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ORIGINAL RESEARCH

Open-label use of an aliphatic polyamine immunomodulator in patients hospitalized with COVID-19

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Abstract

Background: Evidence-based therapies used to treat coronavirus disease (COVID-19) remain limited. Azoximer bromide (AZB; Polyoxidonium®) is an immunomodulating molecule frequently used in the Russian Federation. It offers demonstrable therapeutic benefit in upper respiratory tract infections. This study evaluated the safety and efficacy of AZB when used in combination with standard of care treatment in patients hospitalized with COVID-19.

Methods: Hospitalized patients with COVID-19 ($n=81$; nine sites) received AZB 12 mg intravenously once daily for 3 days then intramuscularly every other day until day 17. The primary endpoint included clinical status at day 15 *versus* baseline. Historical control data of 100 patients from a randomized, controlled, open-label trial conducted in China were included to serve as a direct control group.

Results: Notable clinical improvement, assessed by seven-point ordinal scale (OS) score and National Early Warning Score, was observed. Mean duration of hospitalization was 19.3 days. Indicators of pneumonia and lung function showed gradual recovery to normalization. No patients died but, by day 28, one patient still required respiratory support; this patient died on day 34. A higher

proportion of patients receiving AZB required invasive or non-invasive ventilation (OS 5 or 6) at baseline compared with the historical control group. Improvement in mean OS score by day 14/15 was not notable in the control group (OS 3.99–3.87) but was clear in the AZB group (OS 4.36–2.90). Mean duration of hospitalization was similar in the control group (16.0 days); however, day 28 mortality was higher, at 25.0% ($n=25$).

Conclusion: AZB combined with standard of care was safe and well tolerated. An apparent clinical improvement could not be fully evaluated due to the lack of a direct control group; further assessment of AZB for the treatment of COVID-19 in a randomized, placebo-controlled study is warranted.

Keywords: azoximer bromide, COVID-19, clinical improvement, exploratory research, Polyoxidonium®.

Citation

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Introduction

The clinical presentation of coronavirus disease 2019 (COVID-19) ranges from asymptomatic infection to fatal illness and is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 primarily targets the respiratory system and can cause pneumonia and respiratory failure; severe infection is associated with high rates of intensive care admission.^{1–3} Cases of COVID-19 in the Russian Federation have surpassed 4.7 million, with the death toll recently stated to be over 180,000.^{4,5} While almost 200 candidate vaccines are in development and several have been authorized for use, evidence-based therapies are currently limited.⁶ These include remdesivir, a broad-spectrum antiviral shown to modestly reduce time to recovery in hospitalized adults; dexamethasone, an anti-inflammatory shown to reduce mortality in patients requiring invasive mechanical ventilation; and tocilizumab, a monoclonal antibody shown to improve survival in hospitalized patients with hypoxia and systemic inflammation.^{7–9} ‘Antiviral antibody cocktails’ have also demonstrated capacity to reduce viral load in non-hospitalized patients,¹⁰ while combination therapy with the monoclonal antibodies bamlanivimab and etesevimab has been shown to reduce viral load in outpatients with mild-to-moderate disease.^{10,11} In addition, monoclonal antibodies, such as casirivimab and imdevimab, have contributed to the reduction of medical visits in patients with COVID-19 through the successful *in vitro* activity of REGEN-COV against current SARS-CoV-2 variants of concern.¹¹

Severe respiratory failure in patients with COVID-19 is associated with complex immune dysregulation or macrophage activation¹²; immune dysregulation, mediated by overproduction of IL-6, compromises viral clearance.¹³ Rapid shedding of endogenous IL-6 receptor (IL-6R) occurs during neutrophil pyroptosis, which affects trans-signalling by augmenting the soluble IL-6R (sIL-6R)/IL-6 complex; this stimulates endothelial cells and ultimately increases the inflammatory response.¹⁴ IL-6 blocks dendritic cell (DC) maturation, which can prevent induction of T cell differentiation.¹⁵ The contribution of immune dysfunction to the progression of COVID-19 highlights the requirement for immunological interventions. Multiple randomized trials indicate that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen,¹⁶ presumably by mitigating the COVID-19-induced systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It is also suggested that, as in cases of SARS and Middle-East respiratory syndrome (MERS), regulators and modulators of the immune response, such as interferons, could perhaps alleviate the pathogenesis of SARS-CoV-2.^{17–21}

Azoximer bromide (AZB; Polyoxidonium®) is an immunomodulator, macromolecular compound successfully indicated as an effective agent for the treatment of infectious and inflammatory diseases of viral, bacterial and fungal origin. AZB is licensed in the Russian Federation, Commonwealth

of Independent States (both licensed in 1996) and Slovakia (licensed in 2002) for the treatment of acute and chronic viral and bacterial infections as well as for various other indications, including immunodeficiencies (e.g. infection prophylaxis in rheumatoid arthritis patients taking immunosuppressant medications).²² Azoximer bromide is generally well tolerated with no major safety concerns.²³ *In vitro* studies have shown that AZB can induce T cell proliferation, increase natural killer cell degranulation and increase immature DC expansion; in addition, certain DC costimulatory molecules that function to stimulate T cells proliferate following AZB administration.²⁴ After penetrating leukocytes by endocytosis, AZB localizes in cytosolic endoplasmic vesicles, resulting in significant dose-dependent increases in intracellular hydrogen peroxide.²⁵ Hydrogen peroxide has a role in the activation of NF-κB, which subsequently regulates the transcription of genes involved in the inflammatory and immune responses, thereby coordinating several facets of the immune system necessary for infection resistance.^{26,27}

There is a recognized need to find viable treatments for COVID-19. Amongst other indications, including immunodeficiencies, AZB has proven therapeutic benefits in the treatment of upper respiratory tract infections. We therefore conducted an open-label, multicentre study to evaluate the safety and efficacy of AZB in addition to a complex therapy in patients hospitalized with COVID-19.

Materials and methods

Study design

This was an open-label, multicentre study in patients hospitalized due to COVID-19 conducted between March and July 2020 (ClinicalTrials.gov Identifier: NCT04542226, registered 12 March 2020). The study was exploratory in nature and therefore did not include a placebo group. Eight sites in the Russian Federation and one site in the Republic of Belarus took part. The study was conducted in compliance with the International Council for Harmonisation harmonized tripartite guideline regarding Good Clinical Practice and the principles enshrined in the Declaration of Helsinki, the Medicines for Human Use (Clinical Trials) Regulations 2004, as well as the standards set out by the Research Governance Framework and all local laws and regulations. The study was approved by two Independent Ethical Committees (Ethics Committee LLC ‘PHARMNADZOR’: REC Number 229, 09 April 2020; Local Ethical Committee of the Grodno Regional Infectious Disease Clinical Hospital, 14 April 2020 [patients enrolled in the Republic of Belarus were treated at the Grodno Regional Infectious Disease Clinical Hospital]).

After a screening period (day –1 to day 1), eligible patients were administered AZB for 17 days (day 1 to day 17). Patients were monitored during a planned follow-up period between day 18 and day 29±3; in some patients, the final follow-up visit was performed up to day 73.

Inclusion/exclusion criteria

Adults aged ≥ 18 years hospitalized due to COVID-19 symptoms with a laboratory-confirmed SARS-CoV-2 infection were enrolled after providing informed consent. Infection was confirmed by a polymerase chain reaction from any specimen collected before study enrolment. Patients who were pregnant or breastfeeding, had a history of increased sensitivity to any component of the study treatment, had an acute or chronic renal failure or exhibited pathological conditions judged to make study participation impossible were excluded.

