International Journal of Antimicrobial Agents 48 (2016) 33–40

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Effects of therapeutic and supratherapeutic doses of oral tedizolid phosphate on cardiac repolarisation in healthy volunteers: a randomised controlled study

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ARTICLE INFO

Article history:
Received 8 July 2015
Accepted 8 December 2015

Keywords:
ECG
QT prolongation
Safety
Oxazolidinone
Antibacterial
Heart

ABSTRACT

Drug-induced prolongation of the QT interval on the electrocardiogram (ECG) infrequently results in Torsades de pointes, a potentially fatal arrhythmia. Therefore, thorough QT analysis of new drugs is a regulatory requirement. The objective of this phase 1 study was to assess the effects of oral tedizolid phosphate on the QT interval corrected with Fridericia's formula (QTcF) in healthy adult subjects. A single therapeutic dose (200 mg) and a supratherapeutic dose (1200 mg) of tedizolid phosphate were administered to characterise QTc changes following typical systemic exposure and with markedly higher exposures, respectively. This was a four-way crossover study with 48 subjects randomly assigned to receive therapeutic and supratherapeutic doses of tedizolid phosphate, moxifloxacin (positive control for QT interval prolongation) and placebo (negative control). A continuous 12-lead ECG was recorded from 1 h before drug administration to 23 h after administration. Adverse events, which were generally mild, occurred most frequently with moxifloxacin or with a supratherapeutic dose of tedizolid phosphate; however, all treatments were well tolerated. This study demonstrated that therapeutic or supratherapeutic doses of the antibacterial tedizolid had no clinically significant effect on QT interval in healthy adults [ClinicalTrials.gov registration no.: NCT01461460].

1. Introduction

Tedizolid, the active moiety of the prodrug tedizolid phosphate, is a novel oxazolidinone approved in several countries including the USA and Europe for the treatment of acute bacterial skin and skin-structure infections (ABSSSIs) caused by *Staphylococcus aureus* (including meticillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group and *Enterococcus faecalis* [1,2]. Two phase 3 trials (ESTABLISH-1 and ESTABLISH-2) demonstrated the non-inferior efficacy of tedizolid (200 mg once daily for 6 days) to linezolid (600 mg twice daily for 10 days) in patients with ABSSSI [3–5].

A potential adverse effect of any new drug is a delay of cardiac repolarisation, which can be measured as prolongation of the QT interval on an electrocardiogram (ECG) [6]. A delay in repolarisation creates an inhomogeneous electrophysiological environment for cardiomyocytes that favours the development of cardiac arrhythmias, such as Torsades de pointes, which could lead to sudden cardiac death [6]. QT prolongation and proarrhythmias are among the most common reasons for withdrawal of drugs from the market [7]. Several classes of commonly used antimicrobial agents, including macrolides, quinolones, azoles and protease inhibitors, as well as other types of medications (i.e. antihistamines, antimalarial drugs and psychiatric drugs) can be associated with this adverse effect [8,9]. The only other approved oxazolidinone, linezolid, does not affect cardiac repolarisation at the standard intravenous dose of 600 mg or at the supratherapeutic dose of 1200 mg [10]. Guidelines from the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use recommend that drugs undergo clinical electrocardiographic evaluation early in clinical development, including a thorough QT/QTc study to evaluate their effect on cardiac repolarisation, using moxifloxacin as a positive control [6].

The objective of this phase 1 study was to assess the effects of oral tedizolid phosphate on the QT interval corrected by using Fridericia's formula (QTcF) in healthy subjects. A single therapeutic dose (200 mg) and a supratherapeutic dose (1200 mg) of tedizolid phosphate were used to characterise the effects of typical systemic exposure and to provide an understanding of effects at markedly higher exposures.

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http://dx.doi.org/10.1016/j.ijantimicag.2015.12.015
0924-8579/

2. Methods

2.1. Study design and treatments

This was a double-blind, four-way crossover, single-centre, phase 1 study conducted in Dallas, TX, with 48 subjects randomly assigned to receive therapeutic and supratherapeutic doses of tedizolid phosphate, moxifloxacin (positive control for QT interval prolongation) and placebo (negative control) in various sequences ($N = 6$ subjects per sequence) (Fig. 1). Subjects were randomised using block randomisation generated by a statistician at the investigation site. The treatment arms were as follows: one tedizolid phosphate tablet [200 mg (therapeutic dose)] and five placebo tablets; six tedizolid phosphate tablets [1200 mg (supratherapeutic dose)]; one 400 mg moxifloxacin tablet; and six placebo tablets. Each subject had at least 3 day washout between treatments, and the overall duration of subject participation was ca. 35 days. All treatments were administered orally under fasting conditions in the morning. Subjects and investigators were blinded to the study drugs, with the exception of moxifloxacin. This study was conducted in accordance with current US Food and Drug Administration (FDA) regulations, ICH Good Clinical Practice guidelines and the Basic Principles of the Declaration of Helsinki, and was reviewed and approved by the local institutional review boards. All subjects provided written informed consent.

