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# Novel and Evolving Therapies for COVID-19 Related Pulmonary Complications'



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## ABSTRACT

Coronaviruses disease 2019 (COVID-19) is the most crucial threat, the world has ever witnessed. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of this disease pandemic. The World Health Organization has confirmed the continuing epidemic as a worldwide public health crisis. Presently, the research on COVID-19 is even in the primitive stage. Studies on unveiling the natural route of COVID-19 infection and related pathophysiology, the biology of pulmonary airways pose a more rational restorative approach in the management of COVID-19. Thus, based on the existing facts, we methodically reviewed the efforts put forth by various research institutes, pharmaceutical companies and biotechnology firms in pulmonary delivery to prevent and control the COVID-19. This article would be valuable for the healthcare community, which is efficiently dealing with the SARS-CoV-2 crisis.

**Keywords:** COVID-19; Pulmonary therapy; Inhaled vaccine; Intranasal drug delivery; Dry powders; Drug repurposing and disposable medical devices. [*Am J Med Sci* 2021;361(5):557–566.]

## INTRODUCTION

Once again, the human race is experiencing a global viral pandemic of a zoonotic basis. In December 2019, the novel coronavirus (COVID-19) infecting humans was primarily recognized in Wuhan, China.<sup>1</sup> The National Health Commission of China had reported thousands of COVID-19 positive cases with subsequent COVID-19 victims confirmed worldwide.<sup>2</sup> As of May 9, 3.94 million verified cases of COVID-19 and 2,75,429 fatalities had been reported in 209 nations and territories. Coronaviruses are RNA viruses that are genotypically and phenotypically diverse.<sup>2</sup> Besides, in human beings, coronaviruses are prevalent in other species such as monkeys, birds, cats, dogs, rabbits, pigs, reptiles and bats.<sup>2</sup> They can instigate respiratory, neurological, hepatic and enteric diseases of erratic severity, which may be fatal to human beings.<sup>2</sup> Two of the earlier recognized strains of coronavirus i.e. severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have led to this prevalence of this pandemic which is zoonotic in origin.<sup>1,2</sup>

On February 10 (2020), the World Health Organization (WHO) termed a new virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The rapid spread of person-to-person transmission of SARS-CoV-2 has now been recognized.<sup>3</sup> Vigorous efforts and

investments are made by the individual nations by closing the transportation systems, quarantining whole cities, imposing the use of personal preventive equipment (PPEs) such as face masks and establishing better personal sanitation practice to control the transmission of COVID-19.<sup>4,5</sup> The situation with SARS-CoV-2 is growing exponentially with the numbers of COVID-19 positive cases growing into the thousands.<sup>6</sup> Now, it is apparent that the COVID-19 may turn into an endemic ground of viral pneumonia.<sup>7</sup>

Accelerating the development of useful and safe therapeutic options against COVID-19 is the world's top priority to rescue the lives during the pandemic. The best hope for the prevention or control of COVID-19 is a vaccine. However, no prophylactic (vaccine) option exists to prevent COVID-19 infection. Thus, currently, various health agencies across the globe are actively collaborating with many research institutes, biotechnology, pharmaceutical and medicine product developers for the advancement in effective medicines against COVID-19. Additionally, few dynamic investigators are working on different treatment options such as the codon-optimized MERS-S1 subunit vaccines loaded microneedle arrays,<sup>8</sup> monoclonal antibodies (e.g. tocilizumab; recombinant humanized monoclonal antibody) for passive immunotherapy,<sup>8,9</sup> drug repurposing (e.g. lopinavir, remdesivir, favipiravir, ivermectin, hydroxy-chloroquine, baricitinib and camostat)<sup>10,11</sup> alternative to fight against

the COVID-19. Moreover, the virus-directed therapies such as viral entry inhibitors (e.g. chloroquine), viral fusion inhibitors (e.g. griffithsin), viral helicase inhibitors (e.g. bananins) and viral protease inhibitors (e.g. cinanserin) are also well studied and tested by few active research groups.<sup>12</sup> Further, by understanding the present community needs, few dynamic material engineers fabricated nanoparticle-based superfine filters,<sup>13</sup> surfaces coating agents<sup>13</sup> and reusable silicon-based hydrophobic nanoporous (< 5 nm) anti-COVID face-masks<sup>14</sup> to resist the direct viral contact and transmission. Besides, researchers from Hue University have recently investigated the essential oil from Garlic (*Allium sativum* L.) against COVID-19 in molecular docking studies.<sup>15</sup> The docking results showed that the organosulfur compounds (e.g. allyl disulfide and allyl trisulfide) effectively inhibit the angiotensin-converting enzyme 2 (ACE2; membrane glycoprotein of the host) and attacking the PDB6LU7 protein, the main protease of SARS-CoV-2. This inhibitory action regulates the PDB6LU7 protein maturation of the COVID-19 and the further spread of infection.<sup>15</sup>

