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Regulatory Affairs Fast Track Pathways for Approval and Launch of COVID Related Therapies

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Abstract
Pharmaceutical industry had very responsible job to develop therapies related for COVID-19 related therapies. This responsibility was completed successfully with minimum time for drug approval and review process compared to any other traditional vaccine development plan. This article summarise the challenges Pharmaceutical companies and regulator faced to meet urgent crises in pandemic. It also gives information about the current ongoing major studies for COVID-19.
Keywords: COVID-19 pandemic, SARS-CoV-2

Introduction:

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in Wuhan, China in December 2019.[7] The disease has since spread worldwide, leading to an ongoing pandemic.[1]
Symptoms of COVID-19 are variable, but often include fever,[2] cough, headache, [3] fatigue, breathing difficulties, and loss of smell and taste.[4][5][6] Symptoms may begin one to fourteen days after exposure to the virus. At least a third of people who are infected do not develop noticeable symptoms.[7] Of those people who develop noticeable symptoms enough to be classed as patients, most (81%) develop mild to moderate symptoms (up to mild pneumonia), while 14% develop severe symptoms (dyspnea, hypoxia, or more than 50% lung involvement on imaging), and 5% suffer critical symptoms (respiratory failure, shock, or multiorgan dysfunction).[8] Older people are at a higher risk of developing severe symptoms. Some people continue to experience a range of effects (long COVID) for months after recovery, and damage to organs has been observed.[9] Multi-year studies are underway to further investigate the long-term effects of the disease.

Preventive measures include physical or social distancing, quarantining, ventilation of indoor spaces, covering coughs and sneezes, hand washing, and keeping unwashed hands away from the face. The use of face masks or coverings has been recommended in public settings to minimize the risk of transmissions. Several vaccines have been developed and many countries have initiated mass vaccination campaigns.

Although work is underway to develop drugs that inhibit the virus, the primary treatment is symptomatic. Management involves the treatment of symptoms, supportive care, isolation, and experimental measures.

From early 2020 through 2021, several hundred drug companies, biotechnology firms, university research groups, and health organizations were developing therapeutic candidates for COVID-19 disease in various stages of preclinical or clinical research (682 total candidates in March 2021),(10) with 411 potential COVID-19 drugs in clinical trials, as of March 2021.[11]

Regulatory Affairs Challenges in development and approval for COVID Related Treatment

There has been may principles and strategies challenges for conducting clinical trials in a pandemic and evaluates recent trials for different drug candidates. We have a limited understanding of the SARS-CoV-2 pathogen and currently few ways to treat its victims. There is enormous pressure on our healthcare institutions to preserve the lives of patients while finding effective treatments. We have long understood that the safety and efficacy of new medical treatments can only be evaluated through carefully and systematically designed clinical trials. Some of the key challenges are followings:

1. Conventional drug research and discovery can easily take a decade from target identification to pivotal phase III clinical trials. In this crisis with hundreds of thousands of deaths in just a few months, there is simply not enough time for conventional drug discovery and development. Currently, most efforts focus on identifying existing drugs or drug candidates intended for other indications that may have efficacy against COVID-19 and putting them into accelerated clinical trials. By leveraging pre-existing drugs with known pharmacokinetic, pharmacological and toxicology data, the need for dose-finding and toxicological assessments can be reduced.
2. Our current knowledge of the molecular and biochemical features of the SARS-CoV-2 virus suggest that drugs produced for related RNA viruses (e.g. Ebola) may also be effective for treating COVID-19.(12), (13) The clinical development pathway for an existing drug proposed for a new indication is well understood by regulatory agencies and is relatively brief. However, because SARS-CoV-2 is new, the repurposed drugs will not have undergone research and early development optimization for COVID-19.
3. Regulatory affairs process requires clinical trials design, pre-clinical data, clinical data, drug development, approval, and launch preparation. All process takes very long time and specially review timelines. There should be end point to meet and it is very challenging to recruit patients for the clinical trials. A patent is essential for the sponsor of the development program to ensure return on investment with sales. Patents based on “product” or “composition-of-matter” not only give the patentee the right to exclude others from making and selling the drug for the same purpose as the patentee but also block the marketing of any new use that another party discovers. The patent process also runs alongside extensions of exclusivity built into some regulatory processes. In contrast, so-called “use” patents protect a selected therapeutic use.

