AnnalsofClinicalandMedical Case Reports

ResearchArticle ISSN2639-8109Volume9

# EfficacyandSafetyofBovhyaluronidaseAzoximer(Longidaza)inPatientswith Post-COVID-19 Syndrome: Results of the Open-label Prospective Controlled Comparative Multicenter Clinical Trial Dissolve

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**Keywords:**

Bovhyaluronidaseazoximer(Longidaza);Hyaluronidase; Post-COVID-19 syndrome; Hyaluronic acid; Lung function; Dyspnoea; Pulmonary rehabilitation

Received: 15 Sep 2022
Accepted: 10 Oct 2022
Published:17Oct2022 JShort Name:ACMCR

**Citation:**

ChuchalinAG,Efficacy andSafetyofBovhyaluronidase Azoximer (Longidaza) in Patients with Post-COVID-19 Syndrome: Results of the Open-label Prospective Con- trolled Comparative Multicenter Clinical Trial Dissolve Ann Clin Med Case Rep. 2022; V10(2): 1-9

## 1. Abstract

**Introduction:** Post-COVID-19 syndrome is a condition that develops in the patients recovered from COVID-19 resulting into the cumulative effects of dyspnoea and impaired lung function.

Notably,higherconcentrationsofHAhavebeenfoundinpatients with respiratory inflammation and COVID-19.As, bovhyaluroni- dase azoximer (Longidaza®) catalyses the hydrolysis of HA, the treatment has the potential to lower HA concentrations and im- prove lung function in patients with post-COVID-19 syndrome.

**Aims and Objectives:**The DISSOLVE trial was undertaken atinitialphaseofthepandemicandaimedtostudytheefficacyand safetyofbovhyaluronidaseazoximerinpatientswithpost-COVID symptoms.

**Methodology:** The study was an open-label, prospective, controlled,comparative,multicenterclinicaltrial(NCT04645368) conducted in 160 adult patients with post-COVID-19 syndrome. The Treatment group (n = 81) received bovhyaluronidase azox- imer and the Control group (n = 79) was used as a dynamic ob-servationgroup.Studyparametersincludedphysicalexamination,

forcedvitalcapacity(FVC),dyspnoeamodifiedMedicalResearch Committee (mMRC) scale, 6-minute walking test (6MWT) and pulse oximetry that were collected on three visits: Day 1 (Base- line), Day 75, and Day 180.The number of patients with adverse events (AEs) and serious adverse events (SAEs) were recorded.

**Results:** Baseline characteristics were similar for the Treatment group and the Control group. In theTreatment group, resid- ual pulmonary abnormalities decreased significantly after Visit 2 (Day75)andVisit3(Day180),additionally,forcedvitalcapacity (FVC), pulse oximetry, functional exercise capacity of the Treat- ment group increased significantly from baseline to Day 75 and Day 180. mMRC dyspnoea score of the Treatment group signifi- cantlydecreasedovera75-dayperiod.Patientsreportedafavour- able safety profile throughout the trial.

**Conclusion:** Patients with post-COVID syndrome may benefit from treatment with bovhyaluronidase azoximer, as indicated

bypatientsdisplayinganimprovementintheirFVC,pulseoximetry (SpO(2)), functional exercise capacity and dyspnoea mMRC score.


## 2. Introduction

By February 2022, over 420 million people had been infected with coronavirus disease 2019 (COVID-19) and there had been over5.87millionfatalities[1].Severeacuterespiratorysyndrome coronavirus 2 (SARS-CoV-2) causes pulmonary inflammation andprogressiverespiratoryimpairment.Thoughthemajorityof

individuals fully recover from SARS-CoV-2 infection, symptoms persist in 10–20% of individuals. Mid- and long-term symptoms, i.e.,symptomsthatpersistformorethan12weeks,arecollectively known as post-COVID-19 condition or 'long COVID'[2,3]. Persistent dyspnoea is a common symptom of long COVID [4,5].A recent study reported severe dyspnoea occurring in patients for 2 monthsaftertheinitialCOVID-19infection[6].LongCOVIDcan cause significant impairment in lung function [7,8].

