

Analyzing the Relationship of QT Interval and Exposure to Nitazoxanide, a Prospective Candidate for Influenza Antiviral Therapy—A Formal TQT Study

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Abstract

In this randomized, double-blind, placebo controlled study, the safety of therapeutic (675 mg) and supra-therapeutic (2,700 mg) doses of nitazoxanide was evaluated in accordance with the ICH E14 guidelines. Fifty six (56) subjects participated in four treatment periods and received single doses of nitazoxanide 675 mg, nitazoxanide 2,700 mg, moxifloxacin 400 mg, or placebo. For 675 mg nitazoxanide, the largest change in QTcF from baseline was observed at 12 hours post-dose with a peak value of 1.6 ms (two-sided 90% CI: –0.3, 3.6 ms). The largest negative change in QTcF was observed at 1 hour post-dose (–2.7 ms with two-sided 90% CI: –4.5, –0.8 ms). The largest change in QTcF from baseline for 2,700 mg nitazoxanide was observed at 24 hours post-dose with a peak value of 3.4 ms (two-sided CI: 1.4, 5.4 ms). These findings demonstrate that neither a single dose of 675 mg nor 2,700 mg nitazoxanide prolonged the QT interval in healthy male and female volunteers. The safety results also demonstrate that all four treatments were well-tolerated and the most frequently reported adverse events in the nitazoxanide and moxifloxacin treatment groups were gastrointestinal disorders which were as expected according to the reference safety information.

Keywords

Thorough QT study, ICH E14 guideline, moxifloxacin, nitazoxanide, healthy volunteers

There is a pressing global clinical need for accelerated treatment strategies for viral infections as drug resistance is constantly evolving in viruses thereby limiting treatment options. A striking example of a widespread virus of high genetic variability is influenza. The treatment against influenza virus consists of two major classes of drugs: adamantanes and neuraminidase inhibitors. The viral resistance to the first class is widespread now, whereas resistance to the neuraminidase inhibitors class is limited and hence is a primary option for treatment of influenza. However, resistance to both classes of drugs has been observed, thus raising a medical need for efficacious treatments against influenza.¹

Nitazoxanide is the approved generic name for 2-acetyloxy-N-(5-nitro-2-thiazolyl) benzamine, also known as PH-5776, NTZ, or Alinia[®] (Romark Laboratories, L.C.). This compound was first synthesized by Rossignol.² It was originally approved by the FDA for the treatment of *Cryptosporidium parvum* and *Giardia lamblia* (*G. intestinalis*) infections. Recent studies have shown that nitazoxanide inhibits replication of influenza viruses by a novel mechanism, i.e. blocking maturation of viral hemagglutinin at a post-translational level.³ In a randomized placebo-controlled clinical trial, nitazoxanide administered 600 mg twice daily for 5 days significantly

reduced the duration of symptoms of influenza as well as virus shedding.⁴ Nitazoxanide is presently undergoing a global Phase 3 clinical trial to support licensure as a treatment of influenza.

Previous studies have shown no clinically significant modifications of electrocardiogram (ECG) results including QTc measurements after dosing of nitazoxanide in the fed condition.⁵ However, bearing in mind the development of new therapies, it was necessary to conduct a

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