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INVESTIGATIVE REPORT

Debio 0932, A New Oral Hsp90 Inhibitor, Alleviates Psoriasis in a Xenograft Transplantation Model

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Debio 0932 is a novel oral heat shock protein 90 (Hsp90) inhibitor developed for anti-cancer therapy. Surprisingly, during the first clinical trial, one psoriasis patient experienced complete remission of his skin manifestation. However, a possible therapeutic utility of Hsp90 in psoriasis has not previously been reported. The objective of the present study was to explore the ability of Debio 0932 to alleviate psoriasis in a preclinical model. A psoriasis xenograft transplantation model was employed where skin from 5 psoriasis patients was transplanted onto immunodeficient mice (8 xenografts per donor). Debio 0932 was administered perorally daily for 3 weeks and resulted in significant clinical alleviation of psoriasis by day 11 and reduced epidermal thickness evaluated post-treatment. Alleviation of psoriasis in the psoriasis xenograft transplantation model, which may be due to Hsp90's involvement in signalling pathways that are up-regulated in psoriasis, substantiates a potential role of Debio 0932 in psoriasis treatment. *Key words: Hsp90; psoriasis; xenograft model*.

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Debio 0932 (originally named CUDC-305) is a second-generation, heat shock protein 90 (Hsp90) inhibitor of the imidazopyridine class that displays unique pharmacological properties, such as oral bioavailability, sustained tumour retention and blood-brain barrier penetration (1). Debio 0932 shows high affinity for Hsp90α/β (IC50 ~100 nM) and is a promising anti-tumour drug candidate that is currently being tested clinically in patients with advanced solid tumours, lymphomas or non-small cell lung cancer (registered at http://ClinicalTrials.gov, identifier NCT01168752 and NCT01714037).

Unexpectedly, during the first clinical trials (Debio0932-101), one patient, who had a long-term history of psoriasis, with severe skin manifestation involving more than 40% of the skin surface showed complete remission after 43 days of treatment with Debio 0932 (800 mg once daily; unpublished data, Debiopharm). Of note, this patient was not receiving anti-psoriatic treatment at the time of enrolment. Consequently, we aimed to investigate the potential causal relationship between resolution of psoriasis and treatment with Debio 0932.

Psoriasis is a chronic inflammatory skin disease that generally manifests itself as symmetrical, erythematous, and scaling plaques characterised by hyperproliferating keratinocytes, increased vascularisation and overexpression of pro-inflammatory cytokines (2, 3). Psoriasis affects 2–3% of the population and up to 30% of these patients experience the associated disorder psoriatic arthritis. Moreover, life expectancy of patients with severe psoriasis is significantly decreased (4, 5). The exact cause of psoriasis is not yet understood and the disease represents an unmet need for new and improved treatments.

Hsp90 plays an essential role in maintaining cellular protein homeostasis by acting as an intracellular molecular chaperone involved in stabilisation, correct folding and activity of many client proteins. Hsp90 is highly expressed in keratinocytes and dermal fibroblasts (6) and has been implicated in angiogenesis (7). Among the Hsp90 client proteins are several members of the janus kinase and signal transducer and activator of transcription (JAK/STAT) pathway and the mitogen-activated protein (MAP) kinase pathway, 2 pathways known to be activated in psoriasis by pro-inflammatory cytokines (7–10). Also, Hsp90 chaperones antigenic peptides that are taken up by antigen-presenting cells (APC) to be presented by MHC class I molecules (11). The innate receptor CD91, utilised to facilitate the uptake of Hsp90 chaperoned peptides, is overexpressed in the upper dermis of psoriasis skin (12), suggesting a role for Hsp90 in the interplay between the innate and the adaptive immune system in psoriasis. Furthermore, anti-Hsp90 treatment has been demonstrated to decrease disease severity in animal models of inflammatory diseases such as autoimmune encephalitis (13), sepsis (14) and rheumatoid arthritis (15, 16).

A role for Hsp90 in psoriasis is thus plausible and the objective of the present study was to evaluate the ability of Debio 0932 to alleviate psoriasis in a preclinical model. In the psoriasis xenograft transplantation model where human psoriatic skin is transplanted onto immune-deficient mice, it was demonstrated that Debio 0932 promoted resolution of psoriasis.

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MATERIAL AND METHODS

Hsp90 inhibitor Debio 0932

The Hsp90 inhibitor Debio 0932 (MW = 442.58 g/mol), originally designated CUDC-305 and synthetised by Curis, Lexington, USA was provided by Debiopharm International S.A., Lausanne, Switzerland.