Hyaluronicacid(HA:alsoknownashyaluronan)isakeyconstit- uent of the pulmonary extracellular matrix (ECM). Degradation productsofHAmayplayaroleinthephysiopathologyoftheres- piratory system, and they have been detected at high levels in the respiratorysecretionsofpatientswithvariousformsofrespiratory inflammation [9-13]. Importantly, the accumulation of HA in alveolar spaces has been linked to hypoxemia, respiratory failurein cases of severe COVID-19 [14]. and on the CT scan it look as "ground glass" pattern due to HAhygroscopic properties [15,16]. HumanIdenticalSequences(HIS)ofSARS-CoV-2canupregulate HA, which may contribute to the progression of COVID-19 [17] by enhancing of the cytokine storm and such event is known as "HAstorm"[15].

However,theroleofHAinthepathogenesisofCOVID-19hasyet to be fully elucidated. Bovhyaluronidase azoximer (Longidaza®, NPOPetrovaxPharmaLLC,Moscow,Russia)isabovinehyaluro- nidase that is conjugated to azoximer bromide (Polyoxidonium®, NPO Petrovax Pharma LLC, Moscow, Russia), which increases enzymatic resistance in the presence of inhibitors and increased temperatures [18]. Bovhyaluronidase azoximer regulates the concentrationofHAandretainsthepharmacologicalpropertiesofthe azoximer bromide with chelating, antioxidant, anti-inflammatory and immunomodulating activity. Figure 1 illustratesthe proposed mechanism of action of bovhyaluronidase azoximer. We postu- lated that bovhyaluronidase azoximer may improve respiratory symptoms in patients suffering the effects of long COVID by re- ducing the elevated levels of HA.

Herein, we present data from a comparative trial to study the efficacy and safety of bovhyaluronidase azoximer in patients with post-recoveryrespiratoryimpairmentafterCOVID-19.Following bovhyaluronidase azoximer treatment, this study assessed objective indicators of pulmonary rehabilitation (e.g., FVC, pulse oximetryandexercisetolerance)andmMRCdyspnoeascaleat 2.5 months and 6 months in patients with long-COVID. We determined if marked improvement in lung function corresponded with marked changes in residual pulmonary abnormalities using high-resolution computed tomography.