Study procedures

Demographic data and detailed medical history were collected after obtaining informed consent. Eligible patients received AZB 12 mg (lyophilizate for solution for injections and topical application reconstituted in sterile saline) intravenously once daily on day 1 to day 3 then intramuscularly every other day from day 5 to day 17 (maximum 10 injections). Patients also received standard of care (SOC) treatment for COVID-19 in accordance with existing Russian clinical recommendations; this included the use of certain antibiotics, antivirals, anticoagulants, hydroxychloroquine and other drugs, as appropriate.^{28,29}

Requirement for oxygen therapy, high flow oxygen devices, non-invasive ventilation, mechanical ventilation (via an endotracheal tube or tracheostomy tube) or extracorporeal membrane oxygenation was assessed daily. Other daily assessments included clinical status as determined by a seven-point World Health Organization-recommended Ordinal Scale (OS) (Table 1) and disease severity according to the seven-

parameter National Early Warning Score (NEWS; comprising respiration rate, oxygen saturation (SpO₂), supplemental oxygen, temperature, systolic blood pressure, heart rate and level of consciousness); NEWS parameters were also measured individually as absolute values.³⁰

Other assessments included safety laboratory tests (including C-reactive protein (CRP)), physical examination, clinical signs and symptoms, electrocardiogram, evaluation of chest X-ray/computed tomography scans, nasopharyngeal and/or oropharyngeal smear assessment for polymerase chain reaction, and bacteriological sputum culture. Adverse events (AEs) and serious adverse events (SAEs) were graded according to The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1. Patients were monitored after hospital discharge until completion of an End-of-Study assessment (at least until day 29). Protocol deviations were recorded and classified as either significant or non-significant.

Outcome measures

The protocol-defined primary endpoint was patient clinical status (according to OS) at day 15 compared with baseline. Exploratory analyses included clinical severity as determined by the seven-point OS and NEWS values, hospitalization duration, signs of pneumonia, body temperature and SpO₂. Pneumonia presence was determined according to the criteria outlined in Supplementary File 1 (available at: <https://www.drugsincontext.com/wp-content/uploads/2022/02/dic.2022-1-1-Suppl.pdf>). Patients were assigned COVID-19 severity groups based on their baseline NEWS: 'very severe' (NEWS ≥ 9), 'severe or moderate' (NEWS 5–8), or 'mild' (NEWS ≤ 4). The time-to-event analysis threshold was set to NEWS ≤ 2 and to OS ≤ 2 (equating to hospital discharge). For the over-time dynamics analysis, discharged patients were treated as having an OS score of 2 commencing the day of discharge until an OS score was measured at follow-up.

Outcome measures for safety analysis included the cumulative incidence of AEs/SAEs and the assessment of laboratory parameters. Permanent or temporary discontinuation of infusions and/or injections of the study drug was documented.

Statistical analysis

Statistical analyses were performed using SAS[®] version 9.4 (SAS Institute Inc., Cary, NC, USA). Safety analyses were performed on the intent-to-treat (ITT) population, comprising all patients who received at least one dose of investigational product and had at least one valid post-baseline value for primary endpoint evaluation. All other analyses were performed on the per protocol (PP) population.

Safety outcome measures were presented using frequency counts and percentages. Quantitative data were summarized using descriptive statistics (arithmetic mean and standard

Table 1. Seven-point Ordinal Scale Adapted from the World Health Organization Master Protocol. Adapted from ref.⁴⁹

Ordinal score	Event
1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities
3	Hospitalized, not requiring supplemental oxygen
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, on non-invasive ventilation or high flow oxygen devices
6	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
7	Death

deviation). Qualitative data were presented using incidences, percentages or proportions. The significance level was 0.05 with 95% confidence intervals presented in all analyses. Survival analysis for time-to-event data was performed via the use of Kaplan–Meier curves. Student *t*-test's (for dependent or independent samples) and analysis of variance (for repeated measurements) were the standard parametric tests used for the comparison of quantitative data with normal distribution. Non-parametric Mann–Whitney U, Wilcoxon and Friedman tests were used for the comparison of non-normally distributed quantitative data. Normality of distribution was assessed by the Shapiro–Wilk test, and incidences were compared with Pearson's χ^2 test or Fischer's exact test.

Historical control data

To address the absence of a direct control group, trends in a control group of patients with COVID-19 receiving SOC treatment from a previously published randomized, controlled, open-label trial were analyzed.³¹ The study was identified via conduction of a structured literature search via PubMed and was selected due to the alignment of several outcome measures used in the present study; the search aimed to find clinical trials conducted in patients with COVID-19 with a control arm comprising SOC treatment only (data not published). Standard care included treatment with supplemental oxygen, non-invasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy and extracorporeal membrane oxygenation as necessary. The trial was conducted at a single centre in China between January and February 2020 and recruited 199 patients hospitalized with a confirmed SARS-CoV-2 diagnosis. Patients received lopinavir-ritonavir (400 mg and 100 mg, respectively) twice daily plus SOC for 14 days or SOC alone. The primary endpoint was time to clinical improvement as determined by the same seven-point OS used in the present study. Differences in basic baseline demographics (age, sex, baseline OS score), OS score at the end of study duration, duration of hospitalization and day 28 mortality between the two patient groups (AZB or control) were assessed.

Results

Study population, baseline characteristics and hospitalization

Eighty-one patients were eligible for study inclusion and comprised the ITT population. Eighty patients completed the study. Four patients with very mild COVID-19 symptoms were incorrectly hospitalized and were excluded from the ITT population; they did not require hospital treatment (antibiotics, oxygen support, etc.), had low baseline OS and NEWS values, and recovered by themselves without medical intervention. Seventy-seven patients therefore comprised the PP population. With the exception of safety analyses, all results are presented for the PP population.

Median age was 53.0 years (range 22–81 years) and 54.5% of patients were men (Table 2). COVID-19 severity was assessed as 'very severe' in 30 patients (39.0%), 'severe or moderate' in 28 patients (36.4%) and 'mild' in 19 patients (24.7%). Mean (SD) baseline OS and NEWS values were 4.36 (1.00) and 6.86 (3.14), respectively. Seventy-four (96.1%) patients displayed signs of pneumonia at baseline and 59 (76.6%) patients required respiratory support; 24 (31.2%) patients required oxygen via a mask, 24 (31.2%) patients required non-invasive ventilation or high-flow oxygen devices, and 11 (14.3%) patients required mechanical ventilation. Mean (SD) duration of hospitalization was 19.32 days (5.33; range 10–38 days). Comorbidities were recorded in 58 (75.3%) patients, with diabetes and/or metabolic syndrome ($n=25$) and arterial hypertension ($n=23$) the most frequently reported.

Clinical response including Ordinal Scale and National Early Warning Score values

Mean (SD) OS scores were relatively stable and close to baseline (4.36 (1.00)) during the first 7 days of AZB treatment (Figure 1). Mean (SD) OS score improved to 2.90 (0.95) by day 15 and the number of subjects requiring respiratory support (OS 4–6) was markedly lower on day 15 ($n=14$, 18.2%) compared with baseline ($n=59$, 76.6%). Notable improvements in mean (SD) OS score were observed from day 9 (4.08 (1.10)) until the end of the treatment period on day 17 (2.36 (0.71)); this trend continued until the End-of-Study visit (1.12 (0.71)). This improvement was most prominent in patients with 'very severe' or 'severe-to-moderate' COVID-19 at baseline (Figure 1B); by day 17, the majority of patients (93.5%; $n=72$) had an OS score of 2 or 3. Mean (SD) time to an OS score improving to ≤ 2 was 15.9 (3.72) days. Improvements in observed OS scores were similar between patients <65 years and patients ≥ 65 years of age (Figure 1C).

Improvements in mean NEWS were also observed over time (Figure 2) and were more notable than the improvements in mean OS scores. The most prominent improvement was also observed in the patients with 'very severe' or 'severe-to-moderate' COVID-19 at baseline (Figure 2B). Patients with 'mild' COVID-19 at baseline reached NEWS ≤ 2 (hospital discharge) quicker than patients with more severe disease (Figure 2E); however, all patient groups reached similar scores by day 17 (Figure 2B). Mean (SD) NEWS improved from 6.86 (3.14) at baseline to 1.08 (1.18) by the End-of-Study visit with an improvement probability of $>80\%$ after 15 days of treatment in all patients. Similar improvements in NEWS were observed between patients <65 years and patients ≥ 65 years of age (Figure 2C) and time to discharge was similar between the two groups (Figure 2F).

Individual patient data showing the evolution of OS and NEWS values over time in the ITT population are shown in Supplementary Files 2 and 3, respectively.

Table 2. Demographic and baseline characteristics (intent to treat (ITT) and per protocol (PP) populations).