Another appealing alternative for exploration is to exercise the pulmonary drug delivery system to prevent or control the COVID-19 infection. The site of primary infection (upper respiratory tract and central pulmonary airways via direct surface contact or deposition of inhaled droplets), the way of COVID-19 progression and biology of pulmonary airways represent a more logical remedial tactic for the management of COVID-19.<sup>16,17</sup> Therefore, therapeutics that target the pulmonary airways and generate airways-resident immunity may be principally beneficial for preventing or controlling COVID-19 infection.<sup>18</sup> Based on this concept, the present article summarizes various active efforts put forth by various pharmaceutical organizations, biological multinationals and research institutes to prevent or control the COVID-19 infection via the orally inhaled and nasal drug products (OINDPs) systems. Finally, it also highlights the future aspects of inhalation treatment for COVID-19 infection.

## TREATMENT OPTIONS AND STRATEGIES

The OINDPs such as pressurized metered-dose inhalers (MDIs), dry powder inhalers (DPIs), soft mist inhalers (SMIs) and nebulizing systems are the four most commonly used pulmonary drug delivery systems.<sup>19</sup> Vaccine delivery using the OINDPs approach has been well suggested for improving the systemic and mucosal immunity to airborne viruses such as influenza, measles, cytomegalovirus and papilloma virus.<sup>20</sup> Additionally, the marketed products such as FluenzTetra™ (Respiratory vaccine, EU), Flumist® (MedImmune, USA), Fluenz® (Astra Zeneca, EU) and Nasovac® (Serum Institute of India, India) have influenced the management of viral diseases prominently, which greatly benefited mankind.<sup>20</sup>

Accordingly, several dynamic scientists and researchers have invested similar dynamic efforts to prevent and control the COVID-19. The summary of all active efforts taken by dynamic researcher and clinicians for the clinical development of COVID-19 vaccine are described in **Table 1**.

### Intranasal Coroflu vaccine

The vaccine companies FluGen (US) and Bharat Biotech (India) in partnership with the University of Wisconsin-Madison (US) have initiated the development and testing of a unique intranasal vaccine (CoroFlu) against SARS-CoV-2 for the preclusion of COVID-19. The CoroFlu vaccine will be an adaptation of Madison-based FluGen's intranasal flu vaccine (M2SR).<sup>21</sup> Very recently, phase 2 trial of M2SR showed that the intranasal vaccine defends against the highly mismatched influenza strain. Thus, to formulate a vaccine against COVID-19, gene sequences from SARS-CoV-2 will be affixed into M2SR. Specifically, the spike protein that the coronavirus uses to adhere onto human cells and initiate infection will be pinned into M2SR. The Kawaoka group (University of Wisconsin-Madison) will affix the genetic sequences from SARS-CoV-2 into M2SR and then evaluate CoroFlu's safety and efficacy in animal models. Further, the FluGen will transfer its existing manufacturing technique to Bharat Biotech to facilitate the company to scale up and generate the CoroFlu vaccine for clinical trials. Additionally, the intranasal route mimics the natural route of infection by coronavirus and influenza as well as triggers several types of the immune system. Moreover, intranasal delivery is more efficient in inducing multiple immune responses. The partnership firms are striving hard towards the successful development of a useful COVID-19 intranasal vaccine.<sup>21</sup>

### Inhaled mRNA-based antibody therapy

The Swiss biotech Neurimmune AG (Switzerland) in collaboration with mRNA expert Ethris GmbH (Germany) has initiated the development of inhaled mRNA-encoded, neutralizing anti-SARS-CoV-2 antibodies for the effective treatment of COVID-19. Experts are working on immunotherapy formulation to generate therapeutic antibodies. In this work, Neurimmune AG is contributing by analyzing the immunoglobulin sequence from recovered COVID-19 patients whereas Ethris is working on the use of a unique pulmonary therapeutics platform to deliver the same.<sup>22</sup> The proposed antibody therapy will be based on Ethris' stabilized non-immunogenic mRNA (SNIM®RNA) technology. The Ethris' pulmonary SNIM®RNA technology would assist in the administration of mRNA-encoded, neutralizing anti-SARS-CoV-2 antibodies directly in patients' lungs for rapid attainment of effective pulmonary antibody concentrations. Briefly, this state-of-the-art pulmonary technology offers the prospects to treat the viral lung disease that is the