2.2. Subjects

Healthy male and female subjects included were aged 18–45 years with a body mass index (BMI) ≥ 18.0 kg/m^2 and ≤30.0 kg/m^2. Subjects were excluded if they had a history of risk factors for Torsades de pointes, including unexplained syncope, known long QT syndrome, heart failure, myocardial infarction, angina or clinically significant abnormal laboratory assessments, including hypokalaemia, hypercalcaemia, hypomagnesaemia or family history of long QT syndrome or Brugada syndrome, or were taking medications known to prolong the QT interval as defined in the label of moxifloxacin [11,12]. Subjects were excluded if contraindications to moxifloxacin were present. Subjects were also excluded if, on the day of screening or the day before beginning the study, they had a

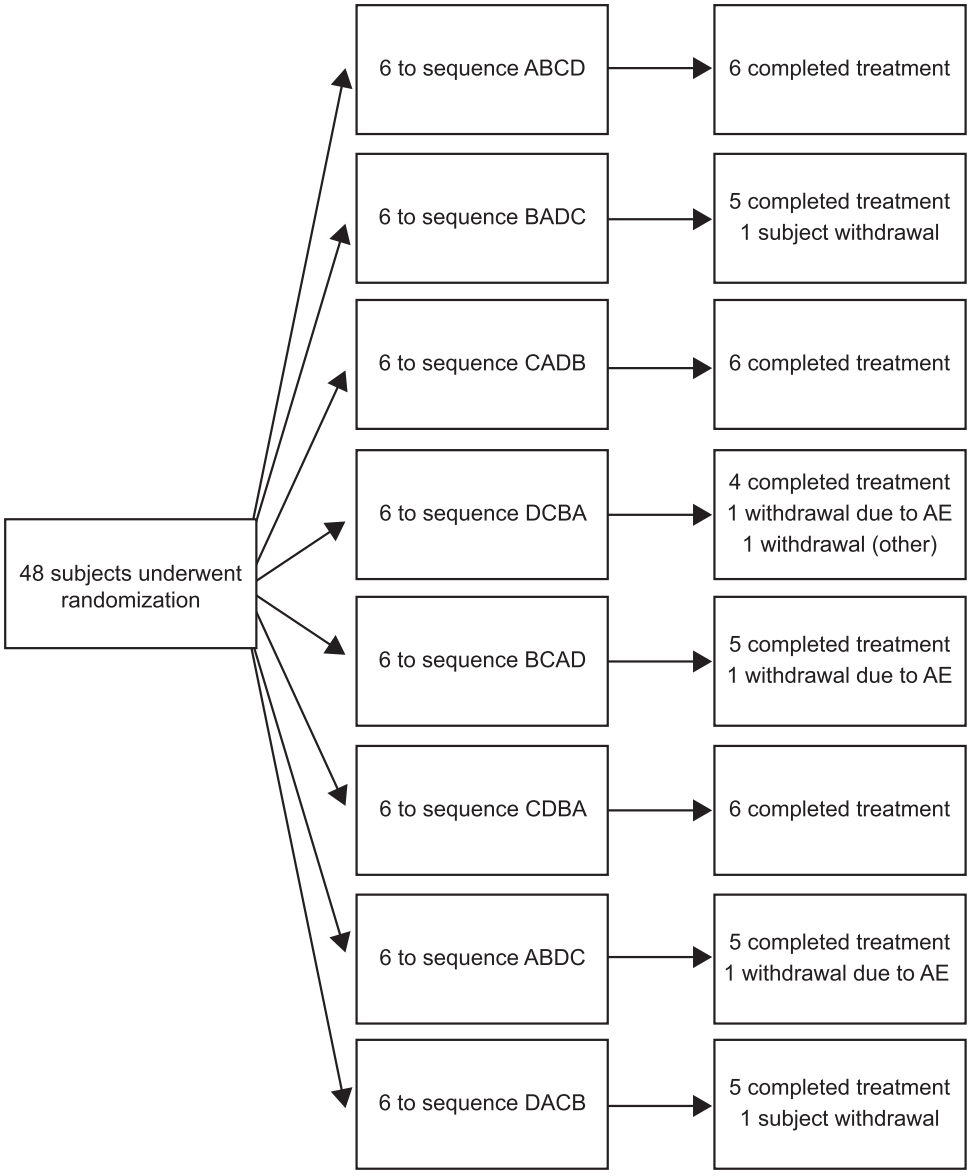

Fig. 1. Subject disposition: (A) 200 mg tedizolid phosphate; (B) 1200 mg tedizolid phosphate; (C) placebo; (D) 400 mg moxifloxacin. AE, adverse event.