	ITT population n=81	PP population n=77
Age, years		
Mean	50.88	52.32
SD	12.81	11.37
Median	53.0	53.0
Min, Max	18.0, 81.0	22.0, 81.0
Age categories, n (%)		
<65 years	71 (87.7)	67 (87.0)
≥65 years	10 (12.3)	10 (13.0)
<60 years	57 (70.4)	53 (68.8)
≥60 years	24 (29.6)	24 (31.2)
Sex, n (%)		
Men	44 (54.3)	42 (54.5)
Women	37 (45.7)	35 (45.5)
Ordinal Scale score, n		
Mean	4.30	4.36
SD	1.02	1.00
NEWS, n		
Mean	6.51 ^a	6.86 ^b
SD	3.41 ^a	3.14 ^b
Severity according to NEWS, n (%)		
Very severe (NEWS ≥9)	30 (37.0)	30 (39.0)
Severe or moderate (NEWS 5–8)	28 (34.6)	28 (36.4)
Mild (NEWS ≤4)	23 (28.4)	19 (24.7)
Signs of pneumonia, n (%)		
Yes	77 (95.1)	74 (96.1)
No	4 (4.9)	3 (3.9)
Oxygen saturation (SpO₂), %		
Mean	92.71 ^c	92.39 ^d
SD	3.53 ^c	3.32 ^d
Respiratory support requirement, n (%)		
Present	59 (72.8)	59 (76.6)
Absent	22 (27.2)	18 (23.4)
Respiratory support type, n (%)		
Invasive lung ventilation	11 (13.6)	11 (14.3)

	ITT population n=81	PP population n=77
Non-invasive lung ventilation or high-flow oxygen devices	24 (29.6)	24 (31.2)
Oxygen therapy	24 (29.6)	24 (31.2)
None	22 (27.2)	18 (23.4)
Time from disease onset to treatment initiation, days		
Mean	6.79 ^e	7.05 ^f
SD	5.16 ^e	5.17 ^f
Duration of hospitalization, days		
Mean	19.13 ^g	19.32 ^h
SD	5.29 ^g	5.33 ^h
Min, Max	10.0, 38.0 ^g	10.0, 38.0 ^h
Concomitant medication by type, n (%)		
Antivirals	46 (56.8)	42 (54.5)
Hydroxychloroquine	37 (45.7)	37 (48.1)
Anticoagulants	41 (50.6)	41 (53.2)
Body temperature, °C		
Mean	38.09	38.14
SD	1.07	1.07
Cough severity, n (%)		
No cough	8 (9.9)	7 (9.1)
Weak	48 (59.3)	45 (58.4)
Strong	25 (30.9)	25 (32.5)
C-reactive protein, mg/L		
Mean	43.21 ⁱ	45.25 ^j
SD	53.03 ⁱ	53.67 ^j

^aNumber of cases/number of missing cases: 80/1.

^bNumber of cases/number of missing cases: 76/1.

^cNumber of cases/number of missing cases: 79/2.

^dNumber of cases/number of missing cases: 75/2.

^eNumber of cases/number of missing cases: 78/3.

^fNumber of cases/number of missing cases: 74/3.

^gNumber of cases/number of missing cases: 80/1.

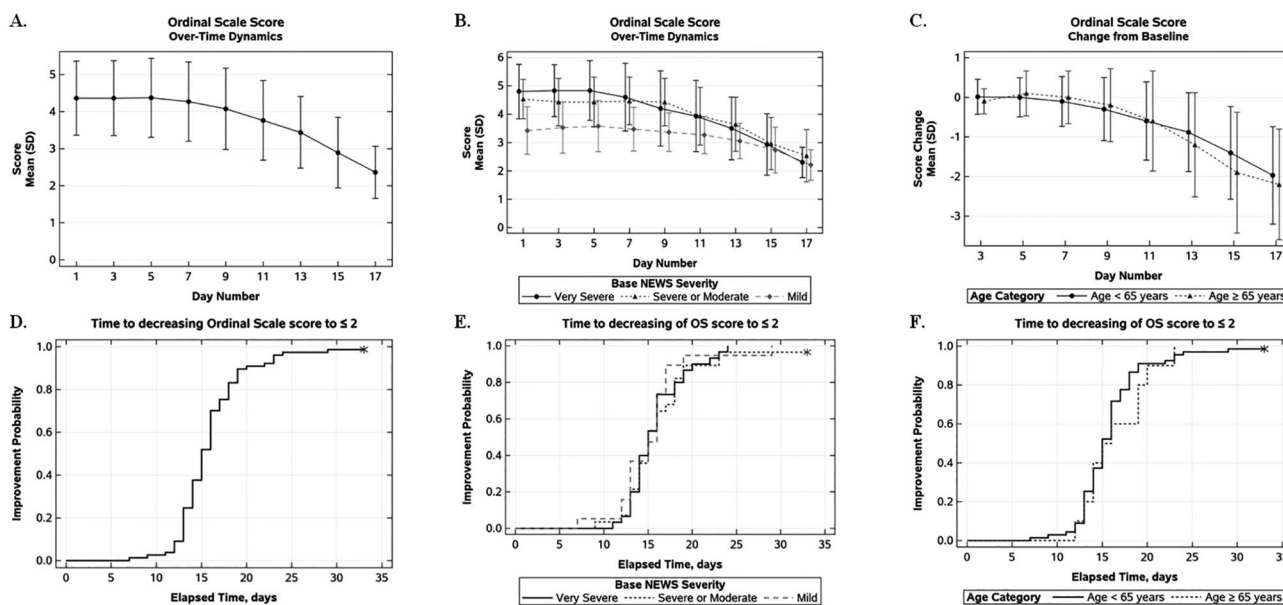
^hNumber of cases/number of missing cases: 76/1.

ⁱNumber of cases/number of missing cases: 79/2.

^jNumber of cases/number of missing cases: 75/2.

NEWS, National Early Warning Score; SD, standard deviation.

Figure 1. Evolution of ordinal scale score and time-to-event analysis during the treatment and follow-up phases.



Data are presented overall and stratified by baseline NEWS and age category (per protocol population [$n=77$]). **A.** Mean Ordinal Scale scores during treatment phase. **B.** Mean Ordinal Scale scores during treatment phase stratified by baseline NEWS severity: 'very severe' (score ≥ 9), $n=30$; 'severe or moderate' (score 5–8), $n=28$, 'mild' (score ≤ 4), $n=19$. **C.** Mean Ordinal Scale scores during treatment phase stratified by patient age: <65 years ($n=67$), ≥ 65 years ($n=10$). **D.** Improvement probability curve plotted for time to decreasing Ordinal Scale score to ≤ 2 . **E.** Improvement probability curve plotted for time to decreasing Ordinal Scale score to ≤ 2 stratified by baseline NEWS severity: 'very severe' (score ≥ 9), $n=30$; 'severe or moderate' (score 5–8), $n=28$; 'mild' (score ≤ 4), $n=19$. **F.** Improvement probability curve plotted for time to decreasing Ordinal Scale score to ≤ 2 stratified by patient age: <65 years ($n=67$), ≥ 65 years ($n=10$). NEWS, National Early Warning Score; SD, standard deviation. Note: Crosses on the graphs denote censored observations where further data from the patients were not available.

