A randomized, multicenter, double-blind, placebo-controlled phase 2 trial of ISA247 in patients with chronic plaque psoriasis

Robert Bissonnette, MD, FRCPC,[a] Kim Papp, MD, PhD, FRCPC,[b] Yves Poulin, MD, FRCPC,[c] Gilles Lauzon, MD, PhD, FRCPC,[d] Launa Aspeslet, PhD, RAC, COO,[e] Robert Huizinga, RN, NNC, MSc(Epi), CNeph(C),[e] Patrick Mayo, BSc, PhD,[e] Robert T. Foster, PhD, MPharm,[e] Randall W. Yatscoff, PhD, FCACB,[e] and Walter P. Maksymowych, BSc, MDChB, LMCC, MRCP, FRCP[d] on behalf of the ISA247 Psoriasis Study Group*

Montreal, Waterloo, Québec City, and Edmonton, Canada

Background: Use of current oral calcineurin inhibitors for the treatment of psoriasis is limited by toxicity.

Objective: Evaluate the safety and efficacy of ISA247, a new oral calcineurin inhibitor, in plaque psoriasis patients.

Methods: This 12-week, randomized, double-blind, placebo-controlled, parallel-group study included 201 plaque psoriasis patients with $\geq$ 10% body surface area involvement. Patients were randomized to placebo, ISA247 0.5 mg/kg/d, and ISA247 1.5 mg/kg/d groups. End points included a 2-point reduction in the Static Global Assessment score and a 75% reduction in the Psoriasis Area and Severity Index.

Results: A 2-point SGA reduction was achieved in 0% (placebo), 15.6% (0.5 mg/kg/d), and 45.1% (1.5 mg/kg/d) ($P < .0001$). A 75% reduction in the Psoriasis Area and Severity Index was achieved in 0% (placebo), 18.2% (0.5 mg/kg/d), and 66.7% (1.5 mg/kg/day) ($P < .0001$). While serum creatinine increased in patients treated with ISA247 1.5 mg/kg/d, it remained within the normal range.

Limitations: Longer-term studies are needed to evaluate the effect of ISA247 on renal function.

Conclusion: ISA247 appears safe and effective for treating moderate to severe psoriasis. (J Am Acad Dermatol 2006;54:472-8.)

Psoriasis is recognized as a complex, chronic skin condition that can have a significant impact on patients' physical and mental health.[1-4] The prevalence ranges from 0.5% to 4.6%, with an increasing prevalence in Caucasians and those living in northern latitudes.[5] Though epidermal proliferation characterizes psoriasis, new treatments

Abbreviations used:

ACE:	angiotensin-converting enzyme
BSA:	body surface area
CNi:	calcineurin inhibitor
ITT:	intention-to-treat
PASI:	Psoriasis Area and Severity Index
SGA:	Static Global Assessment

From Innovaderm Research,[a] Montreal, Probity Medical Research,[b] Waterloo, Centre Dermatologique du Québec Métropolitain,[c] Québec City, University of Alberta,[d] Edmonton, and Isotechnika,[e] Edmonton.

*Members of the ISA247 Psoriasis Study Group are listed in the Appendix.

Funding sources: This research was funded entirely by the study sponsor, Isotechnika International Inc.

Conflict of interest: Drs Yatscoff and Foster are employees of and hold shares in Isotechnika, and have applied for patents for ISA247. Dr Aspeslet is an employee of and holds shares in Isotechnika. Dr Maksymowych holds shares in Isotechnika, and has acted as a consultant for and received honoraria from Isotechnika. Dr Mayo and Mr Huizinga are employees of Isotechnika, while Dr Lauzon has acted as a consultant for Isotechnika. Drs Bissonnette, Papp, and Poulin declare no conflict of interest.

Accepted for publication October 28, 2005.

Reprint requests: Dr Robert Bissonnette, 1851 Sherbrooke St East, Ste 502, Montreal Qc H2K 4L5. E-mail: rbissonnette@innovaderm.ca.

Published online January 24, 2006.