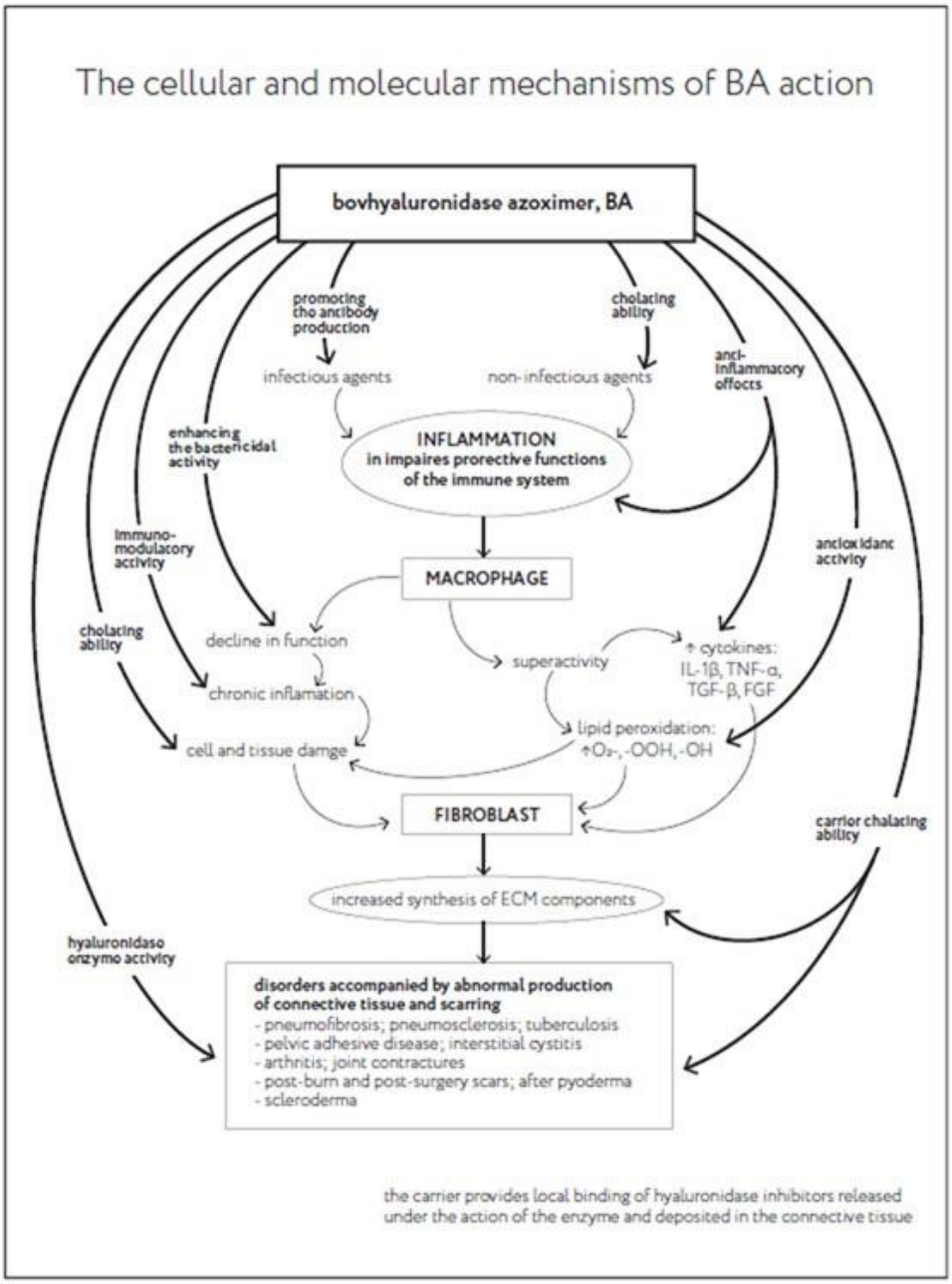


**Figure1:**Proposedmechanism ofaction ofbovhyaluronidase azoximer (AdoptedfromNekrasovAV,IvanovaAS,PuchkovaNG.Longidaza-amoderntreatmentapproachtodisorders,accompaniedbyabnormalproduc- tion of connective tissue. Signature (1). 44-52. 2006)

## 3. MaterialsandMethods

### Study Design

This was an open-label, prospective, controlled, comparative, multicenter clinical trial (NCT04645368) to evaluate the efficacy and safety of bovhyaluronidase axozimer (Longidaza®, lyophilized powder for solution for injection, 3000 IU) in patients withpost-COVID-19syndromecomplicatedbyrespiratorymanifestations (Figure 2).

Patients >18 years with residual pulmonary changes, detected no laterthan2monthsafterdischargefrominpatienttreatment,were eligible to participate in the study.The main non-inclusion criteriawerethepresenceofsevereunderlyingdisease,suchassevere heartfailure,liverandkidneydisease,severebronchialasthma,or severe chronic obstructive pulmonary disorder.

The DISSOLVE trial evaluated the efficacy and safety of bovhyaluronidase azoximer in controlled conditions with the post-treatment follow-up period. The study was conducted during the initialphaseoftheCOVID-19pandemicaspulmonaryfibrosisis apostCOVIDcondition.Antifibroticpropertiesofbovhyaluronidaseazoximerwasparticularlyconfirmedinaclinicaltrialonthe patients of cryptogenic fibrosing alveolitis with concurrent pneumofibrosis [19].

Theobjectiveofthestudywastodeterminethedynamicsofalleviatingpost-COVIDpulmonarycomplicationsusingchesthigh-res-

olution computed tomography (HRCT) scans in patients after a courseofbovhyaluronidaseazoximer(2.5months)incomparison with the Control group.The secondary objective of the study was to evaluate the other parameters of the efficacy and the safety of bovhyaluronidaseazoximerinpost-COVID-19syndrome.Participation duration with follow-up period was 180 ± 6 days.

Atotal of 160 adult patients of either sex was enrolled in the trial at13studysites(Table5).TheTreatmentgroup(n=81patients) received bovhyaluronidase azoximer (3000 IU; intramuscularly) once every 5 days with a course of 15 injections and the Control group(n=79patients)performedadynamicobservationalone.All the parameters were measured at Day 1, Day 75 and Day 180.

The first visit was undertaken on Day 1 and baseline characteristicswererecorded.Thesecondstudyvisit,assessedat75±2Day, correspondedtocompletingthecourseoftherapyinthefirststudy group.Thethirdvisittookplaceafterthefollow-upperiodat180 ± 6 Day Figure 4.