Indicators of pneumonia and lung function

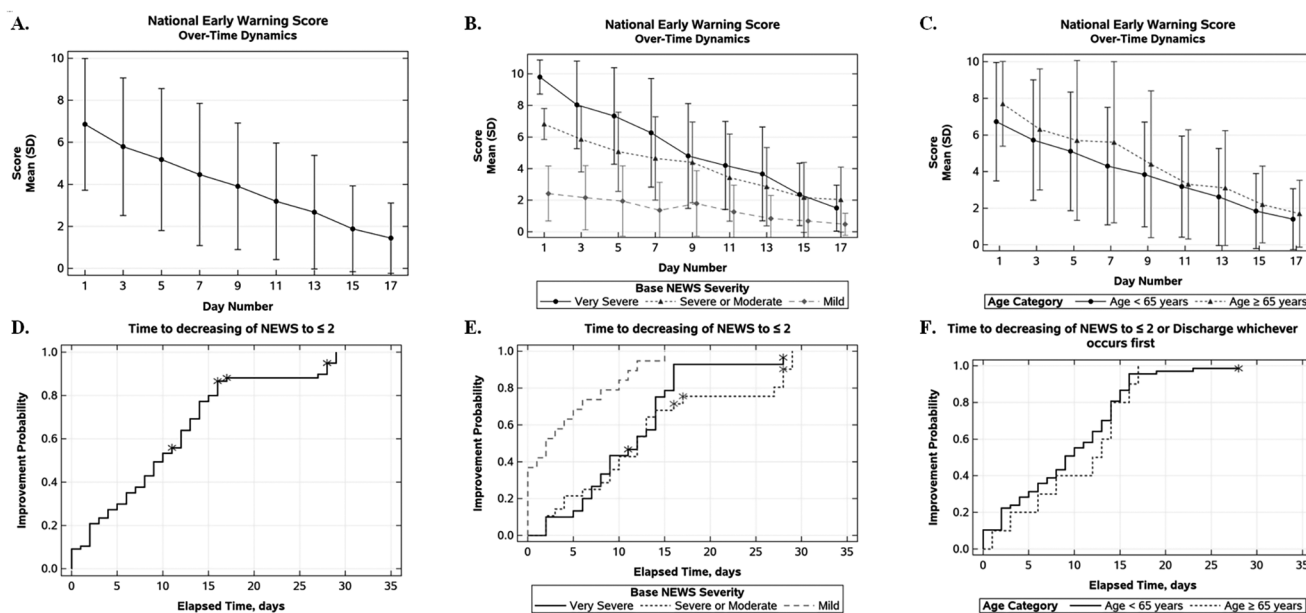
Mean SpO₂ at baseline was 92.4% and steadily improved over the treatment period (Figure 3). This improvement was most prominent in patients with 'very severe' or 'severe-to-moderate' COVID-19 at baseline (Figure 3B) with similar SpO₂ values observed in these two groups from day 3 to day 17. One patient had a slightly low SpO₂ value of 94% at study completion (day 29 \pm 3); values for all other patients were normal (reference range 95–99%). Respiratory support requirement (OS 4–6) improved substantially from 59 (76.6%) patients at baseline to 14 (18.2%) patients at day 15; no patients required respiratory support by their End-of-Study assessment. Mean (SD) SpO₂ was lower in patients ≥ 65 years of age at baseline (90.0% (4.27)) than patients <65 years of age (92.7% (3.07); Figure 3C); however, SpO₂ reached similar levels in both groups by day 17 (≥ 65 years: 96.90% (1.66); <65 years: 96.98% (1.47)).

Signs of pneumonia gradually reduced from 74 (96.1%) patients at baseline to 18 (23.4%) patients by the End-of-Study assessment. Mean (SD) time to vanishing signs of pneumonia

was 18.45 (9.65) days, with standard improvement probability curves shown in Figure 4. The highest recovery probability was in patients with 'mild' COVID-19 at baseline (Figure 4B), suggesting a more rapid recovery. The lowest recovery probability was in the 'severe or moderate' group. Patients <65 years and ≥ 65 years of age had a similar recovery probability (Figure 4C). Patients <65 years of age requiring respiratory support (OS 4–6) decreased from 49 (73.1%) patients at baseline to 3 (4.5%) patients by the end of the AZB treatment period; in patients ≥ 65 years of age, this decreased from 10 (100.0%) patients to 1 (10.0%) patient.

Most patients had elevated body temperatures ($>37^{\circ}\text{C}$) at baseline (Figure 5). This normalized ($\leq 37^{\circ}\text{C}$) in all patients by day 11, and no notable differences were observed when stratified by baseline NEWS severity score (Figure 5B). The probability of achieving a normal body temperature after 10 days of treatment was 90% (Figure 5C).

Mean (SD) CRP decreased steadily from 45.25 mg/L (53.67) at baseline to 13.21 mg/L (19.56) by day 17 (Figure 6).

Figure 2. Evolution of National Early Warning Score values and time-to-event analysis during the treatment and follow-up phases.

Data are presented overall and stratified by baseline NEWS and age category (per protocol population [$n=77$]). **A.** Mean NEWS during treatment phase. **B.** Mean NEWS during treatment phase stratified by baseline NEWS severity: 'very severe' (score ≥ 9), $n=30$; 'severe or moderate' (score 5–8), $n=28$; 'mild' (score ≤ 4), $n=19$. **C.** Mean NEWS during treatment phase stratified by patient age: <65 years ($n=67$), ≥ 65 years ($n=10$). **D.** Improvement probability curve plotted for time to decreasing NEWS to ≤ 2 . **E.** Improvement probability curve plotted for time to decreasing NEWS to ≤ 2 stratified by baseline NEWS severity: 'very severe' (score ≥ 9), $n=30$; 'severe or moderate' (score 5–8), $n=28$; 'mild' (score ≤ 4), $n=19$. **F.** Improvement probability curve plotted for time to decreasing NEWS to ≤ 2 stratified by patient age: <65 years ($n=67$), ≥ 65 years ($n=10$). NEWS, National Early Warning Score; SD, standard deviation. Note: Crosses on the graphs denote censored observations where further data from the patients were not available.

Concomitant medications

Changes in NEWS and OS scores, SpO₂ and body temperature were stratified by antiviral, anticoagulant and hydroxychloroquine usage (Table 2). Baseline mean (SD) NEWS appeared notably worse in patients who were receiving antivirals (8.17 (2.21); 42 patients) than those not receiving antivirals (5.31 (3.38); 35 patients). Similarly, baseline mean (SD) NEWS was worse in patients receiving hydroxychloroquine (5.75 (3.30); 37 patients) than those not receiving hydroxychloroquine (7.85 (2.65); 40 patients). Time-to-event analysis showed that mean (SD) time to NEWS improving to ≤ 2 was faster in patients receiving hydroxychloroquine (7.30 (5.78) days) than those not receiving hydroxychloroquine (13.47 (8.81) days). The opposite trend was noted in patients receiving antivirals (13.40 (8.51) days) than those not receiving antivirals (7.03 (5.99) days).

Safety assessments and compliance

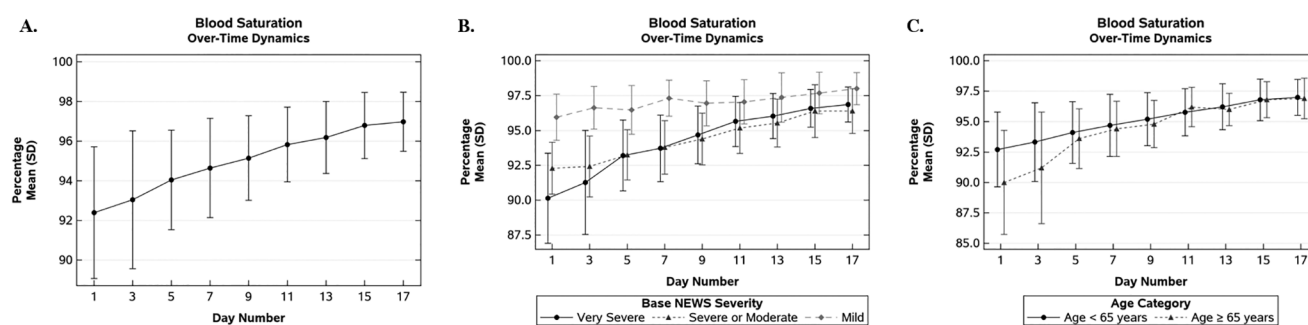
In the ITT population ($n=81$), six (7.4%) patients each experienced one AE of PQ interval prolongation (two events), fever (two events), intermittent fever and bacterial pneumonia. All AEs resolved and none were considered related to AZB

administration. One patient who experienced the event of bacterial pneumonia discontinued from the study after two doses of AZB and required further medication; all other patients completed the study. No deaths were recorded during the study period. One patient experienced an SAE of *Klebsiella* sepsis (determined to not be related to AZB) and died after study completion (day 34), 17 days after the last AZB injection, due to associated complications, including respiratory distress, disease progression, secondary bacterial infection, sepsis and multiple organ failure. The patient was 30 years old with a body mass index of 46.3 and had a history of hospital admissions due to bacterial pneumonia in the previous 3 years.