   All drug regulatory agencies have committed to speeding up regulations and all are collaborating through the International Coalition of Medicines Regulatory Authorities (ICMRA) whose website contains valuable information on COVID-19 trial programmes for medicines and vaccines in development. Each individual agency has also issued guidance which not only speeds the time to obtain clinical trial approval but also makes scientific advice more rapidly accessible, dropping normal agency timelines and conducting video

meetings. With regard to minimal evidence, all major agencies (Europe, United Kingdom, Japan and the United States) already had robust processes in place for accelerated approvals which require minimal evidence. This is illustrated by remdesivir, a repurposed drug that was originally developed for Ebola. Remdesivir received Japanese authorization under the Exceptional Approval Pathway, Emergency Use Authorization in the USA and in the United Kingdom access was granted under the Early Access to Medicine Scheme. Conditional approval for remdesivir by EMA for use to treat COVID-19 in adults and adolescents with pneumonia requiring supplemental oxygen was given under the new accelerated pathway under guidance issued in May 2020 (EMA, 2020).

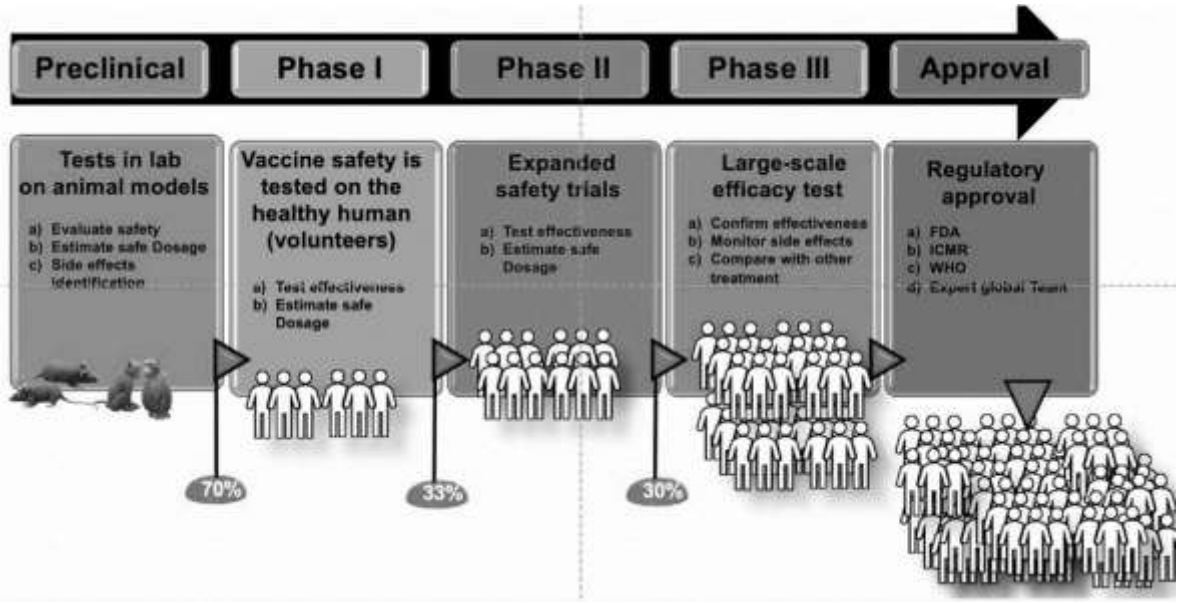

Figure 1: Explains different challenges and process for developing COVID vaccine in five steps:

USFDA Tools

The rising concerns of COVID-19 outbreak, triggered FDA to accelerate the process for quick clinical trials based on pre-IND discussions and highly expedited initial reviews. It is encouraging the sponsors of investigational COVID-19 treatments to submit information and questions through the Pre-IND Consultation Program. Addressing the unmet medical emergencies in treating serious and life threating conditions, FDA has multiple programs to facilitate and expedite development, review and approval of therapies, including biologics.

If the therapies justify their benefits over the risks, they will be available in the market at the earliest with supportive FDA programs like,

- Fast Track Designation
- Breakthrough Therapy Designation
- Priority Review Designation
- Accelerated Approval Pathway

The animal rule and Emergency Use Authorization (EUA) are other FDA expedited approval programs.

4 USFDA Programs for Expedite Approvals

Therapies treating a “serious condition” are all qualified for the four expedited review programs. They include, the diagnostic products, vaccines and products that detect, prevent and treat the effects of serious conditions. Let us understand the programs in detail.

Fast Track Designation: It expedites the review of drugs with a potential to meet the medical emergencies. Demonstrating the drug potential, the sponsors may rely on non-clinical evidences, more frequent meetings and correspondence with FDA, and rolling review of completed sections of the marketing application.

