal antibodies, oral antivirals and immunomodulators.

Following screening of 82 therapeutic candidates in late stage clinical development, experts identified 10 candidates as the most promising. The list represents a snapshot of the frontrunners in the portfolio, recognising the dynamic nature of this list as new scientific & clinical evidence emerges. For many important product categories (such as long COVID treatment) there are not yet candidates that could meet the selection criteria.

The list of ten most promising COVID-19 therapeutic candidates in the EU context:

Antiviral monoclonal antibodies	Oral antivirals	Immunomodulators
casirivimab/imdevimab (Ronapreve)	**molnupiravir**	**tocilizumab** (RoActemra)
sotrovimab (Xevudy)	**PF-07321332**	**anakinra** (Kineret)
tixagevimab/cilgavimab (Evusheld)	**AT-527**	**baricitinib** (Olumiant)
		lenzimulab

Recommendations of the group to the European Commission:

1. Antivirals should not be considered as an alternative to the vaccination.
2. Ensure that the most promising products are tested in randomised, blinded, extensive, multicentre, credible studies which yield data that can be used for regulatory and health technology assessment purposes.
3. Ensure that the most promising products receive sufficient support from regulators, funding bodies, scientists, and medical specialists.
4. Products that are approved for use in the EU should be rapidly and widely available to patients.
5. The three categories listed in the document are all important. All three goals are achievable and required: limiting the infection, and limiting the damage to organs and tissues, which will ultimately lead to reduced potential for long COVID symptoms.
6. Antivirals should be administered as early as possible to prevent viral transmission and uncontrolled disease progression.
7. Emergence of variants should be monitored by genotyping and phenotyping, and special focus should be placed on the development of combined therapies.

1. Task assignment

The European expert group on SARS-CoV-2 variants, and more specifically its sub-group on COVID-19 therapeutics has been requested by the Commission to **establish a broader portfolio of promising therapeutic products**, both authorised and under development, that have the potential to comprise the EU's future therapeutic arsenal to fight COVID-19.

The sub-group is tasked to identify **product categories** that would fit within the scope of the portfolio, and to establish **objective and science-based criteria for selecting products** to the portfolio. Once the product categories and selection criteria have been established, the sub-group shall screen the global COVID-19 therapeutics development pipelines and populate the categories with promising product candidates. By mid-October 2021, the sub-group shall **identify the 10 most promising COVID-19 therapeutic candidates** and formulate recommendations for the European Commission.

2. Working methods

Since different target populations and different stages/severity of the disease require different therapeutic approaches, the sub- group first needed to define a number of product categories, and selection criteria for candidates to populate the categories of the portfolio with actual products.

The selection criteria and product categories were submitted to the Pharmaceutical Committee, which met and discussed the drafts on 17 September. Following the positive opinion from Member States in the Pharmaceutical Committee, the sub-group initiated the identification of candidates.

Experts defined the pool of candidates of focus: candidates already in late stage clinical development (phase III or phase II/III), extended to include products in different clinical stages with particularly promising profiles, if specifically recommended by an expert. To date, more than 80 products have been screened.

Each candidate from the pool was systematically assessed against the selection criteria, and experts ranked them based on the impact the candidate might have in COVID-19 treatment and on the likelihood of success both to achieve the desired impact and to be authorised in the European market. Moreover, experts also considered the timeframe for entry into the European market when deciding which products to prioritise.

Once each product in the pool had been assessed for its individual merits, the experts compiled a portfolio of the best candidates, ensuring a broad coverage of product categories, target populations and technologies.

3. Product categories

COVID-19 is a disease caused by SARS-CoV-2, associated with a wide range of symptoms in infected individuals. While morbidity and mortality are limited in the young and otherwise healthy population, the disease may have a severe course with potentially fatal outcomes in patients with underlying conditions and in both, middle-aged and older populations. Considering the treatment rationale and targets groups for the treatment, it is worth remembering that the disease may have long-lasting consequences in all patient groups, including those with a mild clinical picture.

Moreover, the problem with COVID-19 is all the greater because it is a disease where the virus affects numerous organs and organ systems, leading to complex immunopathogenic disorders.

Since different target populations and different stages/severity of the disease require different therapeutic approaches, the expert group has defined a number of product categories. These help to compare and prioritise the various therapeutic candidates and set the scope for the expert group's work. The identified product categories are set out in the table below, based on the mechanism of action and the target population.

Mechanism of Action / Target Group	I. Antivirals	II. Immuno-modulators	III. Other treatments (eg. symptomatic, anticoagulant)
1. Pre-exposure prophylaxis	**X**		
2.A Post-exposure prophylaxis	**X**		
2.B Asymptomatic virus carriers	**X**		
3.A Outpatients: mild to moderate	**X**	(X)	(X)
3.B Hospitalized: moderate to severe	**X**	**X**	**X**
3.C Hospitalized: critical	(X)	**X**	**X**
4. long COVID			**X**

X – primary product category targets of the portfolio
(X) – additional product category targets

Table 1: Product categories considered by the experts based on mechanism and target population.

Mechanism of action

Based on their mechanism of action, experts grouped COVID-19 therapeutics in three categories: antivirals, immunomodulators, and others. The first category encompasses all the products that interfere with the replication of the virus, e.g., by blocking the entry of SARS-CoV-2 using monoclonal antibodies, blocking virus replication with polymerase or protease inhibitors, or modifying the cellular microenvironment, making it non-permissive to the virus. These products should be administered during the virus replication phase, so as early as possible in the disease course in order to prevent uncontrolled disease progression. The second category encompasses products that aim to down-modulate the uncontrolled and excessive immune responses triggered in the second phase of the disease when the virus replication is already at lower levels. These medicines should be, consequently, administered later during the disease course. This is especially important since modulation of immune responses may, in some cases, enhance the replication of the virus. The third

category of medicines described in this document encompasses therapeutics used to relieve symptoms of the COVID-19 disease, irrespective of the time of occurrence.

The horizontal axis of the table represents these categories:

I. **Antivirals:** targeting the virus entry, replication, preferentially provided in combined therapy to avoid the resistance emergence, particularly in case of some monoclonal antibodies.
II. **Immunomodulators:** limiting the damage resulting from the improper immune responses, including cell-based therapy.
III. **Other treatments:** agents for the treatment of the disease symptoms or complications, responsible for the overall severity of the disease (e.g., thrombosis)

Therapeutic approach

The disease may be divided into three phases, which require different therapeutic approaches. In the first phase, the virus replicates efficiently in the respiratory tract facilitating its spread to other organs. In the second phase, the improper and exaggerated immune response to the virus infection occurs, even though the replication of SARS-CoV-2 is already in decline (NB some immunocompromised patients, especially those on biological therapy, may still have high levels of virus replication). At this stage, the damage results mainly from this exaggerated immune response and disturbed homeostasis. The third phase is referred to as a long COVID, is a direct consequence of phases I and II. The multiorgan damage resulting from the virus replication, improper immune responses, and disturbed homeostasis may leave a long-lasting mark on the individual's health. The impact of SARS-CoV-2 infection on the respiratory tract, cardiovascular system, and neurological system is well described, consequences for other organs are still under debate (e.g. reproductive system or pancreas). In addition, in patients with severe forms of the disease, including critical patients, the disease often results in short-term and possibly long-term consequences for mental health.

All three stages occur sequentially, and each requires a different therapeutic approach. The vertical axis of the product categories table defines the proposed various therapeutic approaches.

1. <u>Pre-exposure prophylaxis</u>

Time frame: before the exposure, when at risk of SARS-CoV-2 infection.

Major aim: to reduce the risk of infection.

Brief description: medicinal products or medical devices in this category should be preferentially administered topically or systematically, in order to limit the patient's susceptibility to being infected with the virus. This may be achieved by inactivating the virus, limiting the virus mobility, restricting the interaction between the virus and its human cellular receptor or co-receptors, or interfering with the cellular pathways critical during the early stages of the infection.