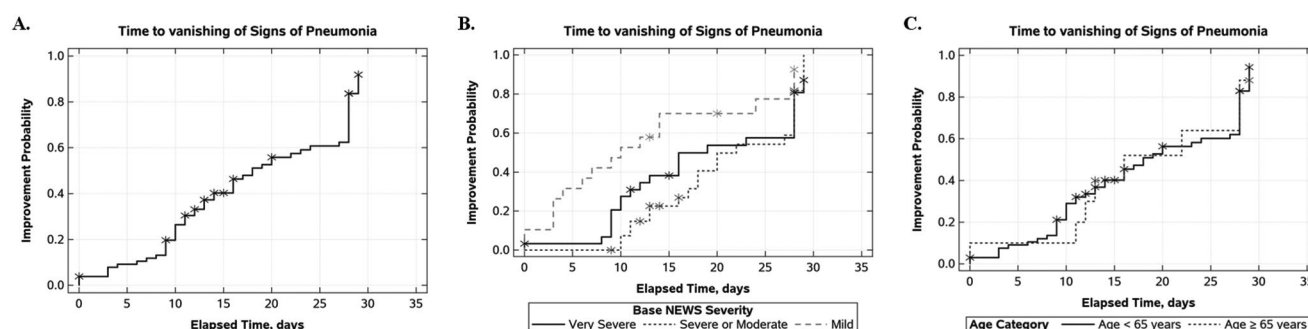
Thirty-six (44.4%) patients received the complete treatment course of AZB comprising 10 injections, 24 (29.6%) patients received 9 injections, 17 (21.0%) patients received 8 injections, 2 (2.5%) patients received 7 injections and 1 (1.2%) patient each received 6 or 2 injections.

Historical control data

The historical control group ($n=100$) from the study conducted by Cao et al. had comparable baseline demographics to

Figure 3. Oxygen saturation over time during the treatment phase.

Data are presented overall and stratified by baseline NEWS and age category (per protocol population [$n=77$]). **A.** Mean blood saturation over time during treatment phase. **B.** Mean blood saturation over time during treatment phase stratified by baseline NEWS severity: ‘very severe’ (score ≥ 9), $n=30$; ‘severe or moderate’ (score 5–8), $n=28$; ‘mild’ (score ≤ 4), $n=19$. **C.** Mean blood saturation over time during treatment phase stratified by patient age: <65 years ($n=67$), ≥ 65 years ($n=10$). NEWS, National Early Warning Score; SD, standard deviation.

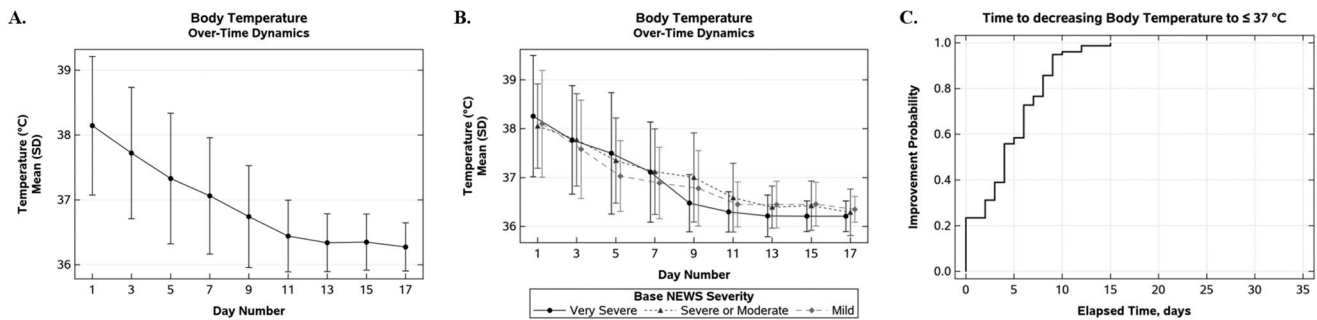
Figure 4. Improvement probability curves plotted for time to vanishing signs of pneumonia.

Data are presented overall and stratified by baseline NEWS severity and age category (per protocol population [$n=77$]). **A.** Improvement probability curve plotted for time to vanishing signs of pneumonia. **B.** Improvement probability curve plotted for time to vanishing signs of pneumonia stratified by baseline NEWS severity: ‘very severe’ (score ≥ 9), $n=30$; ‘severe or moderate’ (score 5–8), $n=28$; ‘mild’ (score ≤ 4), $n=19$. **C.** Improvement probability curve plotted for time to vanishing signs of pneumonia stratified by baseline age category: ‘ <65 years’, $n=67$; ‘ ≥ 65 years’, $n=10$. NEWS, National Early Warning Score; SD, standard deviation. Note: Crosses on the graphs denote censored observations where further data from the patients were not available.

the patients receiving AZB (Table 3): median age was 58.0 years (range 48.0–68.0 years) with a similarly slightly higher proportion of men (59.0%; $n=59$) to women (41.0%; $n=41$).³¹ Pre-existing conditions included diabetes (13.0; $n=13$), cerebrovascular disease (8.0%; $n=8$) and cancer (1.0%; $n=1$). All historical control subjects had $SpO_2 \leq 94\%$ at baseline compared with 59 (76.6%) patients in the AZB-treated patients. Mean baseline OS score was slightly lower in the control group (3.99) compared with the AZB group (4.36). Baseline OS scores ranged from 3 to 5 and the majority of patients (67.0%; $n=67$) had a score of 4; of patients who received AZB, the majority had a score of 3 (23.4%; $n=18$), 4 (31.2%; $n=24$) or 5 (31.2%; $n=24$), whereas 14.3% ($n=11$) of patients had a score of 6 (Figure 7). A

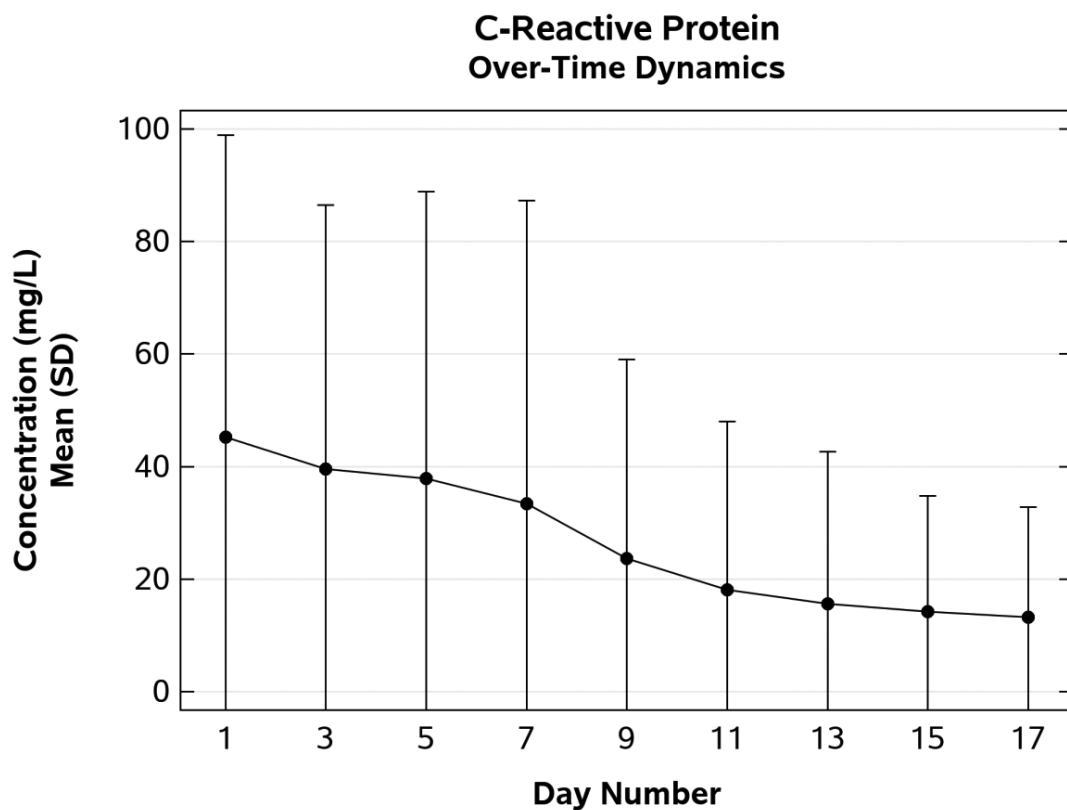
higher proportion of patients receiving AZB therefore required invasive or non-invasive ventilation (OS 5 or 6) compared with the control group. Change in mean OS score from baseline to day 14/15 was not notable in the control group (3.99–3.87) but was more pronounced in the AZB group (4.36–2.90). By day 14 in the control group, most patients had an OS score of 2 (28.0%; $n=28$), 3 (24.0%; $n=24$) or 4 (20.0%; $n=20$) (Figure 7). Six (6.0%) and 5 (5.0%) patients had an OS score of 5 and 6, respectively, while 17 (17.0%) patients had died. By day 15 in the AZB group, the majority of patients had an OS score of 2 (35.1%; $n=27$) or 3 (45.5%; $n=35$). Three (3.9%) and 2 (2.6%) patients had an OS score of 5 and 6, respectively, 1 (1.3%) patient had an OS score of 1 and no patients had died. By day 28, 25 (25.0%) patients in

Figure 5. Evolution of body temperature over time and time-to-event analysis during the treatment and follow-up phases.



