Table 2e. Nitazoxanide: Selected Clinical Data

Last Updated: July 8, 2021

The information in this table may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see ClinicalTrials.gov for more information on clinical trials that are evaluating NTZ for the treatment of COVID-19. The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing recommendations for NTZ.¹²

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
</tr>
</thead>
</table>
| Early Treatment of Mild COVID-19 with Nitazoxanide³ | **Key Inclusion Criteria:**  
• Clinical signs and symptoms of COVID-19 for ≤3 days (fever, dry cough, and/or fatigue)  
• Negative SARS-CoV-2 RT-PCR result from an NP swab  
• Renal, heart, respiratory, liver, or autoimmune diseases  
• Participant had a history of cancer in the past 5 years | **Number of Participants:**  
• NTZ (n = 194) and placebo (n = 198)  
• Median age of patients was 37 years.  
• Percentage of patients aged 18–39 years: 58%  
• Percentage of patients aged 40–59 years: 36%  
• Percentage of patients aged 60–77 years: 6%  
• 53% of patients were women.  
• 69% of patients were White.  
• 31% of patients had a BMI ≥30.  
• 85% of patients had no reported comorbidities.  
• Median time from symptom onset to first dose of study drug was 5 days (IQR 4–5 days).  
• Baseline median SARS-CoV-2 VL was 7.06 log₁₀ c/mL (IQR 5.77–8.13) in NTZ arm and 7.49 log₁₀ c/mL (IQR 6.15–8.32) in placebo arm (P = 0.065). | **Key Limitations:**  
• In general, the patients in this study were young and relatively healthy.  
• At baseline, the median VL was 0.43 log₁₀ c/mL lower in the NTZ arm than in the placebo arm; however, this difference was not statistically significant (trend toward a significant difference; P = 0.065). Although the difference in absolute VLs between the arms at Day 5 was reported as statistically significant, without the information on the change in VL in each arm, it is difficult to interpret the significance of the findings.  
• Some participants who received the study drug were excluded from the analysis population due to discontinued intervention (21 in NTZ arm vs. 18 in placebo arm); AEs (6 in NTZ arm vs. 1 in placebo arm); hospitalization (5 in NTZ arm vs. 5 in placebo arm); and protocol deviations (7 in NTZ arm vs. 7 in placebo arm). This complicates the interpretation of the study results, because an ITT analysis was not included. |
| Randomized, double-blind, placebo-controlled trial in nonhospitalized adults with mild COVID-19 in Brazil (n = 475) | **Interventions:**  
• NTZ 500 mg 3 times daily for 5 days using the oral liquid formulation  
• Color-matched placebo 3 times daily for 5 days | **Primary Endpoint:**  
• Complete resolution of dry cough, fever, and/or fatigue after receiving treatment for 5 days |  
**Key Secondary Endpoints:**  
• Reduction in SARS-CoV-2 VL  
• Incidence of hospital admission after completing therapy  

Primary Outcome:  
• There was no difference in time to complete resolution of symptoms between NTZ and placebo arms (P = 0.277)  

Secondary Outcomes:  
• After 5 days, median SARS-CoV-2 VL was lower in NTZ arm (3.63 log₁₀ c/mL [IQR 0–5.03]) than in placebo arm (4.13 log₁₀ c/mL [IQR 2.88–5.31]; P = 0.006). |  

**Key Exclusion Criteria:**  
• Renal, heart, respiratory, liver, or autoimmune diseases  
• Participant had a history of cancer in the past 5 years  
• Negative SARS-CoV-2 RT-PCR result from an NP swab  
• Participant had a history of cancer in the past 5 years  
• Percentage of patients with a BMI ≥30.  
• 85% of patients had no reported comorbidities.  
• Median time from symptom onset to first dose of study drug was 5 days (IQR 4–5 days).  
• Baseline median SARS-CoV-2 VL was 7.06 log₁₀ c/mL (IQR 5.77–8.13) in NTZ arm and 7.49 log₁₀ c/mL (IQR 6.15–8.32) in placebo arm (P = 0.065).  