Breakthrough Therapy Designation: Potential drugs showing improvement over existing therapies are provided faster approvals through this program. As there is no existing treatment or vaccine for COVID-19 currently, this program is irrelevant at this stage.

Priority Review Designation: It accelerates FDAs projected approval time from ten months to six, provided the drug exhibits effective prominence to treat a serious condition in terms of safety and effectiveness. Though the review is based on clinical trials comparing an investigational drug to a marketed drug, other scientifically valid information can also be used, where inadequate therapy currently exists.

Accelerated Approval Pathway: Diseases with long courses, such as, cancers, demanding excessive time periods to measure ultimate clinical efficacy with adequate and well-controlled clinical trials are reviewed here.

Other Expedited FDA Approval Programs

Animal Rule: Unethical human efficacy studies or unfeasible field trials demand adequate and well-controlled animal studies for drug approvals. Though animal trials are highly probative for human efficacy, developing and validating a predictive animal model has its own unique challenges. For Covid-19 disease, where the human course is still being determined, some researchers are directly proceeding to human clinical trials of investigational vaccines and treatments.

Emergency Use Authorization (EUA): The FDA commissioner is permitted to approve the emergency use of a vaccine or treatment for a particular purpose, irrespective of not having a license. Relevantly, as COVID-19 is declared an emergency by the HHS (Health and Human Services) Secretary, the FDA commissioner may issue an EUA for a Covid-19 vaccine or treatment, after consulting with the directors of NIH (National Institutes of Health) and CDC (Centers for Diseases Control and Prevention) .

With the ongoing pandemic, there is a possibility that an EUA may be issued, if a highly promising COVID-19 vaccine or treatment is developed. Alongside, FDA is already **granting EUAs** for diagnostics and personal protective equipment for treating Covid-19.

Implications of COVID-19 on Health Authority Operations

Many of the identified regulatory approaches have indeed been introduced temporarily to allow health authorities and stakeholders to manage the pandemic and to ensure the continuity of their respective operations. However, even with sustained operations, catching up on backlogs, delayed sponsor

meetings, and other activities that had to be suspended during the pandemic constitute a challenge, as does resuming activities that have not yet been extensively tested in a virtual environment prior to the current pandemic (e.g., remote inspections).

Furthermore, new priorities emerging from the pandemic, such as ensuring supply-chain integrity and managing increasing fake medicines, may require health authorities to seek additional tools and resources. In addition, the pandemic has affected the implementation of some new provisions, such as the EU Medical Device Regulation or Australia's adoption of TGO 91 labels, to which resources have already been initially allocated.

These new and/or emerging challenges can be addressed by continuously leveraging the agile approaches implemented during this pandemic. While these agile approaches have been triggered by COVID-19, there is indeed additional opportunity to expand them beyond the current pandemic and to adopt them to other services or products that could also benefit all stakeholders involved, notably patients.

Leveraging Findings and Opportunities

COVID-19 has precipitated several opportunities that could be sustained beyond the pandemic. Based on the trends discussed earlier and the adoption of such approaches to date, 5 considerations in moving forward can be proposed:

(1) embedding regulatory agility and lessons learned
(2) accelerating the development process of innovative medical products
(3) address manufacturing and supply bottlenecks
(4) strengthening international cooperation, notably for clinical trials and vaccine development
(5) committing to easing the regulatory burden and adopting the use of digital technologies.

Embedding Regulatory Agility and Lessons Learned

Regulators have reacted quickly with the expedited issuance of relevant guidance during the acute phase of the pandemic, while making sure that these remain to meet quality requirements. This reaction was especially useful for the industry's understanding of “current” agency thinking and aligning approaches toward addressing the impact of the pandemic. To fully benefit from the gains achieved in the United States of these agile regulatory approaches and extracted lessons for the future, it would be useful to conduct ex-post or postimplementation reviews. These reviews would allow regulators to determine which specific approaches resulted in the most gains across the sector and to identify those that can be introduced temporarily during emergency situations or permanently adopted. Reviewing such approaches can also help to identify best practices that can be shared across regulatory authorities globally and allow for a closer examination to ensure that regulatory mechanisms remain fit for purpose, are increasingly harmonized, and take into account the possible risks and consequences in its application.