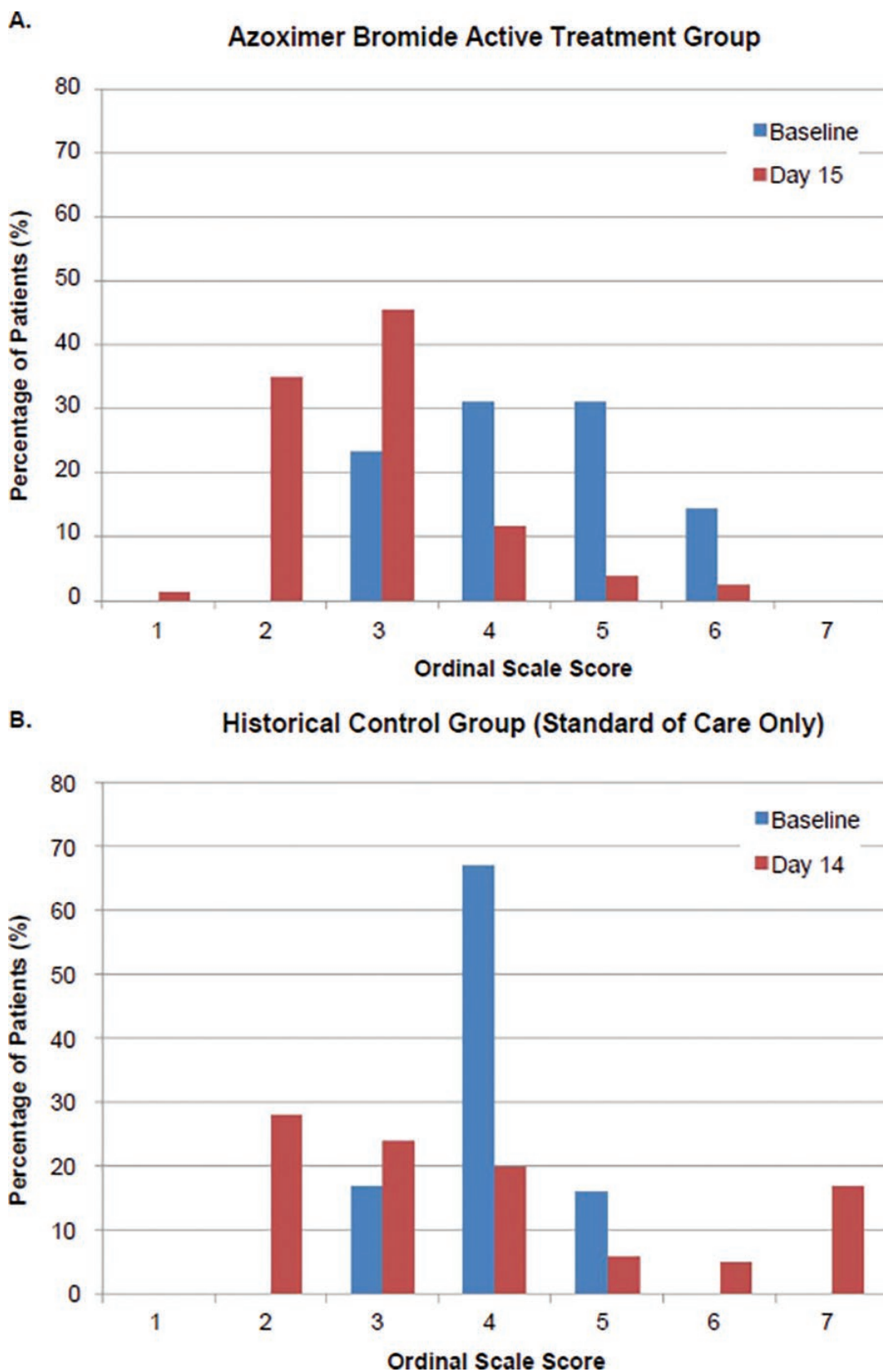
Data are presented overall and stratified by baseline NEWS severity (per protocol population [$n=77$]). **A.** Mean body temperature over time during treatment phase. **B.** Mean body temperature over time during treatment phase stratified by baseline NEWS severity: 'very severe' (score ≥ 9), $n=30$; 'severe or moderate' (score 5–8), $n=28$; 'mild' (score ≤ 4), $n=19$. **C.** Improvement probability curve plotted for time to decreasing body temperature to $\leq 37^\circ\text{C}$. NEWS, National Early Warning Score; SD, standard deviation.

Figure 6. C-reactive protein values over time during the treatment phase.



Data are presented for the per protocol population ($n=77$).

Figure 7. Ordinal Scale scores in the active treatment and historical control groups (baseline and day 14/15).



A. Ordinal Scale scores at Baseline and day 15 in patients who received azoximer bromide treatment.
B. Ordinal Scale scores at Baseline and day 14 in patients in the historical control group who received standard of care only

Table 3. Comparison of demographic, baseline and efficacy endpoints with historical control group (per protocol population).

	AZB (active treatment) n=77	Standard of care (historical control^a) n=100
Age, years		
Median	53.0	58.0
Min, Max	22.0, 81.0	48.0, 68.0
Sex, n (%)		
Men	42 (54.5)	59 (59.0)
Women	35 (45.5)	41 (41.0)
Baseline Ordinal Scale score, n		
Mean	4.36	3.99
Baseline Ordinal Scale score, n (%)		
1. Not hospitalized, no limitations on activities	0 (0.0)	0 (0.0)
2. Not hospitalized, limitation on activities	0 (0.0)	0 (0.0)
3. Hospitalized, not requiring supplemental oxygen	18 (23.4)	17 (17.0)
4. Hospitalized, requiring supplemental oxygen	24 (31.2)	67 (67.0)
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices	24 (31.2)	16 (16.0)
6. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation	11 (14.3)	0 (0.0)
7. Death	0 (0.0)	0 (0.0)
Day 14 or day 15^b Ordinal Scale score, n		
Mean	2.90	3.87
Day 14 or day 15^b Ordinal Scale score, n (%)		
1. Not hospitalized, no limitations on activities	1 (1.3)	0 (0.0)
2. Not hospitalized, limitation on activities	27 (35.1)	28 (28.0)
3. Hospitalized, not requiring supplemental oxygen	35 (45.5)	24 (24.0)
4. Hospitalized, requiring supplemental oxygen	9 (11.7)	20 (20.0)
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices	3 (3.9)	6 (6.0)
6. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation	2 (2.6)	5 (5.0)
7. Death	0 (0.0)	17 (17.0)
Day 28 mortality, n (%)		
Alive	77 (100.0)	75 (75.0)
Dead	0 (0.0)	25 (25.0)
Duration of hospitalization, days		
Median	19.32 ^c	16.0
Min, Max	10.0, 38.0 ^c	13.0, 18.0

^aHistorical control data were obtained from Cao et al.³¹

^bRecorded on day 14 for patients receiving standard of care (historical control) and day 15 for patients receiving AZB (active treatment).

^cNumber of cases/number of missing cases: 76/1.

AZB, azoximer bromide.

the control group had died compared with no patients in the AZB group. Median duration of hospitalization in the control and AZB groups were similar at 16.0 days (range 13.0–18.0) and 19.3 days (range 10.0–38.0), respectively.