**Table 1.** - The summary of the clinical development of COVID-19 vaccine.

Candidate	Delivery technology	Clinical development status	Sponsor	References
CoroFlu vaccine	Intranasal delivery	Pre-clinical development	FluGen, US; Bharat Biotech, India and University of Wisconsin-Madison, US	21
mRNA-based antibody	SNIM® RNA technology	Pre-clinical development	Neurimmune AG, Switzerland and Ethris GmbH, Germany	22
Solnatile	Powder for nebulizer suspension	Phase 2 (EudraCT 2020–001,244–26)	APEPTICO, Austria	23,-25
AdCOVID	Intranasal spray (NasoVAX™ delivery technology)	Phase 2 (NCT03760549)	Altimmune, Inc., US and University of Alabama, US	26,27
Nitric oxide	GeNOsyl® Chronic DS	–	Vero Biotech LLC, Georgia	30,32
Nitric oxide	LungFit™	–	Beyond Air, US	33
Sinapultide	A lyophilized synthetic peptide KL4 surfactant (AEROSURF® delivery technology)	Phase 2a (NCT02074059)	Windtree Therapeutics Inc., US	34,-38
Aspartyl-alanyl diketopiperazine (Ampion™)	Nebulization	An expanded access protocol proposed to US FDA	Ampio Pharmaceuticals, US	39
Interferon beta	Nebulization	Phase 2 (NCT01126177); Phase 2 (NCT03570359) and Phase 2 EudraCT: 2020–001,023–14	Synairgen, UK	40,-43
Vazegepant (BHV-3500)	Intranasal	Phase 2 and 3 (NCT04346615)	Biohaven Pharmaceuticals, Inc, US	44,-46
TD-0903 (JAK inhibitor)	Nebulization	Phase 1 (NCT04350736)	Theravance Biopharma, US	47,48
Carragelose spray	Nasal spray	Phase 1 clinical trial	Marinomed Biotech, Austria	49,50
PUL-042 immunostimulant	Nebulization	Phase 2 (NCT04313023) and Phase 2 (NCT04312997)	Pulmotect, Inc., US	51,-53
GLS-1200	Nasal spray	US FDA has approved an IND application for Phase 2 study	GeneOne Life Science, Inc., South Korea	54,55
siRNA VIR-2703	Nebulization	Planning to proposed an IND application to US FDA	Vir Biotechnology, US and Alnylam Pharmaceuticals, UK	56
Alvesco inhaler (Ciclesonide)	Pressurized meter dose inhaler	US FDA has approved an IND application for Phase 3 study	Covis Pharma, Luxembourg	57
PH94B aloradine	Nasal spray	Planning to proposed an IND application for Phase 2a study to US FDA	VistaGen Therapeutics, Inc., US	58,-61
SPOR-COV (bacillus nasal spray)	Nasal spray	Innovate UK Agency awarded a grant for initial SPOR-COV development	Destiny Pharma, UK and SporeGen Ltd., UK	67
Dioguard™ (synthetic biopolymer material with 414–1 human IgG monoclonal antibodies)	Nasal spray	Planning to proposed a fast track authorization for accelerate human clinical trials to US FDA	Diomics Corporation, US and Active Motif, Inc., US	68
iLeukPulm (leukine sargramostim)	Nebulization	Initiate the Phase 2 clinical trial of in hospitalized COVID-19 patients in respiratory distress (NCT04326920)	Partner Therapeutics, US	69
Aviptadil (a synthetic form of Vasoactive Intestinal Polypeptide)	Nebulization	Phase 2 and 3 (NCT04360096)	NeuroRx, Inc., US	70
AT-301 mucosal vaccine	Nasal spray	Planning to proposed an IND application for clinical development to US FDA	Atossa Therapeutics, US	71
Azelastine (antihistamine)	Nasal spray	Planning for development and production of nasal spray with Sigmapharm GmbH, Austria	CEBINA GmbH, Austria	72
MV-014–210 (live attenuated vaccine)	Intranasal	Preclinical studies initiated and completed a pre-IND meeting with the US FDA	Meissa Vaccines Inc., USA	73
TZLS-501 (anti-IL-6 receptor monoclonal antibody)	Nebulization	Planning to proposed an IND application to US FDA	Tiziana Life Sciences, UK and STC Biologics, US and Sciarra Laboratories, US	74

primary driver of morbidity and mortality.<sup>22</sup> These collaborative firms aspire for rapid development of this novel treatment to curb this pandemic effectively.