Psoriasis patients and keratome skin biopsies

Psoriatic plaque keratome skin biopsies were obtained from 5 patients aged 39–70 years (mean age 55 ± 9 years) with moderate-to-severe plaque-type psoriasis. The psoriatic patients were untreated for at least one month prior to the time of skin biopsy and informed consent was obtained. The study was approved by the Ethical Committee (Region Zealand) and conducted in accordance with the Declaration of Helsinki protocols.

Xenograft transplantation

Each keratome skin biopsy (approximately 5 × 5 × 0.05 cm, containing both epidermis and dermis), taken from the lateral side of the thigh or the upper arm, was cut into smaller grafts (~2 cm^2) before transplantation onto the back of C.B-17 severe combined immunodeficient (SCID) mice (female, 6–8 weeks of age, M&B Taconic, Silkeborg, Denmark) as previously described (17–19). After a healing period of approximately 10 days, the mice were divided randomly into 3 separate treatment groups. Group 1 was treated with Debio 0932 (80 mg/kg, per os [p.o.] once daily for 3 weeks, 4 grafts per biopsy), group 2 was treated with vehicle (5% Kleptose HPB® [Oral grade, Roquette Pharma, Lestrem, France] in deionised water, pH 4.5, p.o. once daily for 3 weeks, 2 grafts per biopsy) and group 3 served as untreated control (2 grafts per biopsy). Throughout the study, vehicle-treated mice appeared identical to untreated mice, thus these animals were grouped together and named negative control. The mice were kept under pathogen-free conditions throughout the study. Animal studies were carried out with permission from the Danish Animal Experiments Inspectorate.

Xenograft evaluation

Twice weekly during treatment, psoriasis severity was assessed clinically, in the human psoriatic skin grafts, in a blinded manner, and given a semi-quantitative clinical psoriasis score according to the clinical signs: scaliness, induration and erythema as previously described (17–19). After 3 weeks of treatment and approximately 30 min after the last p.o. dosing, retro-orbital blood samples were collected in lithium-heparin containing tubes. The mice were killed and 4 mm size punch biopsies were taken centrally from each human psoriatic skin graft and fixed in formalin; the remaining skin graft was collected and snap-frozen in liquid N_2. Blood samples were centrifuged at 1,000 g for 10 min to obtain plasma. The concentration of Debio 0932 in blood plasma and snap-frozen skin was measured by liquid chromatography-tandem mass spectrometry LC-MS/MS. The 4 mm size punch biopsies were embedded in paraffin and on 5 equally distant cut haematoxylin/eosin (HE) stained sections the following parameters were assessed: 1) epidermal thickness, 2) psoriasis pattern, 3) parakeratosis, 4) granulocyte presence, 5) vessel occurrence and 6) lymphocyte infiltration. Epidermal thickness, an accepted end point for measuring psoriasis severity, was measured as an average of 15–20 random measurements of the distance from the stratum corneum to the deepest part of the rete pegs employing LEICA IM50 software, version 4.0. Psoriasis pattern, parakeratosis, granulocyte presence, vessel occurrence and lymphocyte infiltration were evaluated and given scores in the range 0–4 where 0 denotes no psoriasis and 4 denotes full-fledged psoriasis. The psoriasis pattern score gives an overall assessment of the psoriatic phenotype observed in the HE stained sections and sums up the results of the epidermal thickness measure and the parakeratosis, the granulocytes presence, the vessel occurrence, and the lymphocyte infiltration scores. All sections were blinded before evaluation and were evaluated randomly.

Statistical analyses

Student's *t*-test was used to test for differences between treatment groups in epidermal thickness. The non-parametric Mann–Whitney test was used to test for differences between treatment groups in semi-quantitative clinical psoriasis, psoriasis pattern, parakeratosis, granulocyte, vessel and lymphocyte scores. Observations made for different mice were assumed to be independent of each other. All tests were two-sided, and p-values < 0.05 were considered significant.

RESULTS

In a xenograft transplantation model human psoriatic skin from 5 psoriasis patients was transplanted onto SCID mice and the mice treated once daily for 3 weeks with Debio 0932 or vehicle, or left untreated (Fig. S1A[1]).