Discussion

COVID-19 has rapidly spread across the globe since December 2019, leading to >225 million confirmed cases and almost 4.7 million fatalities as of 19 September 2021.³² Although the disease is not as lethal (case fatality ratio (CFR) ~0.3–1%)^{33,34} as MERS (CFR ~35%)³⁵ and SARS (CFR 14–15%),³⁶ it has become clear that morbidity and mortality are much higher than in pandemic influenza (CFR 0.1%),^{37,38} especially amongst the elderly (3%).^{34,39} In addition, the viruses' characteristics are changing with the emergence of new variants and the clinical course appears to depend on a person's age, vaccination status and certain medial conditions.⁴⁰

The results from this open-label, multicentre study in patients hospitalized with COVID-19 demonstrate that administration of AZB over a 17-day treatment period was associated with an improvement in clinical status as assessed by OS and NEWS values. The main indicators of pneumonia and lung function (SpO₂, signs of pneumonia, body temperature, CRP) showed gradual recovery and normalization; the lack of CRP increase indicates the lack of cytokine storm risk in patients treated with AZB.⁴¹ Clinical improvements observed in older patients (≥65 years of age) were similar to those observed in younger patients (<65 years), with similar values obtained by the end of treatment. Azoximer bromide was generally safe and well tolerated with no AEs considered to be related to study treatment.

No deaths occurred during the study period; however, one patient died from complications related to an SAE of *Klebsiella* sepsis after study completion. Results from a retrospective Russian study of 1522 patients with SARS-CoV-2 infection between March and May 2020 identified mortality rates of 36.8% and 76.5% for patients who required non-invasive or invasive ventilation, respectively.⁴² It may therefore have been likely to expect higher mortality in our patient population given that 22.2% and 21.0% of patients required non-invasive and invasive ventilation, respectively. This finding is even more apparent when considering the relatively high incidence of patients exhibiting comorbidities and the number of older patients (≥65 years); comorbidities and age are both known risk factors for severe disease progression and mortality.⁴⁰ In a recent study, treatment with the corticosteroid dexamethasone reduced day 28 mortality only in patients requiring mechanical ventilation or oxygen alone, with no significant benefit observed in patients not requiring respiratory support; in patients not receiving respiratory support, day 28 mortality of 17.8% was observed.⁸ In contrast, day 28 mortality was not observed in any subgroup of patients in the present study, suggesting a treatment advantage of AZB over dexamethasone, particularly in patients with non-severe COVID-19. Furthermore, corticosteroid use has been associated

with increased mortality in other respiratory illnesses, such as flu, which could be due to the known association between corticosteroids and immunosuppression.^{43,44} With known immunomodulating properties, AZB could be used in place of, or in conjunction with, corticosteroids in patients requiring mechanical ventilation to balance the deleterious effects on the immune system and improve overall recovery. These observations merit further investigation.

Improvements in both OS and NEWS values from baseline to day 17 were observed; however, there were notable differences in the behaviour of the two parameters. Mean OS values were relatively stable during the first 7 days of treatment followed by a prominent decrease. The decrease in mean NEWS values was more pronounced, with improvements noted several days earlier, suggesting that OS score is less responsive to early changes in clinical improvement. We conclude that NEWS may provide a more sensitive interpretation of patient clinical status and better reflect overall recovery.

The present study was an open-label study, a major limitation of which was the absence of a formal control group. Not all patients in the AZB treatment group received the same dose. Dosing tended to be driven by the attending physician and dependent on the clinical status of the patients. Administration was often halted as patients showed improvements in their status (67%). Historical control data were identified to provide a comparable group of patients who did not receive active treatment. The two groups had comparable demographics, baseline respiratory support requirements and duration of hospitalization; however, the groups were not matched in terms of factors such as age, underlying medical conditions or treatments, which are known to impact the course of the disease. A lower proportion of patients in the historical control group exhibited clinical recovery (according to OS scores), and a higher mortality rate was observed compared with patients treated with AZB. Key differences between the studies were apparent, including participant ethnicity and at what point during the pandemic the studies were conducted. COVID-19 has affected countries at different rates, making it difficult to directly compare data due to inter-country variation in available treatment options and clinical experience. Furthermore, SOC recommendations differed between the two studies (e.g. no anticoagulants or antivirals permitted in the historical control group); however, both permitted the use of various other treatments and types of respiratory support. As such, treatment benefits solely attributable to AZB cannot be established. In addition, a higher proportion of patients in the historical control group had SpO₂ values of ≤94% at baseline, which could suggest that these patients were clinically more severe than patients in the present study; however, without mean values available, this cannot be established. Comparing the data suggests that some clinical benefit may have been achieved in patients administered AZB, whether directly related to the drug or otherwise. To address this, a randomized, double-blind, placebo-controlled clinical trial is currently under way (ClinicalTrials.gov Identifier: NCT04381377).

Based on the previous studies of AZB, we can propose several explanations for the nature of the observed effect in patients with COVID-19. First, AZB can cause indirect antiviral activity by stimulating interferon release, antigen presentation and antibody development.^{45,46} Second, the detoxicant effect of AZB can participate in symptom reduction (e.g. temperature) and increased wellbeing in some patients.⁴⁷ Another possible explanation of the AZB effect is the prevention of cytokine storm, which serves as a predictive marker of poor COVID-19 outcome.

Conclusion

In conclusion, the devastating impacts of the COVID-19 pandemic are far from over and global collaboration to find effective treatments is paramount. At the time of writing this article, global deaths have surpassed 5.0 million, with the Russian Federation ranking fourth for cases and eighth for deaths worldwide.⁴⁸ The recent deployment of approved vaccines in several countries represents a huge milestone; however, continuing research into other treatments is vital. The promising safety and efficacy results presented herein support further assessment of AZB in appropriately controlled

conditions, which could serve as an add-on treatment for patients with COVID-19.

Availability of data and materials

The datasets used during the current study are available from the corresponding author upon reasonable request.

Disclosure

The study was conducted in compliance with the International Council for Harmonisation harmonized tripartite guideline regarding Good Clinical Practice and the principles enshrined in the Declaration of Helsinki, the Medicines for Human Use (Clinical Trials) Regulations 2004, as well as the standards set out by the Research Governance Framework, and all local laws and regulations. The study was approved by two Independent Ethical Committees (Ethics Committee LLC 'PHARMNADZOR': REC Number 229, 09 April 2020; Local Ethical Committee of the Grodno Regional Infectious Disease Clinical Hospital, 14 April 2020). Informed consent was obtained from all individual participants included in the study.

Contributions: All authors contributed to the study concept and design. SVE, NVM, OVB, LYA, EVK, AAT and EIK enrolled the patients and collected the data. NFK wrote the protocol. AAT and FH managed data collection, monitoring and clean-up. AAT, FH and J-FR analysed the data. TCH, AAT, FH and J-FR wrote the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