Various ways of conducting ex-post evaluations can be pursued, such as in the form of programed review mechanisms or special-purpose reviews. Effective stakeholder engagement throughout this process, through dialogue fora or other structured discussions and consultations, is essential for ensuring the uptake and implementation of any embedded regulatory approaches.

Accelerating the Development Process of Innovative Medical Products

In order to accelerate innovation of treatments and vaccines to meet (unmet) medical needs for the benefit of patients, expedited review and approval pathways continue to play an important role during the COVID-19 pandemic, especially among mature agencies. For example, the EMA implemented a rolling review tool to speed up the entire review process (Table I).

To also stimulate the uptake of innovative medical products in emerging markets, where no expedited pathways are already available, regulatory agencies can consider the use of such pathways beyond COVID-19 and for a wider gamut of products or services, such as in the case of emergency situations or in allowing for an expedited approval of medical products for serious, life-threatening diseases. Nonetheless, any new expedited pathway introduced need to be carefully crafted, and experiences from other regulators that have implemented such pathways can be further leveraged.

In addition, the use of existing expedited pathways during the pandemic also offers an opportunity for regulators to reflect on and review the effectiveness of them to identify challenges and solutions to eventually introduce improvements to the process.

In cases in which the current system of a regulatory authority is still on the path to maturity, and in which resources for dedicated expedited pathways are limited, regulators can adopt reliance or work-sharing approaches that help facilitate the application of such approaches. For example, regulators can rely on trusted regulatory authorities according to the WHO-Listed Authority Interim List of National Regulatory Authorities.56 They can also depend on available global pathways and guidance through the WHO Emergency Use Listing or Prequalification program.

Current ongoing Regulatory Affairs and Drug development Activities for COVID

The US Food and Drug Administration (FDA) has issued emergency use authorizations (EUAs) for a many treatment including Eli Lilly and Company's monoclonal antibodies bamlanivimab with etesevimab; Regeneron's casirivimab and imdevimab; and GlaxoSmithKline/Vir Biotechology's sotrovimab. Several large international trials are underway. The largest, SOLIDARITY, is led by the World Health Organization (WHO). More than 100 countries have joined SOLIDARITY to evaluate high-profile treatment candidates for COVID-19.

Following **Table 1**: will provide latest developments for treatment candidates who have advanced to at least Phase 1 study.

Trade name (generic name)	Developer/Researcher	Sponsor	Trial Phase	Last update
Monoclonal antibody	Lenzilumab	Humanigen; Catalent	NIAID	Phase 3
Monoclonal antibodies	Bamlanivimab + etesevimab	Lilly; Junshi Biosciences	Lilly; Junshi Biosciences; Operation Warp Speed	Phase 2/3
Antigout agent	Colchicine (Mitigare, Colcrys)	NHLBI; Bill and Melinda Gates Foundation; Government of Quebec	Montreal Heart Institute	Phase 2/3
Oral cytoskeleton disruptor	Sabizabulin (VERU-111)	Veru Inc.	Veru Inc.	Phase 2/3
Synthetic human vasoactive intestinal peptide (VIP)	Zyesami (aviptadil, RLF-100)	NRx Pharmaceuticals; Relief Therapeutics	NRx Pharmaceuticals	Phase 2/3
Spleen tyrosine kinase inhibitor	Tavalisse (fostamatinib)	Rigel Pharmaceuticals, Inc	Rigel Pharmaceuticals, Inc; NHLBI; Imperial College London	Phase 1/2/3
IL-6 receptor agonist	Actemra (tocilizumab)	Roche	Various	Phase 3
Antiviral	Ensovibep (MP0420)	Molecular Partners; Novartis	Molecular Partners; Novartis	Phase 2/3
Antibody cocktail	Casirivimab/imdevimab (REGEN-COV, REGN-COV2)	Regeneron; Cipla	Regeneron	Phase 1/2/3
Monoclonal antibody	Sotrovimab (VIR-7831, GSK4182136)	GSK, Vir Biotechnology	GlaxoSmithKline	Phase 1/2/3
Oral sodium-glucose co-transporter 2 (SGLT2) inhibitor	Farxiga (dapagliflozin)	Bristol-Myers Squibb	AstraZeneca	Phase 3
Monoclonal antibody	Vyrologix (PRO 140, leronlimab)	CytoDyn	CytoDyn	Phase 2b/3
Antihelmintic	Ivermectin	Various	Various	Phase 2/3
Monoclonal antibody	Remicade (infliximab)	Janssen	UHB; Birmingham National Institute for Health Research Biomedical	Phase 2/3