### Inhaled solnatide

APEPTICO is well-known Austria-based biotechnology company actively developing peptide-based medicinal products for several life-threatening pulmonary disorders such as severe respiratory failure, acute respiratory distress syndrome (ARDS) and pulmonary edema. APEPTICO's key candidate, solnatide is purposefully developed for the management of life-threatening acute pulmonary dysfunction and pulmonary edema in ARDS subjects. Solnatide is a water-soluble synthetic peptide. It is a resemblance with the lectin-like domain of human Tumour Necrosis Factor-alpha (TNF alpha). Solnatide mainly activates the pulmonary epithelial sodium channel and restores the injured endothelial-epithelial barrier of pulmonary alveoli.<sup>23,24</sup> In 2013, APEPTICO fruitfully concluded phase 1 clinical study in healthy subjects, verifying the safety of solnatide. Additionally, APEPTICO also effectively finished a randomized, double-blinded placebo-controlled phase 2 clinical trial in mechanically ventilated ARDS patients with lung edema, proving the purpose of inhaled solnatide.<sup>25</sup> The clinical facts and figures collected so far from hospitalized COVID-19 patients have revealed that 20% of them experience ARDS and its linkage with pulmonary edema is verified by postmortem sampling of a patient who succumbed to COVID-19 infection. The identified death rate for ARDS is 20–30%. At this moment, no medication has been prescribed particularly for the treatment of ARDS or pulmonary permeability edema. According to the current requirement, APEPTICO signed a funding treaty with the European Commission to speed up the accessibility of an inhaled peptide solnatide for the treatment of COVID-19 patients.<sup>25</sup>

### Intranasal vaccine spray

Altimmune, Inc. (Gaithersburg, USA), a biopharmaceutical company is collaborating with the University of Alabama (Birmingham, USA) for the development of a potential vaccine to avoid COVID-19 disease. The COVID-19 vaccine, termed AdCOVID, is a single-dose vaccine that is administered by an intranasal spray. The University of Alabama will probe immune responses to the AdCOVID in animals while the Altimmune would initiate Phase 1 human safety and immunogenicity assessment in patients during the third quarter of the present year. The AdCOVID vaccine is based on Altimmune's proprietary intranasal vaccine technology i.e. NasoVAX™. The NasoVAX™ is a recombinant intranasal vaccine formulated for both recurring and pandemic purposes. The NasoVAX™ has been shown to activate multiple (humoral, mucosal and cellular) arms for a more inclusive immune response. Recently, the Phase 2

NasoVAX™ trial (NCT03760549) demonstrated potent activation of mucosal and cellular immune responses besides a strong serum antibody response. These firms in collaboration have concluded that the intranasal route of delivery and satisfactory stability report permit for capable and economical allocation of an AdCOVID vaccine across the globe.<sup>26,27</sup>

### Inhaled nitric oxide

Nitric oxide (NO) is an essential endogenous substance obtained from arginine in mammalian cells via three key enzymes i.e. neuronal, endothelial and inducible nitric oxide synthase (iNOS).<sup>28</sup> NO is an important element of the lungs and it plays a vital physiological role in the management of pulmonary vasomotor tone.<sup>29</sup> It increases the levels of cyclic guanosine monophosphate and regulate the pulmonary smooth muscle tone.<sup>29</sup> Additionally, it retains the standard vascular function and control inflammatory progression in the state of moribund endothelial function.<sup>28</sup> Particularly, the inhaled NO therapy is commonly prescribed in the persistent pulmonary hypertension of the newborn (PPHN), acute lung injury and ARDS.<sup>30</sup> The iNOS functioning is normally raised during viral infection (e.g. SARS-CoV-1 infection) and NO hinders the viral replication through a cytotoxic reactions via intermediate, peroxynitrite.<sup>28,31</sup> However, the SARS-CoV-2 infects endothelial cells, which are a key resource of NO synthesis.<sup>28</sup> Therefore, in SARS-CoV-2 management, inhaled NO may be helpful to restore endothelial function and control inflammatory responses. Therefore, two inhaled NO delivery systems i.e. VERO's GeNOsyl® iNO system and Beyond Air LungFit™ platform are discussed below.

### VERO's GeNOsyl® iNO system

Vero Biotech LLC (Georgia) is a biotechnology corporation focused on the design and development of products to tackle the medical needs of patients suffering from pulmonary diseases. VERO Biotech LLC developed next-generation inhaled NO delivery systems. GeNOsyl® Acute DS and lightweight portable GeNOsyl® Chronic DS are designed for use in the hospital and outside the hospital settings, respectively.<sup>30,32</sup> In December 2019, US FDA approved GeNOsyl® iNO system for the treatment of PPHN. The single-use ventilator and nasal cannula or mask are supplied with the GeNOsyl® Acute DS and GeNOsyl® Chronic DS to deliver the NO, respectively. Additionally, the disposable drug cassette is also available to ease the treatment function. Ultimately, the VERO's GeNOsyl® iNO system is helpful in the COVID-19 emergency with shortage of ventilators at medical centers. A handy, disposable GeNOsyl® iNO system in either the medical center or residence enables healthcare practitioners the flexibility to serve patients with inhaled NO effectively.<sup>32</sup>