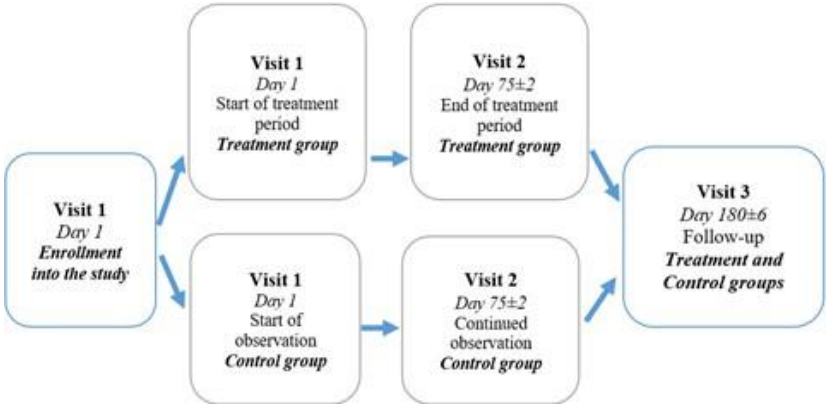


**Figure2:**Studyflowdiagram

### Patients

Patients were required to be over 18 years old with pulmonary manifestations detected no later than 2 months after hospital dischargeowingtoprolongedCOVID-19infection.Patientswererequired to provide negative polymerase chain reaction (PCR) test resultsforSARS-CoV-2infectionontwooccasionsinrespiratory tract samples.

### Assessments

**Vital signs assessment and physical examination:** Vital signs were recorded (heart rate, normalized pulse volume, blood pressure, body temperature) after resting, and physical examinationwereperformed.Thephysicalexaminationevaluatedthemucous membranes and skin, palpation of lymph nodes, assessment ofthemusculoskeletalsystemandauscultationoftheheart,lungs and other organs.

### Instrumental methods

Instrumental analyses including HRCT of lungs and spirometry wereperformed.Residualpulmonaryabnormalitieswererecorded aspercentageoflungvolumewithHRCT-detectedlesions.Forced vitalcapacity(FVC)wasassessedbyutilizingaspirometrymeasurement which was undertaken with ATS/ERS 2005 guidelines [20].

### mMRCdyspnoeascale

AssessmentofthedyspnoeausingthemMRCdyspnoeascale [21] was applied at Days 1, 75 and 180 and scored as follows: 0, shortnessofbreathoccursonlyduringheavyphysicalexertion;1, patients walk slower than their peers or walking at their own pace shortness of breath occurs when walking briskly on level ground orwhenclimbingaslightelevation;2,duetoshortnessofbreath,

on flat terrain, must stop to catch their breath; 3, after walking approximately 100 m or after a few minutes of walking on level ground, the patient must stop to catch their breath; 4, shortness of breath does not allow the patient to leave the house and appears when dressing or undressing [22].

**Six-minutewalktest**

The distance walked in 6 min along a long straight corridor (≥30 m) at the patient's own pace was measured to evaluate functional physical capacity.

**Fingerpulse oximetry**

The finger pulse oximetry was carried out before performing the 6MWT to determine the peripheral capillary oxygen saturation (SpO(2)), which was then recorded as the change from the baseline.

**Statistical methods**

Demographic and other initial characteristics were tested using analysis of variance for quantitative indicators and using the Chi-squaretest($\chi 2$)forqualitativeparameters.Intergroupcomparison of all endpoints, which represented changes from initial values, were performed using analysis of covariance (ANCOVA) with Treatment group as a factor and initial parameter value as a continuouscovariate.Statisticaltestswereperformedtwo-tailedwith a 5% significance level.

**Safety**

Adverse events were coded using Medical Dictionary for RegulatoryActivities (MedDRA).The number (proportion) of patients withadverseevents(AEs)/seriousadverseevents(SAEs)andthe

number of AEs/SAEs were recorded by organ system class and preferred term, and in relation to study therapy and severity, by treatment group. In this case, each patient was counted once with theaimtostudytherapyandtheseverityofthemaximumexpres- sion.

## 4. Results

### Demographicdetailsandbaseline characteristics

Totalnumberofpatientsenrolledinthestudywas160(Treatment group=81patients;Controlgroup=79patients;Table1).Theratio of females to males was approximately 2:1 (female=103 patients; males=57patients)andthemeanageofthepatients(Treatment group=54.60 ±10.02 years; Control group =54.70 ± 12.58 years) andbodymassindex(Treatmentgroup=28.70±5.33kg/$m^2$;Con- trol group= 28.90 ± 5.08 kg/$m^2$) were similar across the groups.