Target groups: Individuals who may not be vaccinated or who do not respond to the vaccination and at the same time belong to the group at high risk of developing severe disease (e.g., age, underlying conditions).

Notes: Inappropriate use of such products is associated with a high risk of resistant variants' development and should be restricted to the special groups of patients described above. Entry inhibitors may be affected in the seropositive individuals, and their efficacy may decrease in time, with the emergence of new variants.

We certainly emphasise and underline that **vaccination is the best form of prophylaxis** and the therapeutic agents may not be considered as an alternative.

2. Post-exposure prophylaxis

A. Exposed to positive COVID-19 contact

Time frame: from the exposure to the development of symptoms.

Major aim: to block the replication of the virus and prevent transmission of infection and the disease development.

Brief description: Medicinal products or medical devices in this category should interfere with virus replication either as directly acting antivirals or indirectly by inhibiting cellular pathways essential for SARS-CoV-2 infection or by activation of innate antiviral immunity.

The main classes are described below:

a) **Entry inhibitors**. Therapeutics affecting the entry of the virus to the susceptible cell. These compounds (small molecules, large molecules, biologicals, and others) may interfere with the interaction of the virus with the receptor, inactivate the spike protein, or limit the presence of receptors/co-receptors on the cells, as well as block the activation of the S protein (serine protease inhibitors) or the fusion process itself (e.g., blocking the structural switch of the S protein, fusion peptide function, or the membrane rearrangements). Examples are monoclonal antibodies targeting the viral proteins, receptor traps or inhibitors of the cellular serine proteases essential for virus entry.

b) **Replication inhibitors**. Any therapy that blocks the replication of the viral genome, affecting the essential viral proteins. It is essential to develop directly acting antivirals targeting particular virus proteins. Primary candidates are the nsp12/7/8/13 polymerase complex, nsp3 (PL^{pro}) and nsp5 (M^{pro}) cysteine proteases, but also nsp14/nsp15 exoribonucleases essential for the viral proof-reading mechanism or nsp14/16 methyltransferases required for the viral RNA cap methylation, and virtually any other viral protein essential for the viral replication would be potential targets. Further, the viral RNA may be targeted using siRNAs or antisense molecules. Replication inhibitors may also modulate cellular pathways required for the viral replication and processes such as Double Membrane Vesicle formation.

c) **Virus assembly and release inhibitors** interfere with RNA packaging, assembly or release of new virions. This category may include inhibitors of viral structural proteins but also intracellular processes required for virus maturation and transport of viable particles within the infected cell.

d) **Modulators of the innate immune response**. These products may directly activate interferon secretion or promote recognition of the virus in infected cells by increasing their sensitivity to the presence of e.g., dsRNA. These therapies will induce intracellular antiviral response pathways.

Target groups: Individuals who have not been vaccinated or who do not respond sufficiently well to vaccination and at the same time belong to the group at high risk of severe disease development (e.g., age, co-morbidity or underlying conditions), such as e.g. immunocompromised patients. Patients with prolonged virus replication and convalescents at risk should also be considered, as they may be re-infected.

Notes: Inappropriate use of such products may be associated with a high risk of development of resistant variants and should be restricted to the special groups of patients. Entry inhibitors may show reduced efficacy in seropositive individuals, and their efficacy may decrease with new SARS-CoV-2 variants emerging.

B. Asymptomatic virus carriers

Time frame: at the time of virus laboratory detection (positive SARS-CoV-2 test).

Major aim: to prevent transmission of infection.

Brief description: Treatment of asymptomatic carriers may be considered using the therapeutics described in section A (antivirals), aiming to decrease the virus load in the bodily fluids and its consequent transmission. However, considering the risk of resistant variants emerging, the most effective and desirable strategy is based on isolation of the infected individuals.

Target groups: persons who do not have clinical symptoms but have a proven positive SARS-CoV-2 testing result in the nasopharyngeal and / or throat swabs.

Notes: Inappropriate use of such products can be associated with a high risk of development of resistant variants and should be restricted to the special groups of individuals who are working in health care system, nursing homes or working in service industries where they are in contact with a large number of people (services to be determined).

3. Treatment of various clinical forms of COVID-19

A. Outpatients- mild to moderate

Time frame: from the development of symptoms to <7 days after the symptoms appear.

Major aim: to limit the replication of the virus and prevent the disease progression.

Brief description: Antivirals, as listed in section 2.A and immunomodulators for consideration with patients with mild disease to prevent the induction of an improper immune response.

Target groups: Individuals who may not be vaccinated or who do not respond to the vaccination and at the same time belong to the group at high risk of severe disease development (e.g., age, underlying conditions). Immunocompromised patients, where the infection may be prolonged and recurrent disease is observed over time. People in high risk groups who have been vaccinated or have had COVID-19 should also be considered. Special consideration should be given to the risk of long COVID development.

B. Hospitalized[1] - moderate to severe

Time frame: immediately and up to 5-7 days post appearance of symptoms (antivirals) and/or 5-7 days post-development of symptoms[2] (i.e., antivirals, Immunomodulators and agents for the treatment of the disease symptoms or complications).

Major aim: To stop viremia, to modulate the immune response and to limit immunopathogenesis and potential complications (e.g. thrombosis)

Brief description: Treatment with antivirals should be considered, as described in the section 2.A. Further, in the second stage of the disease knowledge of both pathophysiology of COVID-19 and immunomodulatory therapy are important to treat COVID-19 appropriately. Pathophysiology is about the disease itself and immunomodulatory therapy is about how we should use immunomodulators to treat moderate/severe COVID-19. The clinical picture may change very quickly, which leaves some areas of uncertainty.

Target groups: Patients with moderate to severe disease course, according to COVID-19 severity index (national/international scales)

Notes: Additional data and studies on the type, timing and duration of immunomodulators administration are required. The use of these medicines can be effective in preventing the development of severe forms of the disease and the long-term consequences of COVID-19, but also inappropriate use can lead to negative consequences.

C. Hospitalized - Critical

Time frame: Immediate critical care therapy

Major aim: haemodynamics maintenance, oxygenation and ventilation, acute kidney injury and replacement therapy, pharmacological interventions (including antimicrobials due to nosocomial infections), extracorporeal membrane oxygenation, antithrombotic therapy, but also immunomodulators.

Brief description: In addition to pulmonary disease, critically ill patients with COVID-19 may experience cardiac, hepatic, renal, and central nervous system disease.

Target groups: critically ill patients.

Notes: Additional life-saving interventions on top of antivirals, and immunomodulators, described in section 3.b.

4. <u>Treatment of long COVID</u>

[1] it will probably be necessary to make subgroups of patients in relation to the underlying conditions, previously healthy vs. chronic diseases e.g. high blood pressure, diabetes, immunocompromised patients e.g. transplantated

[2] It is important to start immunomodulatory therapy as soon as possible due to the rapid development of immunopathogenetic mechanisms, which on the other hand due to viremia may be contraindicated. It will be necessary to define relevant biomarkers for initiating immunomodulatory therapy, with possible detection and monitoring of viremia, which would help in deciding whether to initiate immunomodulatory therapy.

Prevention of severe long COVID development will be best achieved by limiting disease progression as soon as possible.

Treatment of various manifestations of long COVID i.e., pulmonary symptoms; cardiovascular symptoms; fatigue, cognitive and neuropsychiatric symptoms; other organ impairments, should be considered in the future by multidisciplinary team of clinicians. As well as rehabilitation of patients with such long-lasting symptoms.

4. Selection criteria

Experts have identified objective and science-based criteria for selecting promising COVID-19 therapeutics:

Soundness of scientific approach and technology used (pharmacological rationale): Available evidence of potential role of medicinal product in the COVID-19 setting suggests potential therapeutic activity and is supportive of the proof of principle, from non-clinical studies (in vitro and in vivo used animal models) or early clinical studies related to appropriate mechanism of action, safety and efficacy of new medicinal products; or for repurposed medicinal products, already known evidence is available from existing use, relevant to the whole spectrum of COVID-19.