On the last day of treatment, murine blood samples and biopsies from the xenografted skin were collected 30 min after the last dosing, and the concentration of Debio 0932 in plasma and skin samples was measured by LC-MS/MS (5 patients, 19 mice). Mean levels of 995 ± 381 ng/ml (2.25 ± 0.86 µM) and 10,786 ± 3,369 ng/g wet tissue (24.4 ± 7.61 nmol/g) were measured in plasma and skin, respectively (Fig. S1B[1]). Debio 0932 treatment did not affect the well-being of the animals as shown by behavioural patterns and weight gain over the 3-week treatment period (data not shown).

During treatment, psoriasis severity in the xenografted skin was evaluated microscopically twice weekly and given a semi-quantitative psoriasis score based on the degree of scaliness, induration and erythema (Fig. 1A, B). Debio 0932 significantly reduced the psoriasis score by day 11 and onwards; by 3 weeks of treatment the mean ± SD score in the treated group was 1.1 ± 0.2 compared to 2.3 ± 0.3 in the negative control treated group; $p < 0.001$. After completion of the treatment, biopsies from the xenografted skin were analyzed. Debio 0932 significantly decreased the mean ± SD epidermal thickness of the grafted skin (252 ± 46 µm in the treated group compared to 356 ± 52 µm in the negative control treated group ($p = 0.005$, Fig. 1C, D).

The following additional characteristics of psoriasis were also evaluated in the HE stained sections: psoriasis pattern, i.e. the overall histological pathological phenotype of the psoriatic skin (Fig. 2A), parakeratosis,

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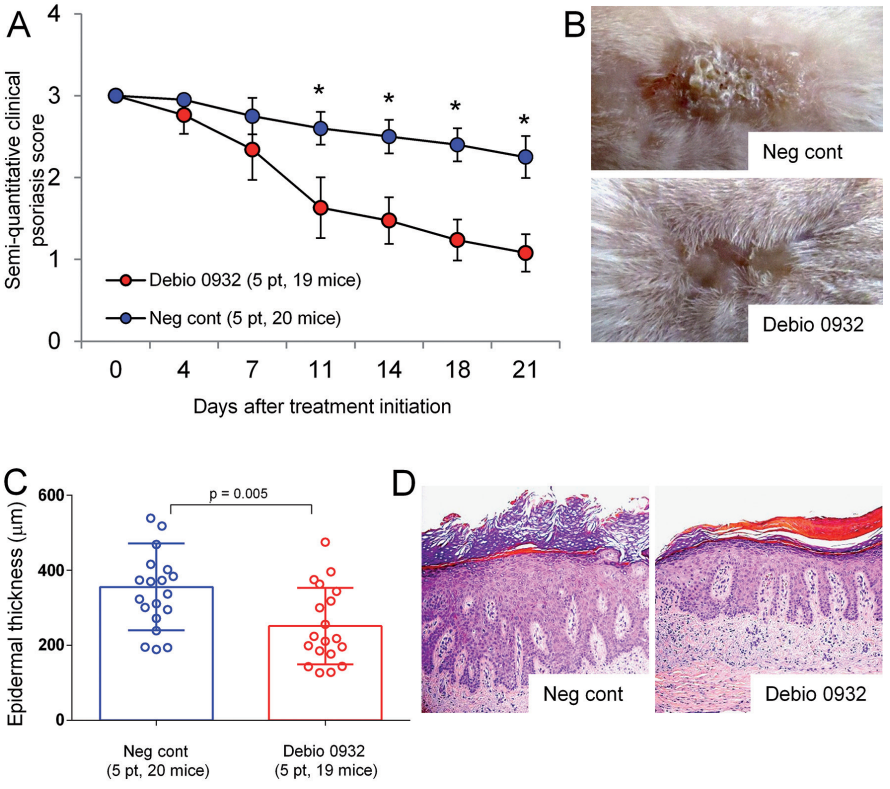

Fig. 1. Effect of Debio 0932 on semi-quantitative clinical psoriasis score and epidermal thickness of xenografted psoriasis skin. (A) Skin was assessed twice weekly, and given a semi-quantitative clinical psoriasis score. Debio 0932 treatment significantly reduced the semi-quantitative clinical psoriasis score as compared with negative control (Neg cont). From day 11 and onwards. Shown is mean ± SEM. *$p < 0.001$. (B) Representative clinical appearances are shown. (C) After 3 weeks of treatment, biopsies from the xenografted psoriasis skin were paraffin-embedded and epidermal thickness was measured on sections stained with haematoxylin/eosin (HE). Treatment with Debio 0932 significantly reduced the epidermal thickness as compared with negative control (Neg cont). Shown are each graft value and mean ± SD. (D) Representative histology of HE-stained sections are shown.

