



CCZ EQUITIES RESEARCH

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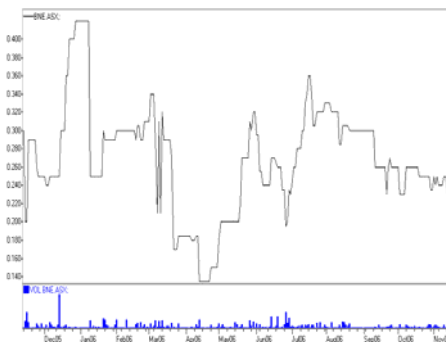
**Recommendation: Buy**

**Valuation: \$0.43**

#### COMPANY DATA

|                       |               |
|-----------------------|---------------|
| SHARE PRICE           | \$0.24        |
| 52-WEEK RANGE         | \$0.14-\$0.42 |
| SHARES ON ISSUE (F/D) | 74.3M         |
| MARKET CAPITALISATION | \$17.8M       |
| DEBT/TOTAL CAP        | n/a           |
| DIVIDEND YIELD        | n/a           |
| CASH POSITION         | \$1.3M        |

#### 12 MONTHS PRICE CHART WITH TRADING VOLUMES



#### BOARD MEMBERS

Paul Hopper (Executive Chairman)  
Dr Roger New (Executive Director)  
Leon Ivory (Non-executive Director)  
Dr Barry Walker (Non-executive Director)

We are initiating coverage on **Bone Medical Limited** (BNE or Bone) with a **BUY recommendation** and a valuation of **43 cents per share**. Bone is a biotechnology company focused on the development of treatments for bone and joint disorders such as osteoporosis, osteoarthritis and rheumatoid arthritis. BNE's drug candidates have been developed using its in-licensed oral delivery technology, Axxess™ and drug discovery technology Mozaic™.

Bone's first two drug candidates are **Capsitonin™**, an oral formulation of calcitonin, and **Perthoxal™**, an oral formulation of parathyroid hormone. Injectable forms of these compounds have already been approved for the treatment of osteoporosis and both compounds have established safety profiles.

#### KEY POINTS

- **Oral formulations of existing drugs** Bone's strategy of developing oral formulations for currently approved injectable drugs is a low risk one which is also expected to yield early regulatory approval due to already available safety and tolerability data.
- **Established safety profiles of excipients** Bone uses the Axxess™ oral delivery technology for Capsitonin™ and Perthoxal™. The absorption-enhancing capability of the Axxess™ technology is based on a combination of pharmaceutical excipients that are approved for human medicinal use already and have well established safety and tolerability profiles.
- **Two lead candidates in clinical trials** Both Capsitonin™ and Perthoxal™ are in clinical trials to evaluate safety and tolerability and to provide early bioequivalence data. The Perthoxal™ trial is expected to be completed by the end of 2006 and the Capsitonin™ trial is planned for early 2007. Licensing of these products is likely in 2008 subject to positive trial results.

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## INVESTMENT HIGHLIGHTS

**No new chemical entity, no molecular risk for lead products** Bone's two lead products are oral formulations of existing therapies in the treatment of bone and musculoskeletal conditions and therefore there is no molecular risk with its product candidates. Calcitonin, as an injectible, has been used for the treatment of osteoporosis for 30 years. The use of parathyroid hormone to treat severe cases of osteoporosis is more recent, however bone building properties of parathyroid hormone have been known for over seventy years.

**No other oral formulation on the market** Bone develops oral formulations for existing treatments where the only other alternatives are injectible or nasal spray forms. There is a clear patient preference to deliver drugs orally rather than via injection. Delivery by nasal spray can be inaccurate, particularly in children, and ineffective in people with respiratory tract infections or hyper-sensitivity. Oral formulations provide ease and accuracy in administering therapeutic agents. It is expected that oral formulations of therapeutic peptides would replace a large percentage of their injectible forms.

**Two lead candidates in phase Ib/IIa clinical trials** Bone's two lead candidate drugs, Capsitonin™ and Perthoxal™, are currently in clinical trials to determine optimum formulation and bioequivalence. It is expected that these trials will be completed in early 2007. Positive results would mean early IND<sup>1</sup> application.

**Fast track to regulatory approval is possible** Since the introduction of section 505(b)(2) in 1984 the Food and Drug Administration (FDA) can fast track applications in which the applicant (sponsor) may not have conducted all of the trials otherwise required, but is able to use published literature or previous approval by the FDA in relation to a particular therapeutic agent. Since calcitonin has been an FDA approved treatment for osteoporosis for over 30 years Bone plans to apply for approval for its oral formulations after establishing bioequivalence and local tolerability, and is unlikely to have to undertake the full phase III trials required for a novel osteoporosis drug.