Stage of development: Progress in development of medicinal product is achieved from non-clinical studies to late phase clinical trials or regulatory process, reflecting the need to enable promising medicines to reach patients in the European Union (EU) as soon as possible.

Availability of relevant clinical outcome results from clinical trial(s): Relevant clinical evidence of medicinal product is announced by manufacturer or is published as preprint or in scientific journals, relevant to the whole spectrum of COVID-19, from living systematic reviews/meta-analysis, platform trials (to generate robust and interpretable evidence that would allow prompt definition of which investigational or repurposed medicinal products are effective and safe for the treatment of COVID-19) or phase II or III non-platform trials, based on the certainty of evidence and effect size.

Relevant clinical effectiveness outcome results:

For *pre- or post-exposure prophylaxis,* related to clinical outcomes: Number of patients infected with SARS-COV-2; Number of patients progressed to COVID-19; Number of patients progressed to mild/moderate COVID-19; Number of patients progressed to severe/critical COVID-19; All-cause mortality; Viral negative conversion (D7);

For *mild/moderate COVID-19 (outpatients),* related to clinical outcomes: Clinical improvement; Number of patients progressed to COVID-19 related hospitalisation; Number of patients with ≥1 COVID-19 related medically attended visit (emergency room visits, urgent care visits, or telehealth/physician office visits); Viral negative conversion (D7);

For *moderate/severe/critical COVID-19 (hospitalised),* related to clinical outcomes: All-cause mortality; Clinical improvement; WHO Clinical Progression Score level 7 or above /i.e., Mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death/; Duration of hospitalisation; Viral negative conversion;

For *long COVID,* related to clinical outcomes: Clinical improvement (related to 4 different syndromes: Pulmonary symptoms; Cardiovascular symptoms; Fatigue, cognitive and neuropsychiatric symptoms;

Other organ impairments); Viral negative conversion; Quality of life; Number of patients progressed to COVID-19 related re-hospitalisation; Number of patients with ≥1 COVID-19 related medically attended visit (emergency room visits, urgent care visits, or telehealth/physician office visits); All-cause mortality

Absence of (new) major identified safety issues that would question the appropriateness of the product in the proposed indication: Adverse events (AEs) and serious AEs of medicinal product are consistent with the mechanism of action and are manageable across the whole spectrum of COVID-19, with absence of (new) major identified safety issues that would question the appropriateness of the product in the proposed indication

Unmet need and/or **therapeutic added value:** Unmet need and/or therapeutic added value of medicinal product is achieved. (No active treatment available for condition; current treatment is suboptimal, e.g., existing treatment has challenging adherence or delivery; new treatment has the potential to provide substantial additional benefits over existing treatment options; new treatment targets different aspects of the condition)

Efficacy against new SARS-CoV-2 variants (relevant only for some product categories): Medicinal product is relevant for those variants of concern with clear evidence available indicating a significant impact on transmissibility, severity and/or immunity that is likely to have an impact on the epidemiological situation in the EU/EEA.

Suitability of the product for the particular healthcare setting: Related to route of administration, treatment regimen, formulation, target populations in the context of proposed indication, medicinal product is suitable for outpatients setting or for hospitalised patients according to disease severity. (e.g. outpatient settings: oral or nasal; s.c. before IV; use in ICU)

Intention to engage at an early stage with EMA to obtaining scientific advice (with the intention to apply for an EU marketing authorisation for the candidate therapeutics): Medicinal product received scientific advice from EMA early in the development process. It is important for ensuring that developers can submit **well-prepared applications** and make use of the rapid procedures EMA has put in place for COVID-19 treatments.

Candidate therapeutics already within the regulatory process: Potential COVID-19 medical product is currently undergoing evaluation by EMA /medicinal product under rolling review, a regulatory tool that EMA uses to speed up the assessment of a promising medicine or vaccine during a public health emergency; or use endorsed after Article 5(3) review to support national decision-making on the possible use of these medicines before a formal authorisation is issued; or medicinal product is under marketing authorisation evaluation/, or medicinal product already received emergency use authorisation (EUA) from FDA.

Apart from assessing candidates against the objective selection criteria, experts ranked them based on the overall **impact** the product might have in COVID-19 treatment and on the **likelihood of success** both to achieve the desired impact and to be authorised in the European market. Moreover, experts considered the prospective **time needed until entry into the European market**.

Diverse portfolio approach: beyond the individual merits of each therapeutic candidate, the portfolio as a whole needs to cover the whole spectrum of COVID-19 and all COVID-19 product categories of new or repurposed medicinal products.

The expert group focused on the scientific/medical merits of the different therapeutics, therefore criteria related to manufacturing, production volumes, prices and access conditions have not been considered. These aspects nevertheless shall be taken into account when the European Commission deploys its support instruments.

5. Pool of products

The sub-group agreed that the pool of candidates should come from a high-quality, well-maintained, independent database. Experts chose the list from the **BioMedTracker database** as the main source for candidates. This proprietary database is maintained by Informa Pharma Intelligence, an industry gold-standard data provider for the pharmaceutical sector for which the Commission has a subscription.

In the BioMedTracker database, there are 182 COVID-19 therapeutic candidates that are already in clinical stage. For the list of 10 therapeutics, experts focused on candidates that are in late stage of clinical development (phase III or phase II/III), of which there were 65 products at the time of accessing the database. The other products in earlier phases of clinical development can be scrutinised in a later stage for building a broader portfolio.

In addition, other lists on COVID-19 therapeutics were considered (e.g. WHO list[3], Austrian Institute for Health Technology Assessment[4] horizon scanning reports). Altogether, experts reviewed a pool of 82 therapeutic candidates.

6. Selected 10 therapeutics

Beginning in 2020, thousands of initiatives aiming to deliver effective therapeutics to mitigate the COVID-19 threat were initiated. By the second half of 2021, this long-term effort brought us much closer to the point when the persons at risk of death, severe, debilitating disease, or long-COVID-19 will receive effective and safe medication. We are not at this point yet.

Unfortunately, the urgent need for anti-COVID-19 medicines during a pandemic led some to cut corners and advise unproven, repurposed treatments for the therapy of severe COVID-19. Such an approach has several adverse effects, from increased moral hazard behaviours, through side effects further deteriorating patient's status, to artificial medicine shortages for already proven indications and increased risk for patients in need.

The expert team appointed by the European Commission has reviewed the medicines and medicine candidates developed for the COVID-19 treatment and selected the ones that are **relatively close to the market** and, if approved, will make a **significant impact on the pandemic and the society**. This included medicines developed *de novo* for the SARS-CoV-2, but also repurposed products. Establishing a portfolio of the most promising medicines has started, and ten products of the portfolio that are most likely to deliver the solution shortly were selected. This list is based on the expert's consensus, and complete datasets predicating the products' efficacy and safety are missing in some cases. Consequently, it is assumed that some of the listed therapeutic candidates, which

[3] https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf
[4] https://eprints.aihta.at/1234/

seem promising in currently available studies, will not ultimately yield the expected results. However, the portfolio will be inclusive, and new compounds will be added based on merit. **This assessment aims not to define the inferiority of the products not listed here but to present the landscape of the so far most advanced and promising COVID-19 therapeutics.**

In selecting the 10 most promising candidates, experts focused on the product categories with the highest and earliest impact on the pandemic: antivirals preventing people exposed to the virus and non-hospitalised patients from hospitalisation, and immunomodulators averting hospitalised patients from evolving to critical or die.

For now, three types of products emerged from the screening against these requirements: **antiviral monoclonal antibodies, oral antivirals and immunomodulators**. High quality evidence related to the third category (Other treatments) as well as evidence related to effectiveness and safety of medicinal **products for treatment of long COVID-19 are still missing**. The below table demonstrates the interplay between the selected types of products and the primary product categories identified earlier.