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2022
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
</tr>
</thead>
</table>
| Early Treatment of Mild COVID-19 with Nitazoxanide\(^3\), continued | • 29.9% of patients in NTZ arm and 18.2% of patients in placebo arm had a negative SARS-CoV-2 RT-PCR result at the fifth treatment visit \((P = 0.009)\).  
• In the ITT study population, 5 patients on NTZ and 5 on placebo were hospitalized due to clinical deterioration; 2 who received NTZ required ICU admission vs. 0 who received placebo. These individuals were excluded from the analysis population because they did not complete the 5-day treatment course before clinical progression occurred. | Interpretation:  
• NTZ did not improve time to resolution of symptoms compared to placebo.  
• Median VL was lower at Day 5 in the NTZ arm than in the placebo arm, but this may reflect differences in baseline VLs.  
• NTZ was well tolerated. |

| Early Treatment of Mild to Moderate COVID-19 with an Investigational Formulation of Nitazoxanide\(^4\) | | |
| Randomized, double-blind, placebo-controlled trial in nonhospitalized patients with COVID-19 in the United States and Puerto Rico \((n = 1,092)\) | Key Inclusion Criteria:  
• Aged \(\geq 12\) years  
• Enrollment \(\leq 72\) hours of symptom onset  
• Mild to moderate COVID-19  
• \(\geq 2\) respiratory symptom domains with a score \(\geq 2\) on FLU-PRO questionnaire at screening, and no improvement in overall symptom severity compared to previous day | Key Limitations:  
• Information is limited in this preliminary report.  
• Because the number of high-risk participants who progressed to severe COVID-19 in this study was small, the results for this subgroup are fragile. Larger studies are needed. |
| | Key Exclusion Criteria:  
• Signs or symptoms of severe COVID-19  
• Previous COVID-19 or any symptom suggestive of COVID-19  
• Recent acute upper respiratory tract infection  
• Severe immunodeficiency  
• Severe heart, lung, neurological, or other systemic diseases | Interpretation:  
• NTZ did not demonstrate significant clinical or virologic benefits when compared to placebo.  
• NTZ was well tolerated. |
| Number of Participants:  
• mITT analysis: NTZ \((n = 184)\) and placebo \((n = 195)\) | Participant Characteristics:  
• Median age of patients was 40 years.  
• 43.5% of patients were men.  
• 87.6% of patients were White.  
• Median BMI was 28.9.  
• Median time from symptom onset to randomization was 45.9 hours.  
• 64.8% of patients had mild disease.  
• 35.2% of patients had moderate disease.  
• 62.8% of patients were at risk for severe illness. | |
| Secondary Outcomes:  
• Progression to severe disease occurred in 1 of 184 patients (0.5%) in NTZ arm and 7 of 195 patients (3.6%) in placebo arm; \(P = 0.07\) | Primary Outcome:  
• NTZ was not associated with a reduction in median time to sustained response compared to placebo \((13.3\) days in NTZ arm vs. 12.4 days in placebo arm; \(P = 0.88\)) | |

\(^3\) Early Treatment of Mild COVID-19 with Nitazoxanide, continued

\(^4\) Early Treatment of Mild to Moderate COVID-19 with an Investigational Formulation of Nitazoxanide

This is a preliminary, unpublished report that has not been peer reviewed.
### Study Design

**Early Treatment of Mild to Moderate COVID-19 with an Investigational Formulation of Nitazoxanide**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
</tr>
</thead>
</table>

#### Interventions:
- 2 investigational NTZ 300 mg extended-release tablets (for a total dose of 600 mg) PO with food twice daily for 5 days
- Matching placebo for 5 days
- All subjects received a vitamin B complex supplement twice daily to mask potential NTZ-associated chromaturia.

#### Primary Endpoint:
- Time from first dose to sustained response

#### Secondary Endpoint:
- Rate of progression to severe COVID-19

#### Results:
- Among a subgroup of patients who had a high risk for severe illness according to CDC criteria, 1 of 112 patients (0.9%) in NTZ arm and 7 of 126 patients (5.6%) in placebo arm progressed to severe disease ($P = 0.07$).
- 1 of 184 patients (0.5%) in NTZ arm and 5 of 195 (2.6%) in placebo arm were hospitalized ($P = 0.18$).
- There was no significant difference in viral endpoints between arms at Days 4 and 10.

#### Other Outcomes:
- The safety analysis included 935 participants (472 in NTZ arm and 463 in placebo arm).
- 2 patients in NTZ arm and 3 patients in placebo arm stopped the study drug due to AEs.

---

**Key:** AE = adverse event; BMI = body mass index; CDC = Centers for Disease Control and Prevention; FLU-PRO = Influenza Patient Reported Outcomes; ICU = intensive care unit; ITT = intention-to-treat; mITT = modified intention-to-treat; NP = nasopharyngeal; NTZ = nitazoxanide; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; RT-PCR = reverse transcription polymerase chain reaction; VL = viral load

### References