### Beyond Air LungFit™ platform

Beyond Air is a US-based biopharmaceutical company actively working on inhaled NO products for several life-threatening pulmonary disorders. Beyond Air's lead platform system, LungFit™ is specially designed to generate and deliver NO from ambient air. Beyond Air already possess the LungFit™ pH and LungFit™ BRO devices to deliver NO dosage to the pulmonary airways for a patient suffering from PPHN and non-tuberculous mycobacteria, respectively. In this prevailing pandemic situation, Beyond Air submitted an investigational device exemption (IDE) to the USFDA for using its cylinder-free LungFit™ BRO inhaled NO delivery system in the treatment of COVID-19.<sup>33</sup>

### Aerosolized KL4 surfactant

Windtree Therapeutics Inc. is a US-based biotechnology firm dynamically working on developing KL4 surfactant therapies for critical pulmonary airway diseases. KL4 surfactant therapy is a life-saving remedy for respiratory distress syndrome (RDS).<sup>34</sup> The KL4 surfactant therapy contains a lyophilized synthetic peptide KL4 (sinapultide), a 21-amino acid peptide that is specifically developed to mimic the vital characteristics of the human pulmonary surfactant protein B (SP-B). The SP-B is one of the most important pulmonary surfactants, apt for the performance of pulmonary system. Additionally, Windtree's purposely designed aerosol delivery system (AEROSURF®) to aerosolize KL4 surfactant effectively.<sup>35,36</sup> Recently, physiological data of phase 2aAEROSURF® clinical trial (NCT02074059) showed that the aerosolized KL4 surfactant reduces the frequency of nasal continuous positive airway pressure (nCPAP) failure.<sup>37</sup> Essentially, the pulmonary airways damages observed in COVID-19 subjects are likely to develop into bronchopulmonary dysplasia with further progression into RDS. Moreover, the COVID-19 virus infects the particular cells that produce pulmonary surfactant and results in insufficient levels of functional pulmonary surfactant. Therefore, the surfactant replacement therapy could potentially help to improve lung function in COVID-19 cases, with the intent of reducing the need for mechanical ventilation. This may help in reducing the mortality rate. Recently, Windtree Therapeutics Inc. has announced that Lee's Pharmaceutical Holdings (HK) Ltd. would offer a financial support for a Phase 2b study of AEROSURF® useful in the treatment of preterm infants' RDS.<sup>38</sup>

### Nebulized aspartyl-alanyl diketopiperazine

Ampio Pharmaceuticals, another US-based biopharmaceutical corporation working on the design and development of novel treatment alternatives for inflammatory diseases. Ampio Pharmaceuticals key platform system, Ampion™ is an aqueous solution containing aspartyl-alanyl diketopiperazine (DA-DKP), an anti-inflammatory, immuno-modulating essence obtained from human

serum albumin (HSA).<sup>39</sup> This DA-DKP plays a vital role in regulating the inflammation by controlling the pro-inflammatory cytokine production in T-cells. Therefore, by knowing COVID-19 pandemic, Ampio Pharmaceuticals plans to submit an expanded access protocol to the USFDA to assess its nebulized Ampion delivery system in the treatment of severe ARDS caused by COVID-19. Ampio Pharmaceuticals further explains that the mechanism of action for Ampion includes several biochemical pathways allied with resolving inflammation, which would make it a potential therapy for ARDS caused by COVID-19. Also, the firm's in-house manufacturing facility have enough capacity to deliver significant quantities of nebulized Ampion™ rapidly.<sup>39</sup>

### Inhaled interferon beta

The UK biotech, Synairgen, is a drug discovery and development company established by the University of Southampton Professors Stephen Holgate, Donna Davies and Ratko Djukanovic. Synairgen is actively designing a formulation of Interferon-beta (IFN-beta), named SNG001 for direct, pulmonary delivery via nebulization for therapy and/or prophylaxis of lower respiratory tract diseases caused by respiratory viruses. IFN-beta is a natural protein, which coordinates the human's antiviral responses. The deficiency of IFN-beta in pulmonary airways may enhance the vulnerability to develop severe lung disease during respiratory viral infections.<sup>40</sup> Additionally, viruses, including coronaviruses, are capable of restraining IFN-beta production, thereby, allowing the virus to escape the innate immune system. Phase 2 clinical trial (NCT01126177) in asthma subjects have shown that therapy with inhaled SNG001 diminished the pulmonary viral load in an in-vivo swine flu-driven model of viral pneumonia.<sup>41</sup> Additionally, Phase 2 clinical trial in COPD (NCT03570359) is continuing.<sup>42</sup> Earlier statistics have revealed that this therapy is well tolerated and up-regulates pulmonary antiviral defenses in COPD. Inhaled IFN-beta could be an important alternative to serve the current COVID-19 epidemic. Accordingly, the UK Medicines and Healthcare products Regulatory Agency (MHRA) and Health Research Authority (HRA) have accelerated the approval for Phase 2 trial of nebulized IFN-beta in the management of COVID-19. This Phase 2 clinical trial called SG016 (EudraCT: 2020-001,023-14) is a double-blinded, placebo-controlled trial.<sup>43</sup>