0190-9622/$32.00

doi:10.1016/j.jaad.2005.10.061

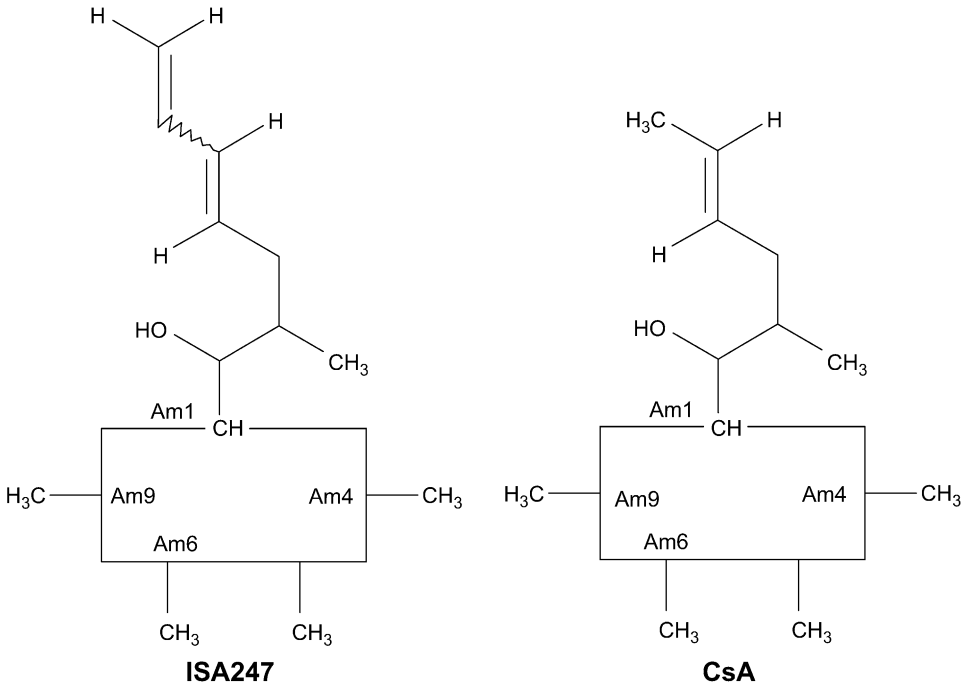

Fig 1. Comparison of the structure of ISA247 and cyclosporine A (CsA).

targeting specific components of the immune cascade have been developed as a result of recent advances in the understanding of the immune system's role in this disease. For example, monoclonal antibodies and fusion proteins have been approved recently in various countries for the treatment of psoriasis.[6,7]

Cyclosporine, a calcineurin inhibitor (CNi), is considered to be one of the treatments that has the greatest efficacy[8-12] and has been in use for more than a decade to treat psoriasis patients. However, the side effect profile of cyclosporine includes nephrotoxicity, hyperlipidemia, hypertension, headaches, hirsutism, tremor, and fatigue.[12-15] Nephrotoxicity remains the major limitation to the long-term use of cyclosporine in patients with psoriasis, and evidence strongly suggests that the nephrotoxicity is dose-dependent.[16-19] Therefore, the Food and Drug Administration labelling recommends that cyclosporine be given only to patients who are refractory to other treatments and for a duration of no longer than 1 year of continuous treatment.[20]

ISA247 is a novel oral CNi that differs from cyclosporine A by the addition of a modified functional group on the amino acid 1 residue (Fig 1). ISA247 has a molecular weight of 1214.63 and binds to calcineurin in a fashion similar to that of cyclosporine (Isotechnika internal data). ISA247 has demonstrated an increased potency and a more favourable side effect profile in animal models, compared with cyclosporine.[21-23] In particular, studies of ISA247 in rats, dogs, and rabbits have revealed significantly less evidence of renal toxicity than with cyclosporine.[22] The primary goal of this dose-ranging, placebo-controlled study was to demonstrate the efficacy and safety of ISA247, compared with placebo in stable plaque psoriasis patients.

METHODS

Patients

Men and women 18 to75 years of age with chronic plaque psoriasis of at least 6 months duration and a body surface area (BSA) involvement of 10% or more were enrolled; patients with erythrodermic, guttate, or pustular psoriasis were excluded. Patients also were excluded if they had (1) serious local infection or systemic infection in the prior 3 months; (2) significantly abnormal hematology, blood chemistry, or urinalysis; (3) positive human immunodeficiency virus, hepatitis C virus, or hepatitis B surface antigen; (4) a history of malignancy other than basal cell carcinoma; or (5) other skin disorders that might interfere with the assessment of psoriasis. Pregnant or nursing women also were excluded.

Within 28 days of the first dose and throughout the study, the only treatments allowed for psoriasis were non–lanolin-based emollients for topical treatment (excepting the target sites) and 1.0% hydrocortisone cream on the groin, armpit, scalp, palms, and soles. Each site's ethics committee or institutional review