			Research Centre (NIHR BRC); NCATS; BARDA	
rhACE2	APN01	Apeiron Biologics	Apeiron Biologics	Phase 2
Immunoglobulin	Convalescent plasma	Various	Various	Phase 1/2
AT1 receptor selective agonist	TRV027	Trevena	Various	Phase 1/4
JAK inhibitor	Olumiant, Baricinix (baricitinib)	Eli Lilly	Eli Lilly; NIAID	Phase 3/4
Angiotensin-(1–7) peptide	TXA127	Constant Therapeutics	Columbia University Irving Medical Center	Phase 2
Monoclonal antibody	VIR-7832 (GSK4182137)	Vir Biotechnology, Inc.; GSK	Vir Biotechnology, Inc.	Phase 1b/2a
Anticoagulant	Heparin (UF and LMW)	NHLBI	Operation Warp Speed; University of Pittsburgh	Phase 2/3/4
Antiviral	Carragelose, Nasitrol (carrageenan nasal spray)	Marinomed Biotech AG	Marinomed Biotech AG; Various	Phase 4
Antiviral	SNG001	Synairgen	Synairgen	Phase 2/3
Glycoprotein receptor binding domain-specific antibody	LY-CoV1404	AbCellera Biologics Inc.; Eli Lilly	Eli Lilly	Phase 2
Monoclonal antibody	BRII-196/BRII-198	Brii Biosciences Limited	NIAID	Phase 3
Antiviral	Avigan (favilavir/avifavir)	Fujifilm Toyama Chemical (as Avigan); Zhejiang Hisun Pharmaceutical	Various	Phase 2/3
Antiviral	NT-300 (nitazoxanide extended-release)	Romark Laboratories L.C.	Romark Laboratories L.C.	Phase 3
Polyclonal antibody	SAB-185	SAb Biotherapeutics	NIAID	Phase 2/3

Monoclonal antibodies	C135-LS/C144-LS	The Rockefeller University/Bristol Myers Squibb	NIAID	Phase 2/3
Antiviral	Veklury (remdesivir)	Gilead Sciences	Gilead Sciences	Phase 2/3
Antiviral	Molnupiravir (MK-4482)	DRIVE; Ridgeback Biotherapeutics; Merck	Ridgeback Biotherapeutics	Phase 2/3
Serine protease inhibitor	Foipan/Foistar (camostat mesilate)	Ono Pharmaceutical	Various	Phase 2/3
Monoclonal antibody	Bamlanivimab (LY-CoV555)	Lilly; AbCellera	Lilly; Operation Warp Speed	No longer being developed for COVID-19
Glucocorticoid	Dexamethasone (many brands and generics)	Various	University of Oxford	Phase 2/3
Monoclonal antibody	Mavrilimumab	Kiniksa Pharmaceuticals	The Cleveland Clinic	Phase 2
Recombinant fusion protein	MK-7110 (CD24Fc/SACCOVID)	OncoImmune; Merck	OncoImmune; Merck	No longer being studied for COVID-19
Anthelmintic	Niclocide (niclosamide), UNI91103	NeuroBo Pharmaceuticals; UNION Therapeutics	Various	Phase 2/3
Host defense protein (HDP) mimetic	Brilacidin (PMX-30063)	Innovation Pharmaceuticals	Innovation Pharmaceuticals	Phase 2
Lipid-lowering agent	Vascepa (icosapent ethyl)	Amarin Corporation	Amarin Pharma Inc.; Kaiser Permanente; Estudios Clínicos Latino América; Canadian Medical and Surgical Knowledge Translation Research Group	Phase 2/3/4

