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2-Year animal carcinogenicity results for crisaborole, a novel phosphodiesterase 4 inhibitor for atopic dermatitis

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ABSTRACT

Background: Crisaborole is a novel, topical nonsteroidal, anti-inflammatory, phosphodiesterase 4 (PDE4) inhibitor for the treatment of mild to moderate atopic dermatitis.
Objective: As part of a nonclinical safety testing program, these 2-year studies tested the carcinogenic potential of crisaborole.
Methods: Crisaborole ointment, 2%, 5%, or 7%, was applied once daily topically to mice, and crisaborole was administered orally to rats at doses of 30, 100, or 300 mg/kg/day for up to 104 weeks. Systemic exposure to crisaborole and its metabolites, moribundity/death, clinical signs, and tumor formation were assessed in each study.
Results: Crisaborole treatment was not tumorigenic in mice at any of the doses administered and did not increase the incidence of neoplastic or nonneoplastic microscopic lesions compared with controls. Oral administration of crisaborole at the high dose (300 mg/kg/day) to female rats increased the incidence of treatment-related benign granular cell tumors in the distal reproductive tract (uterus with cervix and vagina) but did not cause moribundity/death.
Conclusion: Crisaborole was well tolerated and not tumorigenic in mice. It was not tumorigenic in male rats at 300 mg/kg/day at exposures that were 3× the human area under the concentration-time curve (AUC_{24}) and was nontumorigenic in female rats at 100 mg/kg/day at exposures that were 1× the human AUC_{24}.

1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects ~15–30% of children and ~2–10% of adults in industrialized countries [1], and up to 90% of the AD patient population presents with mild to moderate disease [2]. Topical treatments are preferred for mild to moderate AD because they provide a barrier that improves disrupted skin barrier function and prevents transepidermal water loss [3,4] while targeting the site of inflammation with limited systemic drug exposure [5]. Current pharmacologic treatments include topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI); however, safety is a concern with these agents [5]. Long-term TCS use and application sites must be monitored to avoid systemic side effects and cutaneous side effects such as skin atrophy [5]. TCI use may be influenced by burning sensations on application, though these may improve after several days [5]. In addition, in 2006 the US Food and Drug Administration (FDA) Pediatric Advisory Committee and European Medicines Agency (EMA) recommended restricted long-term use of TCI and increased patient education due to the potential risk of malignancy,[6,7] but recent evidence demonstrated that there is no association between TCI use and skin cancer or increased risk for malignancy [8]. Therefore, a topical agent that is effective and safe for application to sensitive skin areas and for long-term disease management is needed for the treatment of AD.

AD is associated with immune dysregulation of a number of factors [9], including elevated phosphodiesterase activity [10,11]. Phosphodiesterase 4 (PDE4) is an intracellular enzyme expressed in a variety of inflammatory cells [12,13] that degrades cyclic adenosine monophosphate (cAMP) and regulates production of inflammatory cytokines [12,14] through the nuclear factor kappa B

Abbreviations: AD, atopic dermatitis; AUC_{24}, area under the concentration-time curve from 0 to 24 h; cAMP, cyclic adenosine monophosphate; CMC, carboxymethylcellulose; ECAC, Executive Carcinogen Advisory Committee; ICH, International Conference on Harmonization; IgE, immunoglobulin E; IL, interleukin; PDE4, phosphodiesterase 4; PGE_2, prostaglandin E2; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

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[15] and nuclear factor of activated T cells pathways [16,17]. Inflammation is associated with elevated levels of PDE4 [12] and is seen in patients with active AD [10]. Inhibition of PDE4 increases intracellular cAMP levels, leading to activation of protein kinase A and subsequent decreased production of proinflammatory cytokines [18,19]. Therefore, therapeutically targeting PDE4 may disrupt and normalize the inflammatory cycle seen in AD flares without the risks associated with broader anti-inflammatory agents.

Crisaborole ointment, 2% (Pfizer Inc., New York, NY), is a, nonsteroidal, topical anti-inflammatory PDE4 inhibitor [20]. As a novel, boron-containing small molecule with low molecular weight (~251 Da) [21], crisaborole effectively penetrates the skin to inhibit elevated PDE4 activity at the site of an AD flare [22].

In vitro studies showed inhibition of proinflammatory cytokine release and no adverse events, mortality, or microscopic or macroscopic changes were observed in nonclinical studies with rodents after 14 days of exposure to crisaborole [21]. Early clinical and two Phase 3 clinical trials with crisaborole ointment for up to 28 days had significantly reduced the signs and symptoms of AD with a low incidence of treatment-related adverse events, none of which were serious, in patients as young as 2 years of age [20,23–26]. Herein, we present the results of nonclinical studies that were performed in accordance with International Conference on Harmonization (ICH) guidelines to assess the carcinogenic potential of crisaborole in mice (topical administration) and in rats (oral administration).