Baselinecharacteristicsofpatientsinbothgroupswerealsosimilar (Table1).Forcedvitalcapacitymeasurementswere88.8±20.50 % prediction in the Treatment group, and 92.1 ± 17.55 % predic- tionintheControlgroup.Thebaselinedyspnoeascore,according to mMRC dyspnoea scale, was 1.3 ± 0.97 in theTreatment group and 1.1 ± 0.78 in the Control group. The baseline 6MWT result was388.9±117.53minTreatmentgroupand430.16±99.42min theControlgroup.Thepulseoximetry(Sp(O)2)was96.7±1.45% in the Treatment group and 97.0 ± 1.10% in the Control group.

**Table1:**Demographicdetailsandbaselinecharacteristics

| Characteristics | Treatmentgroup | Controlgroup |
|---|---|---|
| Age, years | 54.6 ± 10.02 | 54.7 ± 12.58 |
| Female | 66.70% | 62.00% |
| Male | 33.30% | 38.00% |
| Bodymassindex,kg/$m^2$ | 28.7 ± 5.33 | 28.9 ± 5.08 |
| FVC, % pred. | 87.9 ± 21.03 | 92.1 ± 17.55 |
| Dyspnoea (according to mMRC scale), score | 1.3 ± 0.97 | 1.1 ± 0.78 |
| 6-minuteswalkingtestresult,m | 388.9 ± 117.53 | 430.16 ± 99.42 |
| PulseoximetrySp$O_2$,% | 96.7 ± 1.45 | 97.0 ± 1.10 |
| TimefromCOVID-19onsettoVisit1, months | 1.5 ± 0.77 | 1.5 ± 0.89 |

Dataare presented asmean ± SE, 95CI

### Lung Function

We determined the FVC changes from the baseline within each group. Most patients in theTreatment group showed an improve- ment > 5% in FVC at Day 75 compared with baseline (58.4% of patients), which was greater than in the Control group (39.1%; Table3).Thepercentageofpatientsexperienced5–10%improve- ment of their FVC was 13.8% in the Treatment group compared to 20.3% of the Control group, but the percentage of patients that showed over 10% improvement of their FVC was greater in the Treatmentgroup(44.6%)comparedtotheControlgroup(18.8%). ApproximatelyhalfofthepatientsintheControlgroupexperi- enced no improvement (46.4%) compared with approximately 30% in theTreatment group (29.2%).The number of patients ex- perienced>5%worseningoftheirFVCappearstobesimilarinthe Treatment group (12.3%) and the Control group (14.4%).

Next, we investigated relative changes in lung function between the groups (Table 2). At Day 75, the rate of FVC changes was significantly higher in the Treatment group (9.02 ± 1.404%) than intheControlgroup(5.05±1.383%;p=0.046).AtDay180,FVC continuedtobesignificantlyhigherintheTreatmentgroup(9.97 ± 1.443%) compared with the Control group (4.48 ± 1.422%; p = 0.008).

**Table2:**RelativechangesinFVC

| Groups | Treatment(%) Mean±SE 95% CI | Control(%) Mean±SE 95% CI | P-value |
|---|---|---|---|
| Day 75 | 9.024 ± 1.404* 6.248, 11.800 | 5.046 ± 1.383* 2.310, 7.781 | 0.046 |
| Day180 | 9.970 ± 1.443** 7.124, 12.833 | 4.477 ± 1.422** 1.664, 7.290 | 0.008 |

Dataarepresentedasmean±SE FVC: Forced vital capacity

**Table3:** CategoricalanalysisofFVCchangesatDay75frombaseline,% patients

| Changein FVC | Treatment | Control |
|---|---|---|
| Worsening>10% | 7.70% | 7.20% |
| Worsening>5-10% | 4.60% | 7.20% |
| No improvement (worsening⩽ 5% - improvement⩽ 5%) | 29.20% | 46.40% |
| Improvement >5 – 10% | 13.80% | 20.30% |
| Improvement over 10% | 44.60% | 18.80% |
| Total | 100% | 100% |

**Pulse oximetry**

As shown inTable 4, mean increases from baseline inpulse oximetry $SpO_2$were greaterfor patientswho receivedbovhyaluronidaseazoximerthannotreatment(Day75:1.067±0.092%,0.573 ±0.092%,respectively;p<0.001.Day180:0.938±0.170%,0.50 ±0.170%,respectively;p=0.081.).Thedifferencewasstatistical- ly significant compared to the Control group at Day 75.