Monoclonal antibody	Regkirona (regdanvimab, CT-P59)	Celltrion	Celltrion	Phase 3
Monoclonal antibody	AZD7442	AstraZeneca; Vanderbilt University Medical Center	AstraZeneca; BARDA	Phase 3
Anticoagulant	Eliquis (Apixaban)	NHLBI	Operation Warp Speed	Phase 3/4
Antirheumatic agent	Bucillamine	Revive Therapeutics Ltd.	Revive Therapeutics Ltd.	Phase 3
Antiviral	PF-07321332	Pfizer	Pfizer	Phase 1
immunomodulatory antibody	CPI-006	Corvus Pharmaceuticals, Inc.	Corvus Pharmaceuticals, Inc.	Phase 1/3
HIV-1 Rev protein inhibitor	ABX464	Abivax	Abivax	Phase 2b/3
Antimalarial	Pyramax (artesunate/pyronaridine)	Shin Poong Pharmaceutical Co., Ltd	Shin Poong Pharmaceutical Co., Ltd	Phase 2/3
Monoclonal antibody	Otilimab	MorphoSys; GSK	GSK	Phase 2
IL-6 receptor agonist	Kevzara (sarilumab)	Sanofi; Regeneron	Sanofi; Regeneron	No longer being studied for COVID-19
Biguanide	Metformin (Glucophage, Glumetza, Riomet)	University of Minnesota	University of Minnesota	Phase 2/3
Dihydroorotate dehydrogenase (DHODH) inhibitor	PTC299	PTC	PTC	Phase 2/3
H2 blocker	Pepcid (famotidine)	Yamanouchi Pharmaceutical Co.; J&J; Merck	Northwell Health	Phase 3
Kinase inhibitor	Calquence (acalabrutinib)	AstraZeneca	AstraZeneca	Phase 2
Monoclonal antibody	Etesevimab (LY-CoV016, JS016)	Lilly; Junshi Biosciences	Lilly	Phase 1
Monoclonal antibody	Ilaris (canakinumab)	Novartis	Novartis	Phase 3

Anti-TNF	Humira (adalimumab)	University of Oxford; Pharm-Olam	COVID-19 Therapeutics Accelerator; Department of Defense	Phase 2/2
Monoclonal antibody	Ultomiris (ravulizumab)	Alexion	Alexion	Phase 3
Monoclonal antibody	COVI-AMG/COVI-DROPS (STI-2020)	Sorrento Therapeutics	Sorrento Therapeutics	Phase 1
Antiviral	Galidesivir	BioCryst Pharmaceuticals	NIAID	Phase 1b
Nitric oxide	INOpulse	Bellerophon Therapeutics	Bellerophon Therapeutics	Phase 3
HIV protease inhibitor	Kaletra (lopinavir-ritonavir)	AbbVie	Various	Phase 2/4
Tyrosine kinase inhibitor	STI-5656 (abivertinib)	Sorrento Therapeutics	Sorrento Therapeutics	Phase 2
Monoclonal antibody	COVI-GUARD (STI-1499)	Sorrento Therapeutics	Sorrento Therapeutics	Phase 1
VIP receptor agonist	PB1046	PhaseBio	PhaseBio	Phase 2
Small-molecule inhibitor	PF-00835321 (PF-07304814)	Pfizer	Pfizer	Phase 1b
Monoclonal antibody	Takhzyro (lanadelumab)	Takeda (Shire)	Takeda (Shire)	Phase 1b
Glucocorticoid	Hydrocortisone	Various	Various	Phase 3
Small-molecule protein inhibitor	BLD-2660	Blade Therapeutics	Blade Therapeutics	Phase 2
Recombinant human plasma	Rhu-pGSN (gelsolin)	BioAegis Therapeutics	BioAegis Therapeutics	Phase 2
PIKfyve inhibitor	LAM-002A (apilimod dimesylate)	AI Therapeutics, Inc.	AI Therapeutics, Inc.; Yale University	Phase 2
RIPK1 inhibitor	DNL758 (SAR443122)	Sanofi; Denali Therapeutics	Sanofi	Phase 1b
Autologous adipose-derived stem cells	AdMSCs	Celltex Therapeutics	Celltex Therapeutics	Phase 2
Mitogen-activated protein kinase (MAPK) inhibitor	Losmapimod	Fulcrum Therapeutics	Fulcrum Therapeutics	Phase 3

Monoclonal antibody	Gimsilumab	Roivant Sciences	Roivant Sciences	Phase 2
Antiviral	AT-527	Atea Pharmaceuticals, Inc.	Atea Pharmaceuticals, Inc.	Phase 3

Conclusion:

The Covid-19 pandemic tested the regulatory authorities' ability to react to an emergency. In this context, Italy promptly implemented many measures (including centralization of clinical trials approval, simplification of the trial management obligation, financial support for research proposals, off-label use funding and governance) in order to simplify the practice of drug repurposing but also to maintain a strict control on drug access. Although some decisions were later withdrawn, the Italian regulatory authority was vigilant, efficient, and adaptable to face such a great challenge. Moreover, centralization has proven to be a successful choice, and a way forward in the future, albeit perfectible.

This success can be useful in order to start reviewing some old regulations and to further simplify some procedures, to make the system competitive and guarantee equal access to patients.

Finally, a dialogue among European member states and other authorities worldwide is desirable to set common criteria for proper off-label use management.

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