### Intranasal vazepapt

Biohaven (USA) is a clinical-stage biopharmaceutical predominantly working on small molecules like calcitonin gene-related peptide (CGRP) receptor antagonist. The CGRP is an essential sensory neuropeptide expressed in healthy lungs, essential for maintaining lung homeostasis. Targeting CGRP can modulate severity of lung diseases.<sup>44</sup> Basically, lung injury stimulates the release of CGRP, which plays a key role in the progression of ARDS-CGRP antagonists, then, may assist to reduce the

major inflammation allied with COVID-19. Biohaven's key candidate, vazegepant (BHV-3500), is a highly soluble, small CGRP receptor antagonist molecule. Therefore, Biohaven (USA) proposed that the vazegepant molecule may be helpful in effective management of COVID-19 associated pulmonary inflammation. In past clinical trials, (NCT03872453) intranasal vazegepant was administered through the Aptar Pharma Unit Dose System. These clinical trials showed satisfactory outcome with suitability for variety of other delivery routes, including orally inhaled products.<sup>45</sup> Consequently, US FDA has approved the Biohaven's intranasal vazegepant for a Phase 2 clinical trial. This clinical trial is called as the BHV-3500–203 (Zavegepant trial; NCT04346615) is a double-blind, randomized, placebo controlled trial.<sup>46</sup>

### Nebulized lung-selective JAK inhibitor

Theravance Biopharma is a US-based diversified biopharmaceutical corporation mainly focused on the development of organ-selective medicines. Theravance Biopharma has accelerated the development of nebulized lung-selective Janus kinase (JAK) inhibitor, TD-0903 to address the current challenge presented by the COVID-19. In experimental murine models, nebulized pan-JAK inhibitor showed broad inhibition of JAK-signal transducer and activator of transcription signaling pathway in the pulmonary airways.<sup>47</sup> The TD-0903 potentially block the release of cytokines and chemokines associated with acute respiratory conditions and the initiation of a cytokine storm syndrome. Therapy with lung-selective JAK inhibition is considered as a vital anti-inflammatory approach to effectively control the hyperinflammation in hospitalized COVID-19 subjects prone to acute lung injury and ARDS.<sup>48</sup> As well, pre-clinical studies showed that TD-0903 has a high lung: plasma ratio and quick metabolic clearance ensuing in low systemic exposure and delivery route (nebulizer), which improves its pulmonary airway selectivity. Moreover, pre-clinical pharmacodynamic trials exhibited that TD-0903 has an extensive period of action, which allows once or twice daily dosing in subjects. Therefore, Theravance Biopharma submitted the clinical trial application to regulatory authorities to initiate clinical progress of TD-0903 for

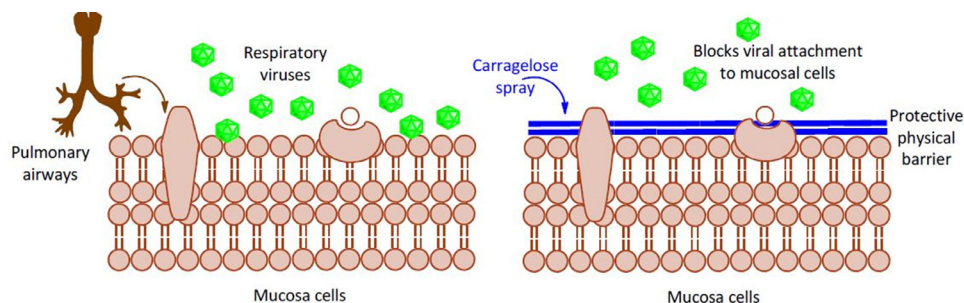
impediment of cytokine storm in hospitalized COVID-19 patients. After Clinical Trial Application approval, Theravance Biopharma will rapidly start Phase 1 single and multiple ascending dose study in UK with 2-part Phase 2 study in hospitalized COVID-19 patients.<sup>47</sup>

