Development and Phase 1 Clinical Results for BA058-coated Microneedles for the Treatment of Osteoporosis

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ABSTRACT SUMMARY
Polymeric microneedle patches were coated with BA058, a novel analogue of hPTHrP (1-34), developed for the treatment of osteoporosis. The coated microneedles (solid Microstructured Transdermal System, sMTS) were characterized in vivo and then utilized in a series of Phase 1 clinical trials designed to characterize product safety, tolerability and pharmacokinetics and to identify optimal wear time and application site. Over 500 applications of the coated microneedles were made in humans. The BA058 microneedle product demonstrated suitable safety and performance profiles and is proceeding through Phase II clinical evaluation.

INTRODUCTION
Effecting over 10 million Americans, osteoporosis is a disease characterized by loss of bone mass, deterioration of bone micro-architecture and reduced bone quality, leading to an increased risk of fractures. Research suggests that half of all women and up to 25% of all men over the age of 50 will break a bone due to osteoporosis. Experts estimate that yearly healthcare costs associated with osteoporosis will top $25 billion by 2025 (1).

BA058 is a synthetic analogue of the first 34 amino acids of human parathyroid hormone related peptide (hPTHrP) being developed as a novel treatment for osteoporosis in postmenopausal women. BA058 stimulates reversal of bone loss by building new bone. Upon daily injection, BA058 has demonstrated safety and bone efficacy in completed Phase I and II clinical trials and is currently in evaluation in a Phase III fracture prevention study (2).

BA058-sMTS have been evaluated previously for in vivo release (swine) and for PK, PD and tolerability endpoints (rats and monkeys) and have been reported elsewhere (8).

EXPERIMENTAL METHODS
Separate lots of BA058-sMTS clinical supplies were manufactured in an isolator in a pilot manufacturing facility; components were sterilized by gamma irradiation prior to being introduced into the isolator. BA058-sMTS placebos were manufactured along with BA058-sMTS patches using a precision coating process that confines the drug formulation to the top 30-50% of each structure. Details of the coating process are available elsewhere (9). The supplies were packaged individually, in foil pouches, and characterized for drug content and impurity level prior to clinical release.

Three Phase 1 clinical trials were conducted in the US and Canada. The study population was comprised of 128 healthy, post-menopausal women, 50-80 years old, with a BMI of 18.5-32. Over the course of these studies, over 500 BA058-sMTS patch applications were completed by clinicians. Patch wear times ranged from 10 seconds to 24 hours.

After application, blood samples were collected over a 15 day period to evaluate the PK of BA058-sMTS and BA058 administered by a standard pen injector. A subset of subjects received repeat-daily administration of the BA058-sMTS patch over a 7 day period so that PD endpoints could be evaluated. The AUC and the Cmax were evaluated across the spectrum of experimental wear times (10 seconds-24 hours) to determine if delivery/absorption changed with respect to exposure to the microneedle array. The application site was examined by clinicians and evaluated for erythema, edema or any other dermal abnormalities. Used patches were also evaluated microscopically to determine if any microneedles were fractured or broken during application or wear.

Although a popular delivery choice of patients (3), up until recently, transdermal delivery technologies have not been applied to biopharmaceuticals. These large, water soluble molecules cannot penetrate the stratum corneum unassisted. Microneedle-based drug delivery devices provide a means of overcoming this barrier while still preserving the “patch” delivery system that patients prefer (4).

Research suggests that for chronic diseases such as osteoporosis, a significant proportion of non-compliance by patients is linked to needle phobia or a dislike of needles. Microneedle-based delivery systems are perceived as less threatening and less invasive than traditional needles and thus may provide a means of significantly improving patient compliance.

Microneedles coated with drug can be inserted into the dermis where the drug is quickly and efficiently delivered into the skin. The dense and active microvasculature in the dermis provides rapid absorption to the systemic circulation. These delivery characteristics are especially ideal when rapid absorption of the drug is desired to enhance the therapeutic profile; this is true for BA05 and other PTH/PTHrP related molecules where intermittent pulsatile exposure achieves maximum bone anabolic efficacy (5-7).

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RESULTS AND DISCUSSION

Pharmacokinetics
The PK profile following administration of the BA058-sMTS patch demonstrated rapid release and fast absorption of the drug. The Tmax for patch recipients was at 10 minutes compared to 29 minutes for SC administration. The half life measured in the BA058-sMTS subjects was significantly shorter than in subjects administered BA058 by injection (12-26 minutes versus 49 minutes). The observed rapid absorption (early Tmax) is characteristic of intradermal delivery of biologics (10, 11).

Patch Wear Time
Comparison of the AUC and Cmax across subjects exposed to the BA058-sMTS patches for 10 seconds to 24 hours indicates the delivery from the needles and absorption of the drug occurs very rapidly. No statistically significant differences in either AUC or Cmax were observed between 30 seconds and 24 hours; the 10 second wear time resulted in incomplete delivery.

Pharmacodynamics
In the subsection of patients that received the 7 day repeat dose of BA058-sMTS, a rapid rise in P1NP (% change from baseline), a biomarker for bone formation, was observed, consistent with historical data collected for BA058 administered by injection. Both populations were different from the placebo control demonstrating that the BA058 delivered off of the microneedles is active.

Safety and Tolerability
The BA058-sMTS administration was generally well tolerated amongst all subjects. No significant adverse events occurred and clinical results were unremarkable. Mild erythema and swelling were the most commonly observed effects associated with the patch but all resolved within 24 hours post-dose. There was no increase in dermal response after repeat patch application. Microscopic analysis of used patches showed no chip or breakages of the microneedles.

CONCLUSION
Several doses of BA058-sMTS, a coated microneedle product were developed and characterized for use in several Phase 1 studies. Administration of BA058 via the microneedle patch resulted in fast delivery, rapid systemic absorption of the drug and evidence of biologic activity. The patch performance, PK, safety and tolerability of the BA058-sMTS was acceptable to move forward into Phase 2 clinical evaluations which are currently underway.

REFERENCES