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References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
2. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. *Clin Immunol*. 2020;215:108427. <https://doi.org/10.1016/j.clim.2020.108427>
3. Abate SM, Ahmed Ali S, Mantfardo B, et al. Rate of Intensive Care Unit admission and outcomes among patients with coronavirus: a systematic review and meta-analysis. *PLoS One*. 2020;15(7):e0235653. <https://doi.org/10.1371/journal.pone.0235653>
4. The official internet resource for informing the population about the coronavirus (COVID-19). <https://стопкоронавирус.рф/> (in Russian). Accessed April 9, 2021.
5. Dyer O. Covid-19: Russia admits to understating deaths by more than two thirds. *BMJ*. 2020;371:m4975. <https://doi.org/10.1136/bmj.m4975>
6. Flanagan KL, Best E, Crawford NW, et al. Progress and pitfalls in the quest for effective SARS-CoV-2 (COVID-19) vaccines. *Front Immunol*. 2020;11:579250. <https://doi.org/10.3389/fimmu.2020.579250>
7. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. *N Engl J Med*. 2020;NEJMoa2007764. <https://doi.org/10.1056/NEJMoa2007764>
8. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021;384:693–704. <https://doi.org/10.1056/nejmoa2021436>
9. RECOVERY Collaborative Group, Horby P, Pessoa-Amorim G, Peto L, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. *medRxiv*. 2021.02.11.21249258. <https://doi.org/10.1101/2021.02.11.21249258>
10. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV, antibody combination and outcomes in outpatients with COVID-19. *N Engl J Med*. 2021;385:e81. <https://doi.org/10.1056/nejmoa2108163>
11. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. *JAMA*. 2021;325:632–644. <https://doi.org/10.1001/jama.2021.0202>
12. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe*. 2020;27(6):992–1000.e3. <https://doi.org/10.1016/j.chom.2020.04.009>
13. Mazzone A, Salvati L, Maggi L, et al. Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent. *J Clin Invest*. 2020;130(9):4694–4703. <https://doi.org/10.1172/jci138554>
14. Rose-John S. IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. *Int J Biol Sci*. 2012;8(9):1237–1247. <https://doi.org/10.7150/ijbs.4989>
15. Park SJ, Nakagawa T, Kitamura H, et al. IL-6 regulates in vivo dendritic cell differentiation through STAT3 activation. *J Immunol*. 2004;173(6):3844–3854. <https://doi.org/10.4049/jimmunol.173.6.3844>
16. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330–1341. <https://doi.org/10.3410/f.738593331.793576979>
17. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. 2020;71:762–768. <https://doi.org/10.1093/cid/ciaa248>
18. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033–1034. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0)
19. Sallard E, Lescure FX, Yazdanpanah Y, et al. Type 1 interferons as a potential treatment against COVID-19. *Antivir Res*. 2020;178:104791. <https://doi.org/10.1016/j.antiviral.2020.104791>
20. Morra ME, Van Thanh L, Kamel MG, et al. Clinical outcomes of current medical approaches for Middle East respiratory syndrome: a systematic review and meta-analysis. *Rev Med Virol*. 2018;28(3),e1977. <https://doi.org/10.1002/rmv.1977>
21. Cinatl J, Morgenstern B, Bauer G, et al. Treatment of SARS with human interferons. *Lancet*. 2003;362(9380):293–294. [https://doi.org/10.1016/S0140-6736\(03\)13973-6](https://doi.org/10.1016/S0140-6736(03)13973-6)
22. Grivtsova LY, Falaleeva NA, Tupitsayn NN. Azoximer bromide: mystery, serendipity, and promise. *Front Oncol*. 2021;11:699546. <https://doi.org/10.3389/fonc.2021.699546>
23. Pružinec P, Chirun N, Sveikata A. The safety profile of polyoxidonium in daily practice: results from postauthorization safety study in Slovakia. *Immunotherapy*. 2018;10(2):131–137. <https://doi.org/10.2217/imt-2017-0116>
24. Alexia C, Cren M, Louis-Plence P, et al. Polyoxidonium® activates cytotoxic lymphocyte responses through dendritic cell maturation: clinical effects in breast cancer. *Front Immunol*. 2019;10:2693. <https://doi.org/10.3389/fimmu.2019.02693>
25. Dyakonova VA, Dambaeva SV, Pinegin BV, et al. Study of interaction between the polyoxidonium immunomodulator and the human immune system cells. *Intern Immunopharmacol*. 2004;4:1615–1623. <https://doi.org/10.1016/j.intimp.2004.07.015>

26. Janssen-Heininger YM, Poynter ME, Baeuerle PA. Recent advances towards understanding redox mechanisms in the activation of nuclear factor kappaB. *Free Radic Biol Med.* 2000;28(9):1317–1327. [https://doi.org/10.1016/s0891-5849\(00\)00218-5](https://doi.org/10.1016/s0891-5849(00)00218-5)
27. Santoro MG, Rossi A, Amici C. NF-kappaB and virus infection: who controls whom. *EMBO J.* 2003;22(11):2552–2560. <https://doi.org/10.1093/emboj/cdg267>
28. Petrovax. Medical application instruction for POLYOXIDONIUM® <http://petrovax.com/upload/produkty/PIL%20with%20Mod%20%E2%84%96%E2%84%961-2%20PO-inj%20P%20N002935.02.pdf>. Accessed September 30, 2020.
29. Ministry of Health of Russian Federation. Interim methodological recommendations: prevention, diagnosis and treatment of new coronavirus infection (COVID-19), 2021. <https://bit.ly/3mA8f6p>. Accessed September 30, 2020.
30. Royal College of Physicians. National Early Warning Score (NEWS): Standardising the assessment of acute-illness severity in the NHS, 2012. <https://www.rcplondon.ac.uk/file/32/download?token=5NwjEyTq>. Accessed September 30, 2020.
31. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med.* 2020;382(19):1787–1799. <https://doi.org/10.1056/NEJMoa2001282>
32. Johns Hopkins Coronavirus Resource Center. COVID-19 dashboard. <https://coronavirus.jhu.edu/map.html>. Accessed September 22, 2021.
33. Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic population. *N Engl J Med* 2020;382:2302–2315. <https://doi.org/10.1056/NEJMoa2006100>
34. Petersen E, Koopmans M, Go U, et al. Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. *Lancet Infect Dis.* 2020;20:e238–e244. [https://doi.org/10.1016/S1473-3099\(20\)30484-9](https://doi.org/10.1016/S1473-3099(20)30484-9)
35. World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV): key facts. [https://www.who.int/en/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-\(mers-cov\)](https://www.who.int/en/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov)). Accessed September 22, 2021.
36. World Health Organization. Consensus document on the epidemiology of severe acute respiratory syndrome (SARS), 2003. https://apps.who.int/iris/bitstream/handle/10665/70863/WHO_CDS_CSR_GAR_2003.11_eng.pdf. Accessed September 3, 2020.
37. Ruan S. Likelihood of survival of coronavirus disease 2019. *Lancet Infect Dis.* 2020;20:630–631. [https://doi.org/10.1016/s1473-3099\(20\)30257-7](https://doi.org/10.1016/s1473-3099(20)30257-7)
38. Piroth L, Cottenet J, Mariet AS, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. *Lancet Respir Med.* 2021;9:251–259. [https://doi.org/10.1016/S2213-2600\(20\)30527-0](https://doi.org/10.1016/S2213-2600(20)30527-0)
39. Centers for Disease Control and Prevention. Risk for COVID-19 infection, hospitalization, and death by age group. <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html>. Accessed January 10, 2022.
40. Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its impact on patients with COVID-19. *SN Compr Clin Med.* 2020;2:1069–1076. <https://doi.org/10.1007/s42399-020-00363-4>
41. Rossi JF, Lu ZY, Massart C, et al. Dynamic immune/inflammation precision medicine: The good and the bad inflammation in infection and cancer. *Front Immunol.* 2021;12:595722. <https://doi.org/10.3389/fimmu.2021.595722>
42. Glybochko P, Fomin V, Moiseev S, et al. Clinical outcomes of patients with COVID-19 admitted for respiratory support to the intensive care units in Russia. *Klinicheskaya farmakologiya i terapiya.* 2020;29(3):25–36. <https://doi.org/10.32756/0869-5490-2020-3-25-36>
43. Zhou Y, Fu X, Liu X, et al. Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis. *Sci Rep.* 2020;10(1):3044. <https://doi.org/10.1038/s41598-020-59732-7>
44. Youssef J, Novosad SA, Winthrop KL. Infection risk and safety of corticosteroid use. *Rheum Dis Clin North Am.* 2016;42(1):157-x. <https://doi.org/10.1016/j.rdc.2015.08.004>
45. Talayev V, Zaichenko I, Svetlova M, et al. Low-dose influenza vaccine Grippol Quadrivalent with adjuvant Polyoxidonium induces a T helper-2 mediated humoral immune response and increases NK cell activity. *Vaccine.* 2020;38(42):6645–6655. <https://doi.org/10.1016/j.vaccine.2020.07.053>
46. Dyakonova VA, Dambaeva SV, Pinegin BV, et al. Study of interaction between the polyoxidonium immunomodulator and the human immune system cells. *Int Immunopharmacol.* 2004;4(13):1615–1623. <https://doi.org/10.1016/j.intimp.2004.07.015>
47. Petrov RV, Khaitov RM, Nekrasov AV, et al. Polyoxidonium: the mechanism of action and clinical application. *Medical Immunology.* 2000;2(3):271–278.
48. WHO Coronavirus Disease (COVID-19) Dashboard. <https://covid19.who.int/>. Accessed April 21, 2021.
49. Master Protocol. A multi-centre, adaptive, randomized, double-blind, placebo-controlled clinical trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalized patients. <https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis>. Accessed March 13, 2020.