**Functionalexercise capacity**

AtDay75,thepercentageofrelativechangesinfunctionalcapacityasmeasuredby6MWTincreasedsignificantlyintheTreatment group(27.76±3.753%)comparedwiththeControlgroup(17.14 ±3.723%;p=0.049;Table4).Astatisticallysignificantincrease occurredalsoatDay180intheTreatmentgroup(30.58±4.104 %)comparedwiththeControlgroup(17.93±4.070%;p=0.032).

**mMRCdyspnoeascore**

SignificantdifferenceinmMRCdyspnoeascorewereobservedbetween theTreatment group (-0.84 ± 0.058) and the Control group (-0.58±0.058;p=0.002)atDay75.AtDay180,improvementsin mMRCdyspnoeascoreappeartobesimilarinbothgroups(-1.13 ± 0.123 and -0.87 ± 0.123, p = 0.142 for Treatment and Control group respectively).

Differencesbetweenthegroupsachievedstatisticalsignificanceat Day 75. Decreases in mMRC dyspnoea score were seen in more patients who received bovhyaluronidase azoximer (Figure 3). Mostnotably,theproportionofpatientswhoshowednochangein theControlgroupwasapproximatelydoubleofthoseintheTreat- ment group (52.2% versus 25.0%).

**Table4:** Resultsofstudyparametersassessment

| Groups | Treatment Mean±SE 95% CI | Control Mean±SE 95% CI | p-value |
|---|---|---|---|
| (a)Relativechangesinpulseoximetry(%) | | | |
| Day 75 | 1.067 ± 0.092*** 0.884, 1.249 | 0.573 ± 0.092*** 0.392, 0.754 | <0.001 |
| Day 180 | 0.938 ± 0.170 0.594, 1.282 | 0.505 ± 0.170 0.161, 0.849 | 0.081 |
| (b)Relativechangesinfunctionalexercise(%) | | | |
| Day 75 | 27.757 ± 3.753* 20.325, 35.188 | 17.143 ± 3.723* 9.773, 24.514 | 0.049 |
| Day 180 | 30.576 ± 4.104 22.450, 38.702* | 17.928 ± 4.070 9.869, 25.987* | 0.032 |
| (c)ChangesinmMRCdyspnoeascore | | | |
| Day 75 | -0.836 ± 0.058** -0.951, -0.722 | -0.582 ± 0.058** -0.695, -0.468 | 0.002 |
| Day 180 | -1.131 ± 0.123 -1.379, -0.883 | -0.869 ± 0.123 -1.117,-0.621 | 0.142 |
| (e)RelativechangesintotallungvolumewithHRCTlesions(%) | | | |
| Day 75 | -8.389 ± 1.024* -10.427, -6.352 | -11.912±1.086* -14.073, -9.751 | 0.021 |
| Day 180 | -13.466 ± 0.186 -13.843, -13.089 | -13.754 ± 0.221 -14.202, -13.305 | 0.327 |