### Carragelose® sprays

Marinomed Biotech (Austria) is a well-known biopharmaceutical corporation that develops novel systems to treat various pulmonary diseases. Marinomed is mainly working on the polymer Carragelose®. Carragelose® is a distinctive, broadly active anti-viral molecule for treating various pulmonary conditions. It is a sulfated polymer obtained from red seaweed algae, approved for marketing in EU, Australia and parts of Asia as component of throat sprays, nasal sprays and lozenges. As per Marinomed, a study performed in 2014 showed that treatment with Carragelose® decreased the period of symptoms by 3 days in patients infected with a coronavirus compared to placebo.<sup>49</sup> Carragelose® forms a protective physical barrier on the oral and nasal mucosa, thereby avoiding entry and/or binding of the pulmonary viruses into the cells (Fig. 1).<sup>50</sup> In this prevailing pandemic, the Austrian Research Promotion Agency signed a funding agreement with the Marinomed Biotech for development of a Carragelose® inhalation solution for COVID-19 pneumonia. Marinomed Biotech plans to utilize the grant for a Phase 1 clinical trial in healthy volunteers and a proof of concept study will be performed at the Medical University of Vienna to assess the efficacy of the Carragelose® inhalation solution in patients with viral pneumonia. (Fig. 1)

### PUL-042 immunostimulant

Pulmotect, Inc. (Houston, USA) is a bio-pharmaceutical organization that develops host-directed/pathogen-agnostic products to treat severe pulmonary diseases. Pulmotect, Inc. is actively working on PUL-042 immunostimulant inhalation solution for the prevention and treatment of COVID-19. PUL-042, a synergistic grouping of two toll-like receptor agonists, is known to trigger the airways' first line of defense, the surface immune system. Primarily, PUL-042 targeted to treat pulmonary



**FIG. 1.** Carragelose® physically interacts with mucosal surfaces and creates a protective physical barrier to prevent binding and/or entry of the respiratory viruses into the cells.<sup>40</sup>

complications of cancer patient treatment was well tolerated in three Phase 1 clinical trial in the US.<sup>51</sup> The PUL-042 showed satisfactory defense against a broad range of pulmonary pathogens, including the coronaviruses that cause MERS and SARS in pre-clinical mice models.<sup>52</sup> Moreover, PUL-042 can reduce the viral load in the pulmonary airways post-infection.<sup>52</sup> Based on this preliminary study, Pulmotect, Inc. (Houston, USA) started clinical trials i.e. NCT04313023 and NCT04312997 to prevent COVID-19.<sup>53</sup>

### GLS-1200 nasal spray

GeneOne Life Science, Inc. (Seoul, South Korea) is well-known biotechnology company focused on various gene-based therapies and vaccines. GeneOne Life Science, Inc. drug development platform mainly consist of DNA-based vaccines, mRNA-based vaccines, DNA-based therapeutics and small molecule immunotherapeutics.<sup>54</sup> The epidemiology of coronavirus is mostly concerted in the nose since the viral receptors are fairly dispersed in the nasal epithelial cells. Thus, researchers from GeneOne Life Science, Inc. are dynamically working on therapeutic agent (GLS-1200) for nasal targeting in therapy of coronavirus. The GLS-1200 nasal spray produces nitric oxide (NO) gas in the nasal epithelial cells, which is secreted out of the cells. It can prevent the replication and infection of the SARS coronavirus. Additionally, the prophylactic treatment like GLS-1200 can be easily scalable.<sup>55</sup> As a result, very recently, US FDA has approved an investigational new drug (IND) application for a Phase 2 double blind study of GLS-1200 nasal spray for the prevention of COVID-19.

### Inhaled siRNA VIR-2703

The Vir Biotechnology (San Francisco, USA), a clinical-stage immunology company in partnership with Alnylam Pharmaceuticals (Cambridge, UK), the RNA specialist has started the development of inhaled siRNA therapeutic agent (VIR-2703). This agent can target the SARS-CoV-2 genome for the effective treatment of COVID-19. In dose-response assays, VIR-2703 revealed to have an effective concentration for 50% inhibition of less than 100 picomolar and an EC95 of less than 1 nanomolar in the SARS-CoV-2 live virus model as an inhibition measure of infectious virion production. Thus, in this existing pandemic state, Alnylam Pharmaceuticals and Vir Biotechnology have publicized that they planned for an IND application for VIR-2703 in the prevention and/or treatment of COVID-19.<sup>56</sup>

### Alvesco inhaler

Ciclesonide, a glucocorticoid normally prescribed for asthma is sold under the brand name Alvesco (Covis Pharma, Luxembourg). Alvesco pressurized meter dose inhaler (80 to 320 µg ciclesonide/actuation) is used for maintenance treatment of asthma as prophylactic

therapy in adult and adolescent patients of 12 years and older age in US. In COVID-19 subjects, the ciclesonide is anticipated to reduce signs and restrain the viral replication. Thus, recently, USFDA has approved an IND application for a Phase 3 clinical study to assess Alvesco (ciclesonide) for the treatment of non-hospitalized, symptomatic COVID-19 patients aged 12 years and above. Similar studies related to ciclesonide are presently investigated for management of COVID-19 in multiple countries such as Sweden, South Korea, Australia, UK, US and Japan.<sup>57</sup>