Mechanism of Action / Target Group	I. Antivirals	II. Immuno-modulators	III. Other treatments (eg. symptomatic, anticoagulant)
1. Pre-exposure prophylaxis	Antiviral mAbs		
2. Post-exposure prophylaxis	Antiviral mAbs Oral Antivirals		
3.A Outpatients: mild to moderate	Antiviral mAbs Oral Antivirals		
3.B Hospitalized: moderate to severe	Antiviral mAbs Oral Antivirals	Immuno-modulator/anti-inflammatory agents	
3.C Hospitalized: critical		Immuno-modulator/anti-inflammatory agents	
4. long COVID			

Table 2: Coverage of target product categories by selected agents

Antiviral monoclonal antibodies (mAbs):

Antiviral monoclonal antibodies mirror the antibodies that are generated in our body in response to immunization by infection or vaccination. However, monoclonal antibodies are not pooled, as in natural situations. The most effective types are carefully hand-picked and amplified to ensure the highest efficacy. Monoclonal antibodies bind to the Spike protein of the coronavirus in regions

responsible for interaction with the cell's surface. This binding sterically blocks the first stage of the infection – the entry to the susceptible cell, and consequently infection and disease. Monoclonal antibodies have many advantages, including the fact that by observing nature, we may develop them relatively quickly. Further, monoclonal antibodies are safe to administer, and they stay in our bloodstream for a prolonged time, delivering extended protection. The main disadvantage is the administration route. They need to be injected, but novel products are developed to allow subcutaneous or intramuscular rather than intravenous administration. The second disadvantage is that they act similarly to the antibodies generated after immunization. If the virus evolves to escape our natural protection (variants), the efficacy of monoclonal antibodies will also wane. For the same reason, the benefit of using monoclonal antibodies in patients who already have natural or vaccine induced immunity is limited.

Oral antivirals:

Antivirals encompass a group of medicines, which affect the virus itself. Commonly, such medicines are small molecules that interact with the selected viral protein, blocking its activity. It is essential to choose a protein indispensable for the virus as a "target" for the medicine, as in such a way, we can block the infection. For that reason, a polymerase (a protein responsible for copying the RNA of the virus) or protease (a protein responsible for the maturation of viral proteins) are often selected.

Antiviral medicines stop the virus replication itself, and therefore it is essential to administer them as quickly as possible after the infection and/or appearance of symptoms; before the virus induces damage and disease progression. That is why oral antivirals are so attractive. They may be administered, e.g., to the high-risk person early in an outpatient clinic or even at home to prevent progression to the severe disease. While such medicines have several advantages, including the fact that they will also work in immunized patients, one should also remember that antivirals may have side effects (e.g., toxicity or genotoxicity). For that reason, they should be used with care and only if required. This is also important, as abuse of antivirals yields the same effect as abuse of antibiotics. The resistance mutants can emerge, and the medicine can become ineffective.

Immunomodulators:

In most cases, the replication of the SARS-CoV-2 in the body is limited by innate and adaptive immunity. However, the virus is trying to hide from recognition, attenuating and skewing the proper immune responses. Still, it triggers some alarms. Consequently, even when the infection is declining, our own body starts to react to the virus in a manner that is delayed but excessive. At the end of the first week of COVID-19, in the unfavourable direction of the disease, immunopathogenetic disorders develop (a cytokine storm or hyperinflammatory syndrome), leading to a severe clinical picture with exacerbation of acute respiratory distress syndrome and multisystem organ failure.

The immunomodulators aim to block this improper and unnecessary response, save lives and limit the immune-mediated damage. Timely anti-inflammatory, immunomodulatory therapy could prevent the development of severe, critical forms of the disease and prevent the need for treatment in intensive care unit. Previous immunopathogenetic studies of COVID-19 indicate the importance of immunomodulatory activity at the level of interleukin-6 (IL-6), IL-1, and Janus kinase (JAK) and the introduction of their inhibitors into therapy. In addition, the studies include inhibitors of other

cytokines, such as IL-7, -12, -18, tumor necrosis factor (TNF), several different chemokines, interferons, topically applied corticosteroids, selective T-cell costimulatory immunomodulators etc.

Here, a number of medicines approved in other indications, such as autoimmune diseases or other hyperinflammatory syndromes, have been tested. Unfortunately, the mechanism of induction of this „cytokine storm" is not fully understood, and the importance of certain pathways has to be tested in clinic.

Therefore, it is possible that the highest effect will be achieved using a combination of inhibitors modulating different pathways. It is important to remember that this class of medicines is very important but is far from ideal. This is a symptomatic treatment to be used in those who got to the severe stage despite vaccination and antiviral therapy.

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Following careful consideration and screening more than 80 products in late stage clinical development, the expert group identified the following 10 therapeutic candidates as the most promising in the EU setting. In Annex, a detailed assessment report and references can be found for each candidate.

Product	Developer	EMA regulatory status
Antiviral monoclonal antibodies		
casirivimab/imdevimab (Ronapreve)	Regeneron Pharmaceuticals, Roche	MA application submitted
sotrovimab (Xevudy)	Vir Biotechnology, GSK	Rolling review
tixagevimab/cilgavimab (Evusheld)	Astra Zeneca	Rolling review
Oral antivirals		
molnupiravir	Ridgeback Biotherapeutics, MSD	
PF-07321332	Pfizer	
AT-527	Atea Pharmaceuticals, Roche	
Immunomodulators/anti-inflammatory agents		
tocilizumab (RoActemra)	Roche	MA application submitted
anakinra (Kineret)	Swedish Orphan Biovitrum	MA application submitted
baricitinib (Olumiant)	Eli Lilly	MA application submitted
lenzimulab	Humanigen	

Table 3: list of 10 most promising COVID-19 therapeutic candidates

Disclaimer: For some candidates complete datasets predicating the products' efficacy and safety is still missing. Moreover, **new scientific and clinical evidence emerges on a daily basis** for both the selected products and other candidates in the portfolio, **leading to dynamic adjustments to the list of 10 most promising candidates**. Therefore, this initial list and the broader portfolio shall be regularly revisited and the current 10 perceived as a snapshot at the day of publication.

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The group wishes to reiterate that **vaccines are our primary tool to combat the pandemic**. History shows us that only vaccination campaigns led to the resolution of the problem with viral diseases, with smallpox and polio as best examples. However, some of us may not be vaccinated, and in a proportion of patients, the response to the vaccine will be insufficient. In those, mainly recruiting from the high-risk groups, the virus may still pose a significant risk. The medicines complement this system, providing means to secure the ones exposed or limit the damage associated with the infection. However, the medicines should only be used when necessary. Except for the side effects associated with the intake of, e.g., polymerase inhibitors, the excessive use of antivirals will render them ineffective due to the emergence of resistance. For that reason, we strongly recommend vaccinating all eligible and limiting the use of medicines to patients at the highest risk of developing the severe form of COVID-19.

7. Recommendations

1. **Antivirals should not be considered as an alternative to the vaccination**.
   Vaccination should be considered as the primary tool to control the pandemic and prevent infection. Even if drugs are available, each infection is associated with the risk of death and long-lasting sequelae. The therapeutics will not replace the vaccination, but will complement it, providing high-quality, durable protection. Further, care should be taken to avoid improper or excessive drug use, as this will yield drug-resistant strains as seen for antibiotics.

2. **Ensure that the most promising products are tested in randomised, blinded, extensive, multicentre, credible studies which yield data that can be used for regulatory and health technology assessment purposes.**
   Several drugs were tested in small or improperly designed clinical studies. Consequently, the results are not credible, and it is difficult to conclude if a certain drug is effective. This may yield drugs that are not effective but will be used in the clinic, potentially even deteriorating the patient's status. What is even worse, such studies may omit effective drugs.