CI=confidenceinterval,mMRC:ModifiedMedicalResearchCouncil,SE=standarderror

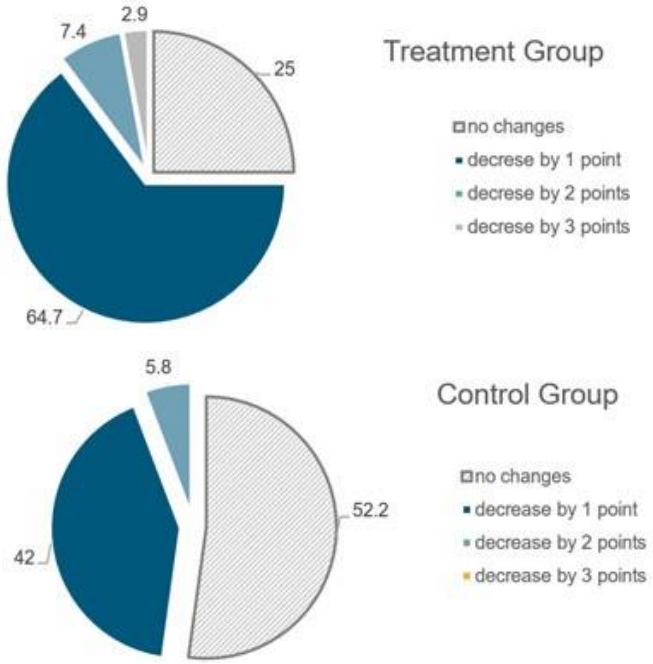


**Figure3:** CategoricalanalysisofmMRCscorechangesatDay75frombaseline,%patients

**Table5:** StudysitesandPrincipalinvestigators

| | City | Trial site | Principal investigator |
|---|---|---|---|
| 1 | Saint Petersburg | "Saint-Petersburg Research Institute of Phthisiopulmonology", | **Petr K.Yablonsky,** Doctor of Medical Sciences, Professor, Saint-Petersburg Research Institute of Phthisiopulmonology, |
| | | MinistryofHealthofRussianFederation | Ministry of Health of Russian Federation |
| 2 | Saint Petersburg | "CityConsultativeandDiagnostic Center No.1" | **TamaraV.Rubanik,**PhD,MD |
| 3 | Volgograd | "VolgogradStateMedicalUniversity", Ministry of Health of Russian Federation | **OlgaA.Chernyavskaya,**PhD,MD,DepartmentforInfectiousDiseaseswith Epidemiology, Tropical Medicine, Volgograd State Medical University, Ministry of Health of Russian Federation |
| 4 | Volgograd | "City Clinical Hospital No. 4" | **VladimirV.Naumov,**PhD,MD |
| 5 | Moscow | "CityPolyclinicNo.180",Moscow Healthcare Department | **Ludmila I. Korneva**, MD |
| 6 | Novosibirsk | "StateNovosibirskRegionalClinical Hospital" | **Lyubov'M. Kudelya,** Doctor of Medical Sciences, Professor, Department of Internal Diseases named after academician L.D. Sidorova, Novosibirsk State Medical University,Ministry of Health of Russian Federation |
| 7 | Yekaterinburg | "Central City Clinical Hospital No. 6" | **AnnaY.Petukhova,**PhD,MD |
| 8 | Perm | Medical Center "Philosophy of Beauty and Health", Ltd. | **OlgaV.Masalkina,**PhD,MD |
| 9 | Chelyabinsk | "City Clinical Hospital No. 8" | **YuliaV.Argamakova,**MD |
| 10 | Chelyabinsk | "Regional Clinical Hospital No. 3" | **Galina L. Ignatova,** Doctor of Medical Sciences, Professor, Department of Therapy,InstituteofPostgraduatePhysicianTraining,SouthUralStateMedi- cal University,Ministry of Health of Russian Federation |
| 11 | Krasnoyarsk | "Research Institute for Medical ProblemsintheNorth",SiberianBranchof the Russian Academy of Sciences | **AlexanderG.Borisov,**PhD,MD,DepartmentofInfectiousDiseasesandEpidemiology,KrasnoyarskStateMedicalUniversitynamedafterV.F.Voino-Yasenetsky |
| 12 | Astrakhan | "AstrakhanStateMedicalUniversity", Ministry of Health of Russian Federation | **Tatyana R. Kasyanova,** Doctor of Medical Sciences, Department of Faculty Therapy and occupational diseases with a course of post-graduate education, AstrakhanStateMedicalUniversity,MinistryofHealthofRussianFederation |
| 13 | Moscow | "CityClinicalHospitalD.DPletneva", Moscow Healthcare Department | **AngelinaK.Suleymanova,**MD,PhD,DepartmentofHospitalInternalMedicine,PediatricFaculty,FederalRussianStateNationalResearchMedicalUniversity named after N.I. Pirogov,Ministry of Health of Russian Federation |

**Residual pulmonary abnormalities**

Highresolutioncomputedtomographyrevealedtypicalpatternsof groundglassopacityandconsolidationinpatientsinbothgroups. We use the term 'pulmonary abnormalities' to describe the total volumeoftheseHRCTlesions.AtDay180,meandecreasesinthe total volume of pulmonary abnormalities appear to be similar up toalmostfull-volumeresolutionforthetwogroups(Treatment: -13.47 ± 0.186%, Control: -13.75 ± 0.221%, respectively; p = 0.327), although a significantly greater decrease was observed at Day 75 for the Control group (-11.91 ± 1.086%) compared with the Treatment group (-8.39 ± 1.024%; p = 0.021).

