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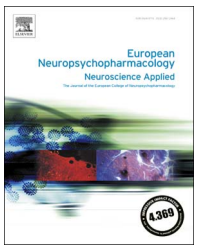

The safety, tolerability and pharmacokinetics of BI 409306, a novel and potent PDE9 inhibitor: Overview of three Phase I randomised trials in healthy volunteers

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Abstract
Safety, tolerability and pharmacokinetics of BI 409306, a potent and selective phosphodiesterase 9A inhibitor, were assessed in healthy subjects in three Phase I, within-dose group, double-blind trials. Trial 1 randomised young and elderly subjects to receive BI 409306 25, 50, 100 mg, placebo once daily (OD) or BI 409306 50 mg twice daily (young) for 14 days. Trial 2 randomised young poor metabolisers (PM) of cytochrome P450 isoform 2C19 (CYP2C19) and elderly subjects to receive BI 409306 25, 50 mg or placebo OD for 14 days. Trial 3 randomised Chinese and Japanese extensive metabolisers of CYP2C19 to receive single doses (SD) of BI 409306 25, 50, 100 mg or placebo and Chinese (PM) to SD of BI 409306 100 mg or placebo (Part 1). Japanese PM received SD of BI 409306 100 mg or placebo (Day 1) followed by BI 409306 100 mg or placebo OD for 7 days after a 48-hour washout period (Part 2). Reported adverse events (AE) were mild-to-moderate intensity and increased with BI 409306 dose. Eye disorders were most commonly reported (Trial 1: 40.0–41.7%, Trial 2: 29.2–37.5%, Trial 3: 18.2–66.7%) and increased with dose and systemic exposure. PM reported more AEs than other treatment groups, corresponding to higher systemic exposure to BI 409306. Systemic exposure to BI 409306 produced dose-dependent increases and was slightly

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greater in elderly versus young subgroups (Trial 1). Steady state was achieved by Day 2–3. Overall, BI 409306 demonstrated good safety, tolerability and minor accumulation after multiple dosing.

1. Introduction

One of the key characteristics of schizophrenia and Alzheimer's disease (AD) is an abnormality in glutamatergic neurotransmission related to *N*-methyl-D-aspartate (NMDA) receptor hypofunction in cortical and hippocampal brain areas.(Lee et al., 2002; Lewis and Moghaddam, 2006; Stephan et al., 2009) NMDA receptor activation produces postsynaptic signalling events through elevation of second messengers such as cyclic guanosine monophosphate (cGMP).(Bales et al., 2010) In conditions of NMDA receptor hypofunction, it has been hypothesised that inhibition of phosphodiesterase 9A (PDE9A), which hydrolyses cGMP, may increase cGMP levels and improve NMDA receptor signalling. This would lead to strengthened synaptic plasticity and stabilisation, as determined by enhanced long-term potentiation (LTP), and thus improving cognitive function (Figure S1).(Bales et al., 2010; Cooke and Bliss, 2006; Rezvani, 2006; Moschetti et al., 2016; Dorner-Ciossek et al., 2017).

This hypothesis has been supported by results from animal models of cognitive impairment, using the novel PDE9A inhibitor BI 409306. In rodents, BI 409306 was shown to be a potent and selective PDE9A inhibitor, which induced a dose-dependent increase in cGMP levels in the pre-frontal cortex and cerebrospinal fluid (CSF), reversed dizocilpine-induced memory deficits in the T-maze continuous alternation task and improved memory performance in the object recognition task.(Rosenbrock et al., 2015; Dorner-Ciossek et al., 2015).

In a first-in-human trial, single doses (SD) of BI 409306 $\leq$ 350 mg showed an acceptable safety and tolerability profile for young, healthy males genotyped as extensive metabolisers (EM) of cytochrome P450 isoform 2C19 (CYP2C19) and for males genotyped as poor metabolisers (PM) of CYP2C19 at doses of 10 and 100 mg. (Moschetti et al., 2016). CYP2C19 is an enzyme involved in oxidative metabolism of BI 409306. The absorption and elimination of BI 409306 was rapid, and plasma concentrations increased with the dosage. Males with two non-functional alleles of CYP2C19 (PM) displayed higher exposure compared with EM carrying two functional alleles of CYP2C19: the maximum measured concentration in the plasma (C_{max}) was 2.2- to 2.3-fold higher, and the area under the concentration-time curve of the analyte in plasma from time 0 extrapolated to infinity ($AUC_{0-\infty}$) was 4.1- to 5.0-fold higher after a single dose. The reported adverse events (AEs) were mild to moderate in intensity and mostly related to nervous system or eye disorders and were resolved within 2 hours. (Moschetti et al., 2016).

In addition, results from a proof-of-clinical-mechanism trial in healthy males showed that SD of BI 409306 25–200 mg were rapidly absorbed in plasma and distributed in CSF. This pattern of absorption subsequently resulted in a dose-dependent increase in concentrations of cGMP within the CSF, indicating functional target engagement.(Boland et al., 2017).

Following on from the first-in-human and proof-of-mechanism trials, where single doses were applied, the intention of this publication is to provide an overview of safety, tolerability and pharmacokinetic (PK) data from three Phase I trials where repeat doses of BI 409306 were administered to healthy subjects. These trials include subjects who were young and elderly, of Caucasian and Asian ethnicities and genotyped for CYP2C19.

2. Experimental procedures

2.1. Trial designs

The three trials were randomised (BI 409306 3:1 placebo), placebo-controlled and double-blinded within-dose groups, single-centre trials. The primary objective of each trial was to establish the safety and PK for SD and multiple doses (MD) of BI 409306 in selected populations.

All three trials were approved by an institutional review board/independent ethics committee and competent authority and conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (GCP) guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996), the Japanese GCP regulations (Ordinance of the Ministry of Health and Welfare, 2011), and the Declaration of Helsinki.(World Medical Association, 2013) All subjects provided written, informed consent prior to participation.

2.2. Subjects

In Trials 1 (NCT01505894) and 2 (NCT01611311) conducted in Germany, subjects were healthy volunteers of either 21–50 years of age (young subgroup) or 65–80 years of age (elderly subgroup), with a body mass index (BMI) of 18.5–29.9 kg/m^2. In Trial 2 the healthy young subjects were prospectively genotyped as homozygous for CYP2C19 PM (definition included in Table 1 (The Human Cytochrome P450 (CYP) Allele Nomenclature Database)). Trial 3 (NCT01841112), conducted in Korea, enrolled healthy Japanese and Chinese male volunteers of 20–45 years of age and a BMI between $\geq$ 18.5 and $\leq$ 25 kg/m^2, who were prospectively genotyped as homozygous for CYP2C19 EM or PM (Table 1 (The Human Cytochrome P450 (CYP) Allele Nomenclature Database)). If not specified prospectively with an explicit entry criterion, the CYP2C19 metaboliser status (PM, intermediate [IM], EM or ultra-rapid metaboliser [UM]) was determined retrospectively for all subjects (Table 1 (The Human Cytochrome P450 (CYP) Allele Nomenclature Database)).

Key exclusion criteria included: any findings from the medical examination that showed deviation from the normal range for systolic and diastolic blood pressure ($<$140 mmHg and $<$80 mmHg, respectively), resting pulse rate (60–90 beats per minute [bpm]), 12-lead electrocardiogram (ECG) and clinical laboratory tests of

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