3. **Ensure that the most promising products receive sufficient support from regulators, funding bodies, scientists, and medical specialists.**
   The development of selected medicines and other promising candidates in the portfolio will depend on the support they receive from all the stakeholders, including the scientific analysis, scientific advice and clinical studies. Clinical studies shall be sufficiently funded from private and public sources and supported by the regulatory bodies from the early phases.

4. **Products that are approved for use in the EU should be rapidly and widely available to patients.**
   The joined work of commercial companies, scientific and medical teams, and regulators should allow for rapid and efficient development. It is essential to plan the production and distribution of the medicine already at an early stage, with the support of the stakeholders. Product availability should also include a fair pricing strategy.

5. **The three categories listed in the document are all important. All three goals are achievable and required: limiting the infection, and limiting the damage to organs and tissues, which will ultimately lead to reduced potential for long COVID symptoms.**
   This document identifies several promising drugs or drug candidates that target the first two points. While there is still room for improvement in these categories, there is an unmet need to support the development of therapeutics aiming to relieve the symptoms associated with the infection and the symptoms or causes of long COVID.

6. **Antivirals should be administered as early as possible to prevent viral transmission and uncontrolled disease progression.** Immunomodulators should be administered in the second phase of the disease, when the extensive and improper immune response takes place.

7. **Emergence of variants should be monitored by genotyping and phenotyping, and special focus should be placed on the development of combined therapies.**
   SARS-CoV-2 is an RNA virus, and consequently, its genetic variability is higher than observed for bacteria or DNA viruses. While due to the unique proof-reading mechanism, its genome is relatively stable, the emergence of resistance mutations must be considered. For this reason, the emergence of variants should be monitored by genotyping and phenotyping, and special focus should be placed on the development of combined therapy, particularly in the case of monoclonal antibodies.

8. Conflict of interest

The experts were required to submit in writing a declaration on the absence of any conflict of interest impacting the work of the sub-group prior to taking up their duties in the sub-group and to update this declaration whenever necessary. At the time of drafting of the report, no conflicts were declared.

9. EMA's participation

The European Medicines Agency supported the work of the sub-group through participation of an EMA expert. The expert was invited as external expert to the meetings of the sub-group and responded to questions on general issues, product categories and selection criteria. The expert did not participate in the deliberations for the selection of individual products and had no voting rights.

10. Confidentiality

Experts in the sub-group are bound by strict confidentiality rules and were requested to sign a confidentiality and non-disclosure agreement.

Annex I – Individual Assessment reports

Anakinra

Product name	Developer
anakinra (Kineret)	Swedish Orphan Biovitrum

Description

Anakinra is an immunosuppresive medicine, recombinant non-glycosylated, human interleukin-1 receptor antagonist (IL-1Ra), that acts on several autoinflammatory and rheumatoid diseases. IL-1 is a strong proinflammatory cytokine, which mediate cellular inflammatory response.

Endogenous IL-1 levels are elevated in individuals with COVID-19 and other conditions, such as severe CAR-T-cell–mediated cytokine-release syndrome. It is administered by subcutaneous injection.

Several randomised clinical trials are currently ongoing, evaluating anakinra alone and in combination with other medicinal products. It is also investigated in children > 1 year old with hyperinflammatory syndrome associated with COVID-19 (RECOVERY trial).

The results from few randomized trials comparing anakinra with placebo or standard of care has been reported in the scientific literature with positive results in severe COVID-19 patients (NCT04680949, SAVE-MORE) but not in critical COVID-19 (NCT02735707, REMAP-CAP). One randomised clinical trial in severe COVID-19 (NCT04341584, CORIMUNOANA-1) was stopped early for futility after the recruitment of 116 patients (59 were assigned to the anakinra group and 57 were assigned to the usual care group).

In SAVE-MORE trial (hospitalized patients with COVID-19 at increased risk for respiratory failure and guided by the biomarker suPAR) 405 patients were allocated to the anakinra arm plus standard of care (SoC) and 189 patients were allocated to the SoC and placebo arm. Results showed that 28-day mortality decreased (hazard ratio: 0.45, p=0.045). Significant improvement was shown also after treatment with anakinra compared with placebo. At 28 days, 204 (50.4%) of the anakinra-treated patients had fully recovered, with no detectable viral RNA, compared with 50 (26.5%) of the placebo-treated patients (p<0.0001).

It is currently under EMA marketing authorisation evaluation to extend the use of anakinra to include treatment of COVID-19 in adult patients with pneumonia who are at risk of developing severe respiratory failure.

This medicine covers our majority applicable selection criteria including diverse portfolio approach, soundness of scientific approach and technology used, late stage of development (ongoing phase I randomised clinical trials, including one in children), availability of relevant clinical outcome results from clinical trials (although limited to one trial, see above), absence of major safety issues, added therapeutic value (it provides additional benefit in reduction of mortality to dexamethasone), it is not affected by the new SARS-CoV-2 variants, and is suitable for hospitalised patients. In addition, EMA is already reviewing the possibility of extending the approval of anakinra for hospitalised adult patients with pneumonia who are at risk of developing severe respiratory failure.

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AT-527

Product name	Developer
AT-527	Atea Pharmaceuticals, Roche

Description

AT-527 is a small molecule broad-spectrum antiviral against RNA viruses, which was initially developed to treat hepatitis C infection (flavivirus). Chemically, it is a guanosine nucleotide analogue. It is administered orally as a pro-drug, which inside the cell is converted by phosphorylation into its active form (AT-9010). The compound interferes with the activity of the viral enzyme, which is carrying out the replication of the viral genome, by unique dual mechanisms targeting both RNA dependent RNA polymerase (RdRP) and the nidovirus RdRp-associated nucleotidyltransferase (NiRAN) of viral non-structural protein (nsp12) polymerase.

Already in 2020, AT527 has been proposed as a potential medicine for use in COVID-19 patients. The laboratory research utilizing the immortalized cell lines and ex vivo tissues showed promising activity at nanomolar concentrations. The medicine also showed activity against other alpha and betacoronaviruses. It is likely to limit the replication of the future pandemic coronaviruses.

Considering the mechanism of action and the fact that the polymerase is a highly conserved protein, it is not expected that novel variants of the virus characterized by improved transmission or immune escape would be less susceptible to the medicine. Furthermore, the dualistic target specificity on nsp12 allows hoping that the resistance emergence will be slower or will not occur.

AT-527 is being developed for patients with mild to moderate COVID-19. The medicine is administered orally at 550 mg (two tablets) twice daily for five days. It is now tested in two phase 2 clinical trials (NCT04396106 and NCT04709835 – MOONSONG trial) for its safety and efficacy. The interim analysis in NCT04396106 showed a rapid decrease in the virus load (starting on day 2) and faster virus clearance. Further, the medicine is being tested in one phase 3 global multicenter trial (NCT04889040, MORNINGSKY trial) evaluating efficacy and safety in patients with mild to moderate COVID-19 in outpatient setting; the results are expected in fall 2021. An update on MOONSONG trial suggests that the study did not meet the primary endpoint in reducing viral load across the overall study population, however there is a significant reduction of viral load in high risk patients. Adjustments to the phase 3 trial protocol is considered in the light of the results. No serious safety concerns or risks have been identified thus far.

The medicine affects the virus replication and therefore should be given early during the disease to prevent uncontrolled disease progression. Consequently, AT-527 should be considered a category I product, an antiviral, for use in pre- and post-exposure prophylaxis and in hospitalized and non-hospitalized patients with active infection.

This medicine covers majority of our applicable selection criteria including diverse portfolio approach, soundness of scientific approach and technology used, late stage of development (ongoing large global phase 3 trial), availability of announced interim results from one phase 2 clinical trial (not yet reported as peer reviewed material, see above), absence of major safety issues, unmet need satisfied (no active treatment is available or has challenging route of administration), received scientific advice from EMA early in the development process, and suitability for mild to moderate COVID-19 patients in outpatient setting.