i.e. the retention of nuclei in the stratum corneum due to the increased turnover and perturbed differentiation of the keratinocytes in psoriasis (Fig. 2B), granulocytes i.e. granulocyte infiltration in the stratum corneum (Fig. 2C), vessel occurrence, i.e. vascularisation in the dermal compartment (Fig. 2D) and lymphocyte infiltration, i.e. lymphocyte infiltration into both the epidermal and dermal compartment (Fig. 2E). Debio 0932 significantly improved the mean pathological psoriasis pattern in the histological sections (psoriasis pattern score, 1.5 ± 0.3 in the treated group compared to 2.3 ± 0.5 in the negative control treated group ($p = 0.006$) and decreased the degree of vascularisation in the dermal compartment (vessel score, 2.1 ± 0.3 in the treated group compared to 2.6 ± 0.4 in the negative control treated group ($p = 0.049$).

DISCUSSION

Hsp90 inhibitors have attracted great interest over the past 20 years due to their promising therapeutic effect in targeting cancer. The nature of their effect is likely to be broad due to the role of Hsp90 in supporting multiple cellular client proteins that are critical to tumour proliferation and survival. Hsp90 is ubiquitously expressed and the 2 major isoforms Hsp90α/β may constitute 1–3% of the cellular proteins. Hsp90 inhibitors bind to the ATP binding "pocket" of Hsp90, impairing its chaperone activity, leading to degradation of its client proteins (20). Many of the Hsp90 client proteins play important roles in psoriasis; however, a possible therapeutic utility of Hsp90 inhibition in psoriasis has never been reported.

The psoriasis xenograft transplantation model is widely accepted in research on the psoriasis pathogenesis and has been extensively employed to screen new therapeutics with potential anti-psoriatic effect (21, 22). Well-known and clinically established anti-psoriatic therapeutics have confirmed the validity and predictability of the model (for review see supplementary table 1 and table 2 in (23)). In our hands, known anti-psoriatic drugs such as cyclosporin A (CsA, (23)) and efalizumab (anti-CD11a, (18)), as well as new potential drugs such as anti-IL-20 (19), and LtxA (18) have shown significant effects in this model.

Daily oral dosing of Debio 0932 (80 mg/kg) of the xenotransplanted psoriasis mice lead to plasma levels of ~2 µM and skin levels of ~24 pmol/mg of wet tissue, 30 min post-dosing, on the last day of treatment. Assuming that 1 g of tissue equals 1 ml biological fluid and taking into account the free (unbound) plasma fraction of Debio 0932 (6%, unpublished data, Debiopharm), and if the free drug concentration is similar in plasma and skin, the anticipated free Debio 0932 concentrations should be ~0.1 µM in plasma and ~1 µM in skin. The concentration in skin thus exceeds IC50 of Debio 0932 for Hsp90α/β (IC50 ~0.1 µM) by an order of magnitude establishing a realistic ground to investigate the effect of Debio 0932.

Debio 0932 alleviated psoriatic lesions in the psoriasis xenograft transplantation model as measured

