CT327, A NOVEL THERAPEUTIC AGENT FOR TOPICAL TREATMENT OF PSORIASIS

Barone Domenico, Bertarione Rava Rossa Luisa, Traversa Silvio, Mainero Valentina, Oderda Cecilia, Pincelli Carlo*, Marconi Alessandra*, and Fumero Silvano

Creabilis therapeutics SpA, Via Ribes, 5 – 10010 Colleretto Giacosa (TO), Italy
*University of Modena e Reggio Emilia, Via del Pozzo, 71 – 41100 Modena, Italy

Introduction – Synthesised and released by human keratinocytes (KCs), NGF induces their proliferation by acting with an autocrine/paracrine mechanism and seems to play a pivotal role in epidermis homeostasis. NGF levels are increased in psoriatric skin as compared to normal skin. Psoriatric KCs express higher amounts of NGF than normal ones and its high affinity receptor (TrkA) is expressed not only in the basal epidermal layer as in normal skin, but in the full thickness of psoriatic skin. The alkaloid K-252a, a potent inhibitor of TrkA phosphorylation, blocks NGF-induced KC proliferation *in vitro* and improves psoriatic plaques in a SCID mouse-human skin model of psoriasis. CT327, a mini-PEGylated K-252a derivative specifically designed for the topical treatment of psoriais – a therapeutic area which has seen no innovative treatment for several years - has been selected and developed. The main purpose was to obtain a molecule able to maintain the ability to enter KC and exploit its biological effect on TrkA, but with better PK (reduced systemic absorption) and safety/toxicology profiles than K-252a which, being a highly lipophilic and extremely non-selective molecule on phosphokinases, is unlikely to become a drug. **Materials and methods –** CT327 was obtained by conjugating K-252a to a 2 kD linear methoxy-polyethylene glycol chain via a stable carbamate bond. CT327 was characterized in terms of in vitro antiproliferative activity, kinase selectivity, PK, safety and toxicity profiles. **Results –** CT327 met all the targets set: it is highly soluble and biologically stable, inhibits human KC proliferation, greatly improves kinase selectivity (IC_{50} on TrKA = 186 nM), its absorption after dermal administration is extremely low and its renal clearance very rapid, it is non-irritant and non-mutagenic, as well as having a very favourable toxicology profile - no toxicology findings after 14 days in rodents (i.v. and dermal) or 28 days in rabbits (dermal). In Irwin test and HERG assay CT327 was very well tolerated. **Discussion and conclusion –** CT327 is neither a pro-drug, nor a drug delivery system, but a true novel chemical entity providing a successful way to improve the physicochemical features, PK/PD performance, kinase selectivity and, finally, the overall safety/toxicology profile of K-252a, while retaining its ability to enter the cells, bind TrkA and inhibit KC proliferation. All these characteristics are ideal for a drug to be used in topical treatment of psoriasis. CTA/IND filing and the subsequent Phase I study are planned in the second quarter of 2007.