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Baricitinib

Product name	Developer
baricitinib (Olumiant)	Eli Lilly

Description

Baricitinib is an inhibitor of Janus kinase 1 and 2 (JAK 1 and 2), which are mediators of the inflammatory response, and is approved for its use by EMA in rheumatoid arthritis and atopic dermatitis. In addition, it has shown to have some activity against SARS-CoV-2, the cause of COVID-19, in laboratory studies. It is administered orally.

Baricitinib is considered an immunomodulator medicine, targeting patients with severe COVID-19 (admitted to hospital and needing supplementary oxygen). This medicine may cause immunosuppression and therefore facilitate secondary infections, although the available data from two randomised controlled trials did not suggest important safety concerns.

The efficacy of baricitinib (one daily dose orally or via nasogastric tube, up to 14 days) in COVID-19 was studied in two randomized trials (NCT04401579, ACTT-2 and NCT04421027, COV-BARRIER). In both, patients admitted to the hospital with COVID-19 were included. In one of them, baricitinib plus remdesivir was compared to remdesivir alone, and showed a modest reduction in time to recovery, without significant impact in mortality; the other trial, baricitinib was compared to placebo, while most patients in both arms also received dexamethasone; baricitinib did not show a significant reduction in disease progression (which was the primary endpoint for the study, for which the sample size was calculated) but resulted in lower mortality (which was a secondary endpoint in this trial, despite being so relevant). The medicine is being also tested in some other ongoing randomized trials.

In addition, on August 3, 2021 Eli Lilly and Company announced results from an additional cohort of 101 adult critical COVID-19 patients from the above mentioned COV-BARRIER trial. In this sub-study, patients with COVID-19 on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) who received baricitinib plus standard of care were 46 percent less likely to die by day 28 compared to patients who received placebo plus standard of care; a similar mortality benefit was observed by day 60. These findings are consistent with the reduction in mortality observed in the overall COV-BARRIER patient population. However, it should be noticed that results of subgroups analysis are less reliable than those of the whole study. By day 28, the frequency of adverse events, serious adverse events and serious infections were similar in the baricitinib group (88%, 50% and 44%, respectively) compared to placebo (95.9%, 71.4% and 53.1%, respectively). Venous thromboembolic events were reported in 6% of patients treated with baricitinib and 6.1% of patients treated with placebo. No new safety signals were identified.

This medicine covers our applicable selection criteria including diverse portfolio approach, soundness of scientific approach and technology used, availability of relevant clinical outcome results from clinical trials (see above), absence of major safety issues, added therapeutic value (it provides additional benefit in reduction of mortality to dexamethasone), it is not affected by the new SARS-CoV-2 variants, and is suitable for hospitalised patients. The medicine received scientific advice from EMA early in the development process and now is under the marketing authorisation evaluation by EMA for the treatment of patients with severe COVID-19.

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Casirivimab/imdevimab

Product name	Developer
casirivimab/imdevimab (Ronapreve)	Regeneron Pharmaceuticals, Roche

Description

Ronapreve is a combination of two monoclonal antibodies (casirivimab and imdevimab) which neutralize the circulating SARS-CoV-2 and protects against virus variants that have arisen in the human population. It is administered intravenously or subcutaneously in either outpatient clinics or by physicians in private practice. The recommended dosing is 1200 mg (600 mg casirivimab and 600 mg imdevimab).

The clinical development of the medicine was primarily targeted to non-hospitalized ambulant patients with mild COVID-19 disease that are in high risk to progress to more severe stages as a post-exposure prophylaxis treatment. However, results from a clinical trial in hospitalized patients that were seronegative (did not develop antibodies against the virus) showed equally good effects. In any case, the medicine has to be administered in the early phases of the disease – with 7 days of symptom onset - to evolve its effectiveness of reducing the viral load and the accordingly the risk of progressing and the length of the disease.

The medicine has been evaluated in three clinical trials so far. In one trial (NCT04425629) 4057 outpatients, mildly diseased but with at least one risk factor for severe disease, received either 2400 mg or 1200 mg of RONAPREVE, intravenously or placebo. Both dosing regimens proved to significantly reduce COVID-19-related hospitalization (71.3% reduction: 1.3% vs 4.6%1) or all-cause death (70.4% reduction: 1.0% vs 3.2%) compared to placebo. The time to resolution of COVID-19 symptoms was 4 days shorter compared to placebo (10 vs 14 days). In the second trial (NCT04452318) 753 pre-symptomatic outpatients received 1200 mg subcutaneously, or placebo. Symptomatic SARS-CoV-2 infection developed in 1.5% compared to 7.8% in the placebo group (81.4% reduction). RONAPREVE also prevented symptomatic and asymptomatic infections overall (66.4% reduction). Among symptomatic infected patients the time to resolution of symptoms was two weeks shorter with RONAPREVE than with placebo (1.2 weeks vs. 3.2 weeks). In the third trial (NCT04381936, RECOVERY) 9785 hospitalized patients received RONAPREVE, intravenously, or usual care. Seronegative patients (patients without antibodies) had a significantly lower mortality than those patients who have already progressed or developed antibodies. In any of the three studies, serious adverse events did not occur more frequently than in those patients treated with placebo, or in different dosing regimens. Infusion-related reactions were infrequent and no dose-limiting toxic effects of REGN-COV were noted.

The criteria considered for the selection were diverse portfolio approach, soundness of scientific approach and technology used, availability of relevant clinical outcome results (as three large and well-controlled phase 3 study are available and the outcomes of these show significant and relevant results), absence of major safety issues, unmet need satisfied (no active treatment is available), and received scientific advice from EMA early in the development process. Additionally, medicinal product shows no resistance also against new variants, such as delta. The population targeted are patients in the early stages of infection in outpatient setting. However, a limiting factor is that the medicine has to be administered in health care institutions, though it is recommended that patients with mild disease stay at home. The clinical development is already advanced and the marketing authorisation approval process has started. It is expected to be approved in Europe in late 2021.

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Lenzilumab

Product name	Developer
lenzimulab	Humanigen

Description

Lenzilumab is a humanized monoclonal antibody which acts by blocking of the action of granulocyte-macrophage colony stimulating factor (GM-CSF), which plays an important role in the hyperinflammation process occurring in severe COVID-19. It is administered intravenously every 8 hours, in 3 doses.

Lenzilumab is considered an immunomodulator medicine, targeting patients with severe COVID-19.

Currently, results from one phase 3 randomised clinical trial (NCT04351152, LIVE-AIR) were published as preprint, related to effectiveness and safety of lenzilumab in hospitalised sever COVID-19 patients.

Lenzilumab showed a significant advantage in survival without the need of mechanical ventilation compared to placebo in patients hospitalised with COVID-19 and needing supplementary oxygen; most of the patients also received corticosteroids and remdesivir. No important safety concerns were raised.

NIH's ACTIV-5/BET-B platform trial is ongoing (BET-B stage evaluates lenzilumab as a concomitant therapy with remdesivir compared with remdesivir alone) and expected to provide further data on effectiveness and safety of lenzilumab.

Administering this medicine intravenously to the target patients is not a problem.

This medicine covers majority of our applicable selection criteria including diverse portfolio approach, soundness of scientific approach and technology used, late stage of development (ongoing platform trial), availability of relevant clinical outcome results from clinical trials (although limited to one trial, not yet reported as peer reviewed material, see above), absence of major safety issues (but with limited evidence so far), added therapeutic value (it provides additional benefit in reduction of mortality to corticosteroids), it is not affected by the new SARS-CoV-2 variants, and is suitable for hospitalised patients. The medicine received scientific advice from EMA early in the development process.

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Molnupiravir

Product name	Developer
molnupiravir	Ridgeback Biotherapeutics, MSD

Description

Molnupiravir is a ribonucleoside analog, which does not inhibit the activity of the viral polymerase (enzyme responsible for replication of the SARS-CoV-2 genome). Instead, it is incorporated into the newly formed RNA strand what results in mutagenesis and production of deficient genomes. This activity raises some concerns about its possible mutagenic activity in mamalian cells as seen in vitro assays. However, the phase 1 safety assessment (NCT04392219) did not reveal any serious adverse events. Molnupiravir is a pro-drug, which is delivered to the cell and then converted into its active form.