**Safetyandtolerability**

Therewerenopatientsthatdiscontinuedtreatmentandnoserious adverseeventswerereported.Early-onsetlocalinjectionreactions were the most common adverse events experienced by patients in the trial. In the Treatment group, one patient experienced pruritus with local reaction at the injection site, and one patient developed local reaction. Another patient developed pruritus after the firstinjection,andthepatientwastreatedwithantihistamineswith completelyrecovered.Therefore,therapywasnotsuspended.One patientfromeachgroupdevelopedbronchitis.Therewasonecase ofrhinitisintheTreatmentgroup,onecaseofentericfeverandone case of chest injury in the Control group.

## 5. Discussion

Complications of post-COVID-19 syndrome include dyspnoea and impairmentoflungfunction,bothofwhichcanbevastlyaffectan individual's qualityoflife[23].Hereweinvestigatedtheeffectof thetreatmentwithbovhyaluronidaseazoximer,whichbreakdowns HA, had on lung function in patients suffering long-COVID. We foundthatlungfunctionwasmarkedlyimprovedinthesepatients over time.

Hyaluronic acid is a glycosaminoglycan that is a key component of the pulmonary ECM and has been shown contribute towards tissue viscoelasticity [24-28]. Degradation products of HA have been shown to be higher in the respiratory secretions of patients with various forms of respiratory inflammation [9-13].Anumber ofstudiessuggestthatHAanditsdegradationproductsmayunderliethephysiopathologyoftherespiratorysystem.Accumulationof HAin alveolar spaces has been linked to hypoxemia and respiratoryfailureinsevereCOVID-19[14].Anotherstudyfoundhigher levelsofHAcomparedtonormallungsinthealveolarspacesand thickened perialveolar interstitium in lungs of deceased COV-ID-19 patients, compared with normal lungs [29].Abnormal metabolismofHAalongwithotherinflammatoryfactorsmayleadto complicationssuchasacuterespiratorydistresssyndrome(ARDS) andpulmonaryedemainCOVID-19patients[30].Furthermore, excessive HAdeposits stimulate fibroblasts proliferation, thereby promptingthesynthesisofnewmucopolysaccharidesandthecon- version of fibroblasts to myofibroblasts, indicators of a reactive proinflammatory stroma [31].

Post-COVIDinfectioncanreducegasexchangeefficiencyanddecreaseFVCvalues[32,33].WefoundthattargetingHAwithahyaluronidaseconjugatedtoazoximerbromideimprovedpulmonary function in patients with post-COVID infection, as observed by marked improvements in their FVC, pulse oximetry, and mMRC dysponeascale.Weinvestigatediftheimprovementsinlungfunc- tion could be observed by computed tomography. However, we foundnosignificantdifferencesintheimprovementofpulmonary abnormalities between the Treatment and Control groups. Although bovhyaluronidaseazoximeralleviateddyspnoeainpatients withpost-COVID-19syndrome,itwasnotdrivingdrasticchanges oftheHRCTpatternsobservedinDISSOLVEtrialsample.While theactivityofhyaluronidasemayreducethelevelsofHA,itisalso possiblethatazoximerbromide,towhichthehyaluronidaseiscon- jugated,mayalsobeactiveinmodulatingtheimmunesystemand further alleviating respiratory symptoms. Overall, data indicates that bovhyaluronidase azoximer plays an anti-inflammatory role (Grivtsova et al., 2021).

In our study, bovhyaluronidase azoximer administration benefited patients with post-COVID-19 syndrome. However, HAlevels werenotdeterminedinrespiratorysamplesofpatients,alimitation of this study. The molecular mechanism by which bovhyaluronidase azoximer alleviates the respiratory symptoms of post-COVID-19 syndrome therefore has yet to be elucidated. Further work isneededtodeterminetheeffectofbovhyaluronidaseazoximeron levels of HA and other molecular markers.

In conclusion, this study has demonstrated a role for bovhyaluronidase azoximer in improving lung function in patients with post-COVIDsyndrome.Thesedatasuggestthatbovhyaluronidase azoximer is a viable treatment option to help manage post-COVID-19 syndrome.

## 6. Conclusion

The DISSOLVE trial aimed to evaluate the efficacy and safety of bovhyaluronidaseazoximerinpost-COVID-19syndrome.Bovhyaluronidase azoximer demonstrated significant increase in lung function measured by FVC as well as significant improvementsinmMRCdyspnoeascale,pulseoximetryandfunctional exercise capacityatDay75andoverthestudyperiodof180days.Only a minimal number of subjects reported mild to moderate adverse events,indicatingafavourablesafetyprofileforbovhyaluronidase azoximer.

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