



## **Capsitonin Oral Calcitonin - Synopsis of First in Man Study**

Eight (8) subjects, all healthy post-menopausal females, were given three comparative treatments of salmon calcitonin.

The study was open label and sequential meaning that each subject received the same treatments and each was given the treatments in the same order; there was no blinding in the study, the parameters being examined in the study were derived from blood and subjective bias in the data collected was thus minimised.

The first treatment was Miacalcin<sup>®</sup> Nasal Spray (200 I.U. of salmon calcitonin per 0.09 ml activation), which because of the difficulty experienced by subjects in using the nasal device, was administered by the study nurse. This product was included to provide guidance for future dosing and bioequivalence studies.

The second treatment was BN002 Investigational Medical Product, containing 1250 I.U salmon calcitonin in an oral tablet dose form.

The third treatment was BN002 Investigational Medical Product, containing 2500 I.U salmon calcitonin in an oral tablet dose form.

After administration the subjects were kept in the hospital for 24 hours, while blood tests and monitoring were performed. There was a 48 hour washout period between doses.

The blood tests were taken and measured for the following:

- Serum calcitonin levels;
- Serum C-telopeptide fragment of type 1 collagen (CTX); and
- Blood calcium levels

The study sought to answer the following questions in the form of primary and secondary endpoints:

- Determination of whether BN002 delivered bioavailable / biologically active calcitonin or not;
- Determination of the safety & tolerability of BN002; and
- Determination of the biological effect of BN002 doses on calcium levels and CTX.

The conclusions of the study are as follows:

- BN002 shows evidence of bioavailability & is biologically active in humans;
- The changes in CTX levels in all treatment arms were significant when compared to baseline ( $P < 0.001$ ) and historical control responses of 15% ( $P < 0.001$ ) and 20% ( $P < 0.03$ ),

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**ATTACHMENT 5**

- The CTX changes were not directly comparable to the nasal formulation because of the time variation in response (320 mins was the end of frequent sampling for efficacy tests).
- Time to response between subjects appears to vary with BN002 as shown in the following table:

	<b>Mean Time to Peak CTX Reduction</b>	<b>Range of time-responses</b>	<b>Mode</b>
<b>Nasal Calcitonin</b>	144 minutes	110-170	170
<b>BN002 1250iu</b>	470 minutes	170-720	720
<b>BN002 2500iu</b>	426 minutes	110-720	290/720

Excludes non responders                      **All times in Minutes**

- BN002 appears to be safe & well tolerated;
- The biological effect of oral BN002 appears to be delayed when compared to the nasal formulation;
- The impact of 1250iu & 2500iu of BN002 on CTX levels appeared to be similar throughout the study;
- The duration of frequent blood sampling may have been inadequate to clearly demonstrate the efficacy of BN002 against the active comparator;
- The timing of response (particularly of CTX) in the study to BN002 may be predicted to have been beyond the “frequent blood sampling” period, meaning that the study may not predict the true efficacy of BN002;
- Because of the limitations of the study, exact bio-equivalence between the comparator and the BN002 doses was not able to be calculated; and
- Calcitonin was measurable in a minority of patients in each of the study arm