Molnupiravir was originally developed for the treatment of influenza, but was also shown to affect replication of other RNA viruses, including filoviruses, alphaviruses, and coronaviruses. In 2020 it was reported as possible medicine against SARS-CoV-2 virus, and its activity has been documented in vitro on cell lines, ex vivo on tissue cultures including lung epithelial cells and in various in vivo models, including mice, hamsters, and ferrets.

Considering its broad-range activity and the conservancy of the polymerase protein, it is not expected that novel variants of the virus characterized by improved transmission or immune escape would be less susceptible to the medicine. However, as there is only one molecular target one may expect emergence of resistance mutants in time.

The clinical development of the medicine has initially targeted hospitalized and non-hospitalized patients in the early phases of the diseases. However, due to first results, it is now developed for non-hospitalized at-risk patients with asymptomatic or mild disease and a symptom onset of less than 5 days. There is also a study that evaluated the medicine for its use in PEP (post-exposure prophylaxis) and imminently also for early presumptive treatment.

Molnupiravir is coming in an oral formulation, and a dose of 800 mg daily over 5 days has been recommended for further evaluation in a phase one study.

A phase 2/3 study for hospitalized patients has been closed due to non-efficacy (NCT04575584, MOVe-IN), but the study for non-hospitalized patients has stopped recruiting at more than 1,550 patients because of a significant advantage on hospitalisation and death in the treatment group (NCT04575597, MOVe-OUT trial). Manufacturer announced a statistically significant advantage with molnupiravir for the compound endpoints of hospitalisation and death when given 5 days after the beginning of symptoms. The incidence of any adverse event and the incidence of drug-related adverse events were comparable in the molnupiravir and placebo groups. Part of these results were published at a major conference and in an interim analysis. The pre-publishing from phase 2a randomised clinical trial (NCT04405570) showed a significantly better viral clearance with molnupiravir than with placebo. Manufacturer also announced the initiation of the phase 3 MOVe-AHEAD (NCT04939428) clinical trial to evaluate molnupiravir for the prevention of COVID-19 infection.

This medicine covers majority of our applicable selection criteria including diverse portfolio approach, soundness of scientific approach and technology used, late stage of development (a large and well-controlled phase 3 study for treatment in outpatient setting is expected to be available shortly and it is likely that important outcome results will be favourable; one ongoing phase 3 trial for prevention), availability of relevant clinical outcome results (phase 2a study results published as preprint, announced interim results from one phase 3 clinical trial, see above), absence of major safety issues, unmet need satisfied (no active treatment is available or has challenging route of administration), efficacy against new SARS-CoV-2 variants, received scientific advice from EMA early in the development process, and suitability for mild to moderate COVID-19 patients in outpatient

setting (patients in the early stages of infection, in which there is a need for therapeutic agents that can be quickly and easily distributed, prescribed and administered. Here, the oral formulation weighs in as being beneficial). An application for EUA has been filed with the FDA in the US and has been announced to follow soon in Europe.

The medicine affects the virus replication and therefore should be given early during the disease to prevent uncontrolled disease progression. Consequently, molnupiravir should be considered a category I product, an antiviral, for use in pre- and post-exposure prophylaxis and in hospitalized and non-hospitalized patients with active infection.

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PF-07321332

Product name	Developer
PF-07321332	Pfizer

Description

PF-07321332 is a protease inhibitor designed and developed as a selective anti-SARS-CoV-2 medicine. SARS-CoV-2 encodes two cysteine proteases (M^{pro} and PL^{pro}; enzymes able to cut other proteins), which are indispensable for the virus replication. They carry out maturation of the replicatory machinery, and inhibition of their action hampers viral replication. Proteases are considered to be amongst primary molecular targets for antiviral therapy, what has been successfully demonstrated in the past for other viruses (eg. HIV, HCV). The main challenge for inhibitors targeting cysteine protease is the development of highly specific molecules, which do not affect the activity of human enzymes. For now, the literature on the product is relatively limited, and the inhibitor structure has only been revealed in Q2 2021.

The activity of the medicine has been shown *in vitro* and *in vivo* (mouse model), but no peer-reviewed manuscripts are available thus far. Phase I clinical trials have demonstrated good safety and pharmacokinetic profile.

PF-07321332 is currently developed for outpatients with COVID-19, with special care on the pre- and post-exposure prophylaxis. PF-07321332 is administered orally in combination with ritonavir, to improve the pharmacokinetic properties and prolong the medicine's half-life. Ritonavir is frequently used as a booster for other protease inhibitors, e.g., during HIV-1 therapy. PF-07321332 is currently under investigation in three phase 3 clinical trials (NCT05047601 in post-exposure prophylaxis, NCT05011513 in non-hospitalised low-risk adults, NCT04960202 in non-hospitalised high-risk adults), and the results are expected this year. No credible data on clinical efficacy and safety are available.

The medicine affects the virus replication and therefore should be given early during the disease to prevent uncontrolled disease progression. Consequently, PF-07321332 should be considered a category I product, an antiviral, for use in pre- and post-exposure prophylaxis and in hospitalized and non-hospitalized patients with active infection.

This medicinal product covers some of our applicable selection criteria including diverse portfolio approach, soundness of scientific approach and technology used, late stage of development (ongoing large phase 3 trials), unmet need satisfied (no active treatment is available or has challenging route of administration), received scientific advice from EMA early in the development process, and suitability for mild to moderate COVID-19 patients in outpatient setting.

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Sotrovimab

Product name	Developer
sotrovimab (Xevudy)	Vir Biotechnology, GSK

Description

Sotrovimab is a monoclonal antibody product originally isolated from B-memory cells of a SARS-CoV-1 infected individual that has been shown to be directed against epitopes SARS-CoV 2 spike protein. It is believed that these epitopes are conserved in different Coronavirus and are thus thought to be stable against SARS-CoV-2 mutants. Preclinical in vitro data have shown activity against B.1.1.7, B1.351, P.1 and B1.427/B1.429 variants. The substance has been developed to be well available to lung tissue and also possesses a longer half-life.

A large placebo-controlled study (NCT04545060, COMET-ICE trial) has been conducted in high-risk patients with mild to moderate COVID-19 in the ambulatory setting. The dosing schedule was a single infusion of 500 mg of Sotrovimab. There is an interim analysis available (as preprint) in which 583 patients were included. Here, the primary end-point defined by hospital admission was met as 21 pts. In placebo but only 3 pts. in verum had shown disease progression on day 29, which was a highly significant difference. Approx. 1,300 patients were included in the study with the final results not available at this time. However, data from the preliminary were included in a Cochrane review where there were concerns that mainly were bases on the fact that not enough information are available at the moment. There were no safety signals reported in both analyses. There is a further phase 3 study that explores the intramuscular treatment with Sotrovimab. One phase 3 randomised clinical trial (NCT04913675) is ongoing to assess efficacy and safety of VIR-7831 given intramusculary vs intravenously for the treatment of mild to moderate COVID-19 in high-risk non-hospitalised patients. The agent was also part of the comparative ACTIV-3/TICO study (NCT04501978) in hospitalised adults, in which recruitment in the VIR-7831 sub-study was stopped due to futility.

Concerning the efficacy against variants, although not being available in a co-formulation, there is reasonable in vitro evidence in cell culture that has shown a stability in effect when being used against a number of variants. One recent study has included the crucial mutations S477N and E484K.

Sotrovimab data are being reviewed by EMA, it has EUA in the US for mild and moderate COVID-19 at high risk and was licensed in other countries (e.g. Australia, Canada, Singapore).