### PH94B aloradine nasal spray

VistaGen Therapeutics, Inc., US is a clinical-stage biopharmaceutical group dedicated to develop distinguished therapies for central nervous system diseases and disorders.<sup>58</sup> The COVID-19 pandemic has shaped uncertainty, fear and anxiety about wellbeing and life that have challenged mental health, globally. To manage anxiety-related disorders, the safe and novel fast-acting treatment options are needed. Therefore, to address the current mental health challenges, VistaGen Therapeutics, Inc. emerged with the PH94B neuroactive nasal spray. The PH94B is a novel, odorless, rapid-onset nasal drug delivery system. PH94B specifically binds to nasal chemosensory receptors and trigger neural circuits in the brain that suppress anxiety and fear allied with everyday social conditions and other routine situations. Additionally, VistaGen Therapeutics, Inc. completed Phase 2 (NCT01217788)<sup>59</sup> and Phase 3 (NCT02622958)<sup>60</sup> clinical trials effectively. Also, they proved the PH94B nasal spray (8 µg spray) efficacy in acute treatment of social anxiety disorders. Following these clinical trials, VistaGen Therapeutics, Inc., proposed the Phase 2a study of PH94B nasal spray for the treatment of anxiety related to the COVID-19 pandemic to US FDA.<sup>61</sup>

### Remdesivir inhalation powder

Sahakijpijarn et al. (2020) formulated remdesivir inhalation powder using novel thin film freezing technique (TFF) and thoroughly analyzed for in-vitro and in-vivo aerodynamic properties. Particularly, the TFF generates brittle matrix nanostructured aggregates with aerodynamic size suitable for pulmonary delivery. During an in-vitro aerodynamic study, the TFF-remdesivir-Captisol® (80:20 w/w) and TFF-remdesivir-leucine (80:20 w/w) showed the satisfactory fine particle fraction of 78.08% and 89.68% respectively, using RS00 high resistance monodose device at a flow rate of 60 l/min. In in-vitro release study both batches demonstrated more than 80% of remdesivir release within the initial 90 min using simulated lung fluid. Furthermore, during in-vivo pharmacokinetic study after intratracheal administration (10 mg/kg) to Sprague-Dawley rats using the DP-4 M dry powder insufflator TFF-remdesivir-Captisol® demonstrated increased systemic uptake as compared to TFF-



remdesivir-leucine. Interestingly, the concentration of GS-19 441,524 metabolite (nucleoside analog of remdesivir) within the lung was superior for the TFF-remdesivir-leucine as compared to TFF-remdesivir-Captisol® formulation.<sup>62</sup> Thus, combination of remdesivir with judiciously chosen excipients and dry powder processing method may be a treatment option in clinical practice to deal with COVID-19 infection.<sup>62</sup>

In short, vaccination through pulmonary airways is an appealing strategy for several applications in preventive as well as therapeutic immunization. All these active efforts denote a bridgehead for the clinical development of COVID-19 vaccine. However, many human clinical trials of inhaled vaccines are yet to be performed for prevention and/or treatment of COVID-19. The novel formulation technologies and simple handling of the delivery devices provide space for the development of new products. Additionally, few recently published articles showed that point-of-care ultrasound, single-use ultrasound gel, monolithic disposable cartridge for saliva analysis, patient-centric stethoscopes and electronic monitoring devices could avoid direct contact during the COVID-19 initial examination and pulmonary management, which could probably minimize the risk of exposure and transmission.<sup>63-66</sup> Likewise, formulation development with single-use (rescue or relief) disposable inhaler can be considered as an important extension for preventing or controlling the COVID-19 infection in near future.

## CONCLUSION

Collaborative and team efforts across the globe illustrate the pace at which therapy against COVID-19 can be designed and developed with the recent advances in science and technology. Presently, treatments for COVID-19 are limited. However, many of the COVID-19 indications are treated with early care, social distancing and containment measures. Many pre-clinical and clinical trials for drugs and vaccine candidates are ongoing to support and verify the effectiveness of believed hypothesis. With the combined efforts of the scientific society and the healthcare experts worldwide, it may be possible to rapidly-produce clinically translatable treatment measures against the COVID-19. Meanwhile, the individual and healthcare providers should utilize PPEs and take great concern during routine practice to strengthen the battle against the present adverse zoonotic spillover.

## DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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