2. Materials and methods

Two studies lasting up to 2 years each were performed to investigate the potential carcinogenicity of crisaborole. One study examined crisaborole ointment topically applied to shaved skin of mice at 0%, 2%, 5%, and 7%. The clinical concentration of crisaborole ointment is 2%. The second study dosed rats orally with crisaborole or 1% w/v carboxymethylcellulose (CMC) as a control; crisaborole was administered at doses that exceeded systemic exposures observed clinically. All studies were performed under Good Laboratory Practices conditions in accordance with ICH and FDA guidelines. In addition, all studies were carried out in compliance with the recommendations in The Guide for the Care and Use of Laboratory Animals of the US Department of Agriculture (USDA) and the Public Health Service Policy on Humane Care and Use of Laboratory Animals. The protocol was approved by the Institutional Animal Care & Use Committee of MPI Research (Certificate Number: 34-R-0031).

2.1. Topical carcinogenicity study in mice

2.1.1. Vehicle and test article information

All formulations (crisaborole ointment, 0%, 2%, 5%, and 7%) were manufactured by DPT Laboratories, Ltd. (San Antonio, TX). All formulations were stored at room temperature. Concentrations were verified at the beginning and end of the study for each sample lot.

2.1.2. Animals

Experimentally naive male and female (325 each) Crl:CD1(ICR) mice (Charles River Laboratory, Portage, MI) were individually housed in suspended, stainless steel, wire mesh cages in an environmentally controlled room with fluorescent lighting (12 h/day). Temperature and humidity were continuously monitored and continually recorded. Mice were fed Lab Diet® (Certified Rodent Diet #5002, PMI Nutrition International Inc.; St Louis, MO), and water was available *ad libitum*.

Mice were assigned to untreated, 0% (vehicle control), and crisaborole ointment, 2%, 5%, and 7%, treatment groups (Fig. 1). Topical treatment of mice was performed for at least 99 weeks and 104 weeks in female and male mice, respectively.

2.1.3. Dose justification and test article administration

Doses for the study were based on a 13-week mouse topical toxicity study in which CD1 mice were treated topically with crisaborole ointment, 2%, 5%, or 7%, twice daily. The identical dosing procedures were used without application of crisaborole or vehicle ointment for an untreated control group. Crisaborole ointment, 7%, was the highest concentration that could be prepared owing to process limitations because drug strengths greater than 7% cannot be poured and dispersed into the petrolatum base to form a stable ointment formulation.

Crisaborole was administered once daily at a dose volume of 1.1 μL/g of body weight to a region of skin trimmed to be free of hair that encompassed no less than 10% of the total body surface area. Individual doses were based on most recent body weight.

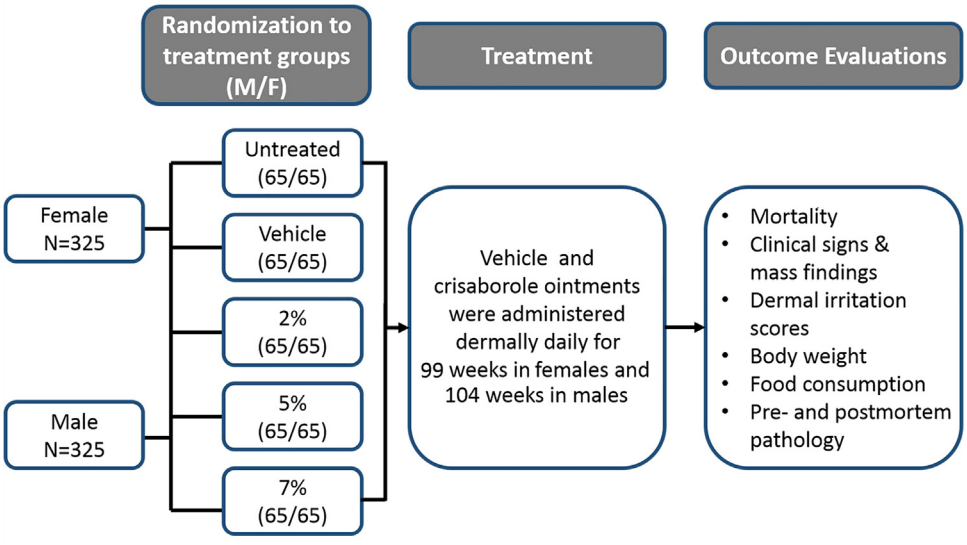

Fig. 1. Study design and dosing assignment for mouse topical administration of crisaborole ointment. Treatment administered and outcomes evaluations are described.

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