The criteria considered for the selection were diverse portfolio approach, soundness of scientific approach and technology used, availability of some relevant clinical outcome results (the scientific data available are from one large controlled study in the form of a preprint; although more data than the mentioned interim analyses will be ultimately needed, these results do show a significant protective effect), absence of major safety issues and unmet need satisfied (no active treatment is available). Furthermore, a body of in vitro data have not shown major concerns with resistant variants at the time. The clinical development of the medicine has already advanced with licenses granted in several countries and a major study that has already completed recruitment.

The medication is addressing patients in the early pre-hospital stages of disease but bears a potential to be used in post-exposure prophylaxis. The impact in preventing hospitalizations and severe disease can be of significant importance for mortality as other substances of the class of mAB have shown, but the intravenous administration can be a challenge in achieving the number needed to treat. However, the intramuscular administration which is currently being studied could well improve the applicability and make sotrovimab more suitable for the setting indicated.

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Tixagevimab/cilgavimab

Product name	Developer
tixagevimab/cilgavimab (Evusheld **,** AZD7442)	AstraZeneca

Description

Evusheld or AZD7442 is a combination of two monoclonal antibodies (tixagevimab + cilgavimab) derived from convalescent patients with SARS-CoV2 infection. Discovered by Vanderbilt University Medical Center and licensed to AstraZeneca in June 2020. The mAbs were optimised by AstraZeneca with half-life extension and reduced Fc receptor binding. The half-life extension more than triples the durability of its action compared to conventional antibodies and could afford up to 12 months of protection from COVID-19 following a single administration; data from the phase 1 trial show high neutralising antibody titres for at least nine months. Evusheld neutralises recent emergent SARS-CoV-2 viral variants, including the Delta and Mu variants, according in vitro findings. It is administered by intramuscular injection.

The medicinal product is in the late phase of development and positive results were announced by Manufacturer related to two ongoing randomised clinical trials: one on pre-exposure prophylaxis (NCT04625725, PROVENT phase 3 trial), and one on treatment of mild to moderate COVID-19 patients at high risk (NCT04723394, TACKLE phase 3 trial). In PROVENT trial AZD7442 achieved a statistically significant reduction in the incidence of symptomatic COVID-19. AZD7442 reduced the risk of developing symptomatic COVID-19 by 77%, compared to placebo. There were no cases of severe COVID-19 or COVID-19-related deaths in those treated with AZD7442. Results from the TACKLE phase 3 trial AZD7442 achieved a statistically significant reduction in severe COVID-19 or death compared to placebo in non-hospitalised patients with mild-to-moderate symptomatic COVID-19. The AZD7442 was well tolerated in both trials. ACTIV-2 phase 2/3 randomised clinical trial (NCT04518410) in ambulant patients and DisCoVeRy clinical trial (NCT04315948), in hospitalised patients with COVID-19 are also ongoing.

On 5 October 2021, the Company announced that it had submitted a request to the US Food and Drug Administration for Emergency Use Authorisation for AZD7442 for prophylaxis of COVID-19. EMA's human medicines committee has started a rolling review of Evusheld (AZD7442), for the prevention of COVID-19 in adults.

The criteria considered for the selection were diverse portfolio approach, soundness of scientific approach and technology used, the clinical development is already advanced, availability of relevant clinical outcome results (announced by Manufacturer related to pre-exposure prophylaxis and treatment, see above), absence of major safety issues, unmet need satisfied (no active treatment is available or has challenging route of administration), suitability for the outpatients setting (easily administered by IM injection). Additionally, medicinal product shows no resistance also against new variants, such as delta. It received scientific advice from EMA early in the development process. The product is already in regulatory process by EMA (under rolling review) and FDA (request for EUA).

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Tocilizumab

Product name	Developer
tocilizumab (RoActemra)	Roche

Description

Tocilizumab is a blocker of the action of interleukin-6 (IL-6), which plays an important role in some autoimmune diseases (it is approved for its use in rheumatoid arthritis and other conditions) and also in the pathogenesis of severe COVID-19. It is administered intravenously (most experience in COVID-19 used this route) or subcutaneously, in one dose (in some studies, a second dose was administered 24-48 hours after).

Tocilizumab is considered an immunomodulator medicine, targeting patients with severe COVID-19 (admitted to hospital and needing supplementary oxygen) and critically ill patients (needing mechanical ventilation) already receiving corticosteroids.

This medicine may cause immunosuppression and therefore facilitate secondary infections, although the available data from several randomised controlled trials did not suggest important safety concerns. The cost of the medicine and the possibility of shortage of supply are to be considered. Administering this medicine intravenously to the target patients is not a problem.

The results from several randomized trials comparing tocilizumab with placebo or standard of care has been reported in the scientific literature; while no relevant differences in the risk of death were found in some studies, other studies and meta-analyses (which are quantified weighted summary of the results of individual studies) provided evidence that tocilizumab is associated with lower risk of needing mechanical ventilation and a reduction in the mortality risk.

This medicine covers our applicable selection criteria including diverse portfolio approach, soundness of scientific approach and technology used, availability of relevant clinical outcome results from clinical trials (see above), absence of major safety issues, added therapeutic value (it provides additional benefit in reduction of mortality to dexamethasone), it is not affected by the new SARS-CoV-2 variants, and is suitable for hospitalised patients. In addition, it received scientific advice from EMA early in the development process and EMA is already reviewing the possibility of extending the approval of tocilizumab for hospitalised adult patients with severe COVID-19 who are already receiving treatment with corticosteroids and require extra oxygen or mechanical ventilation.

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Annex II – List of revised therapeutic candidates

In the first stage of building the COVID-19 therapeutics portfolio, the experts reviewed 82 candidates, most of them in late-stage clinical development phase:

- AB201
- ADG-20
- anakinra
- anti-SARS-CoV-2 Hyperimmune Globulin Therapy
- APN01
- apremilast
- Artesunate
- AT-527
- aviptadil acetate
- AZD7442
- Azelastine
- Bamlanivimab/etesevimab
- baricitinib
- BIO-101
- bisindole
- brexanolone
- BRII-196/BRII-198
- bucillamine
- budesonide
- budesonide, formoterol fumarate dihydrate
- C-135-LS + C144
- C21
- Camostat Mesilate
- Canakinumab
- carrimycin
- casirivimab/imdevimab
- ciclesonide
- COVID-HIG
- dactolisib
- Darunavir
- dociparstat sodium
- EB05
- emvododstat
- ensifentrine
- ensovibep
- favipiravir
- fluvoxamine
- fostamatinib disodium hexahydrate
- FP-025
- gimsilumab
- imatinib mesylate
- infliximab
- invimestrocel
- Ivermectin
- lenzilumab
- leronlimab
- mavrilimumab
- MBM-02
- molnupiravir
- niclosamide
- nitazoxanide
- nitric oxide
- octagam
- olokizumab
- opaganib
- pacritinib
- pamrevlumab
- Pegylated Interferon Lambda
- PF-07321332
- plitidepsin
- plonmarlimab
- proxalutamide
- ravulizumab-cwvz
- regdanvimab
- remestemcel-L
- rivaroxaban
- RPH-104
- ruxolitinib phosphate
- SAB-185
- sarilumab
- SCTA-01
- siltuximab
- SNG001
- solnatide
- sotrovimab
- tocilizumab
- tofacitinib
- tradipitant
- umifenovir
- upamostat
- vazegepant
- Vitamin D

Annex III – Members of the COVID-19 therapeutics subgroup

Experts	
Alemka MARKOTIC*	Director of the Infectious Diseases Clinic "Dr. Fran Mihaljević", Zagreb
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*Members of the European expert group on SARS-CoV-2 variants too

Observer	
Marco CAVALLERI	Head of Office, Biological Health Threats and Vaccines Strategy at the European Medicines Agency

Meetings chaired by European Commission staff	
Ferenc MAROFKA	DG Health and Food Safety
Fergal DONNELLY	DG Research and Innovation