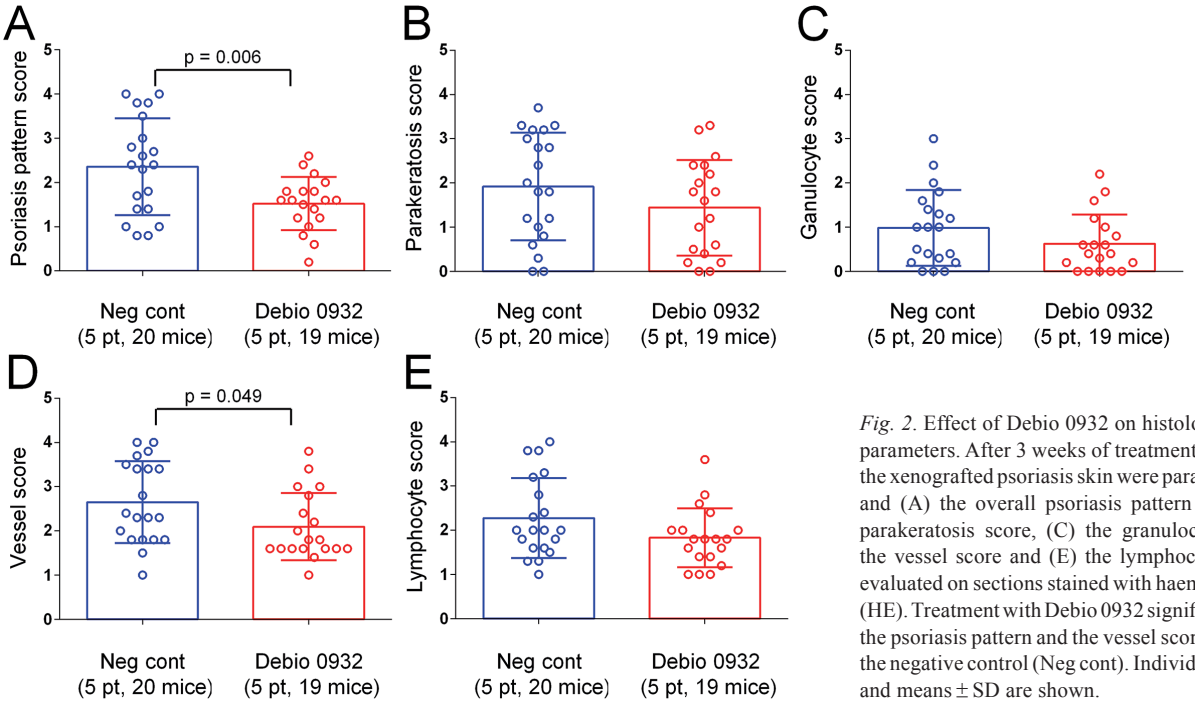

Fig. 2. Effect of Debio 0932 on histological psoriasis parameters. After 3 weeks of treatment, biopsies from the xenografted psoriasis skin were paraffin-embedded and (A) the overall psoriasis pattern score, (B) the parakeratosis score, (C) the granulocyte score, (D) the vessel score and (E) the lymphocyte score were evaluated on sections stained with haematoxylin/eosin (HE). Treatment with Debio 0932 significantly reduced the psoriasis pattern and the vessel scores compared to the negative control (Neg cont). Individual graft values and means ± SD are shown.

both clinically by a reduction in the semi-quantitative clinical psoriasis score and histologically by a reduction in epidermal thickness. A reduction of about 29% in epidermal thickness was observed during daily Debio 0932 treatment. This data underlines the efficacy of Debio 0932 treatment as compared with the well-known drug CsA that resulted in an approximately 20% reduction in epidermal thickness after 3 weeks daily treatment (19). Additional histological parameters (psoriasis pattern, parakeratosis, granulocyte presence, vessel occurrence and lymphocyte infiltration) were affected by Debio 0932 treatment, albeit only to a significant degree for psoriasis pattern and vessel occurrence.

The favourable effect of Debio 0932 on psoriasis in this study might occur through a regulation of the IL-23/IL-17 pathway which is linked to psoriasis induction and progression (24). The inflammation observed in psoriatic skin is characterised by an increased expression of pro-inflammatory cytokines such as IL-1β, IL-12 and IL-23 that promote development of Th1 and Th17 cells and subsequent downstream secretion of IFNγ, IL-6, TNFα, and IL-17A. Several key molecules involved in the signal transduction cascades, employed by the pro-inflammatory cytokines, are client proteins of Hsp90. For example, IL-1β signalling is dependent upon transforming growth factor beta-activated kinase 1 (TAK1) and IKK (25). IL-12, IL-23 and IFNγ signalling is dependent upon the JAK/STAT pathway where both JAK1, JAK2 (26), STAT1 (27) and STAT3 (28) have been shown to be client proteins of Hsp90. Moreover, Hsp90 inhibition has been shown to down-regulate phosphorylated STAT3 (29). IL-6 signalling is not only dependent upon the JAK/STAT pathway but also the MAP kinase pathway where Raf and its substrate MEK have been shown to be client proteins of Hsp90 (30, 31). TNFα signalling activates NF-$_{K}$B where the indispensable kinase receptor interacting protein (RIP) is a client protein of Hsp90 (32) and IL-17A signalling requires Act1, which is a client protein of Hsp90 (10).

Further knowledge on Hsp90 expression levels and activity, depending upon post-translational modifications that modify client affinity, ATPase activity and/or co-chaperone association, in psoriatic skin is needed. Hsp90 inhibition may affect multiple signalling pathways in psoriasis leading to a more beneficial treatment of the disease, and a broader clinical advantage, as opposed to targeting a single pathway that may be overruled by compensatory activation of alternative pathways.

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Conflicts of interest. KS and CR state no conflict of interest. BG and GV are employed and TND is a consultant at Debiopharm International S.A. Debiopharm International S.A. provided the drug Debio 0932.

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