**Billion dollar markets** The annual spending on various treatments of osteoporosis is estimated to be around US\$40 billion in North America and Europe alone, with over 200 million women suffering from the condition. Injectible and nasal calcitonin sales total around US\$700 million annually; a number which could potentially be higher if an oral formulation would become available. Current annual spending on injectible parathyroid hormone is around US\$560 million.

**Upside potential in osteoarthritis** Research published in 2005 from early clinical trials indicated potential for calcitonin for the treatment of osteoarthritis. Osteoarthritis is the most common form of arthritis and should these initial results be supported by further clinical data, the market potential and value for calcitonin-based products, particularly oral calcitonin, may increase significantly.

## INVESTMENT RISKS

**Relying on external contractors** Like most other biotechnology companies Bone uses external service providers for its pre-clinical and clinical trials, licensing discussions and regulatory work. Members of the board, in particular Executive Chairman Mr Paul Hopper, are looking after the coordination. While this structure is cost effective and has been useful so far to deliver results at a relatively low cost, a formal senior management team may become necessary in the future to achieve the Company's clinical and commercial objectives.

**Competition from other delivery systems** Bone will not only face competition from companies like Emisphere and Unigene with oral products in development, but it will also have to compete with transdermal (through the skin) and nasal delivery methods for its target peptides as well as other forms of treatments for the same conditions.

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<sup>1</sup> Investigational New Drug: FDA exemption from application for marketing approval for clinical trials

## VALUATION

**Bone is currently trading at a 40% discount to our rDCF valuation of 43 cents per share**

We have valued Bone at **43 cents per share** using the rDCF method looking at three of its most advanced drug candidates; Capsitonin™, Perthoxal™ and BN006. Table 1 provides a summary of our key valuation assumptions.

**TABLE 1 - KEY VALUATION ASSUMPTIONS**

| Drug Candidate | Market size (A\$M) | Product launch Year | Peak market share           | Market growth rate % | Royalty | Probability of success |
|----------------|--------------------|---------------------|-----------------------------|----------------------|---------|------------------------|
| Capsitonin™™   | 600 <sup>2</sup>   | 2010                | 60% of non-nasal calcitonin | 0%                   | 6%      | 30%                    |
| Perthoxal™™    | 725 <sup>3</sup>   | 2011                | 30%                         | 7.5%                 | 7%      | 30%                    |
| BN006          | 3,300              | 2013                | 10%                         | 2%                   | 7%      | 10%                    |

**TABLE 2 – VALUATION**

| Year to June                              | 2006        | 2007       | 2008       | 2009        | 2010       | 2011        | 2012        | 2013        | 2014        | 2015        | 2016        | 2017        | 2018        | 2019        | 2020        |             |
|---|-------------|------------|------------|-------------|------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| <b>REVENUE (A\$M)</b>                     |             |            |            |             |            |             |             |             |             |             |             |             |             |             |             |             |
| <b>1. Capsitonin</b>                      |             |            |            |             |            |             |             |             |             |             |             |             |             |             |             |             |
| Calcitonin market for osteoporosis        | 600         | 600        | 600        | 600         | 600        | 600         | 600         | 600         | 600         | 600         | 600         | 600         | 600         | 600         | 600         |             |
| Market penetration %                      | 0%          | 0%         | 0%         | 0%          | 30%        | 40%         | 50%         | 60%         | 60%         | 60%         | 60%         | 60%         | 60%         | 50%         | 40%         |             |
| Capsitonin sales                          | -           | -          | -          | -           | 180.0      | 240.0       | 300.0       | 360.0       | 360.0       | 360.0       | 360.0       | 360.0       | 360.0       | 300.0       | 240.0       |             |
| Adj for probability of success (30%)      | -           | -          | -          | -           | 54.0       | 72.0        | 90.0        | 108.0       | 108.0       | 108.0       | 108.0       | 108.0       | 108.0       | 90.0        | 72.0        |             |
| Licensing revenue (35% probability)       | -           | -          | -          | 7.0         | 3.5        | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           |             |
| Royalty @ 6%                              | -           | -          | -          | -           | 3.2        | 4.3         | 5.4         | 6.5         | 6.5         | 6.5         | 6.5         | 6.5         | 6.5         | 5.4         | 4.3         |             |
| <b>Revenue</b>                            | -           | -          | -          | <b>7.0</b>  | <b>6.7</b> | <b>4.3</b>  | <b>5.4</b>  | <b>6.5</b>  | <b>6.5</b>  | <b>6.5</b>  | <b>6.5</b>  | <b>6.5</b>  | <b>6.5</b>  | <b>5.4</b>  | <b>4.3</b>  |             |
| <b>2. Perthoxal</b>                       |             |            |            |             |            |             |             |             |             |             |             |             |             |             |             |             |
| Injectible PTH market                     | 725         | 779        | 838        | 901         | 968        | 1,041       | 1,119       | 1,203       | 1,293       | 1,390       | 1,494       | 1,606       | 1,727       | 1,856       | 1,996       |             |
| Market growth                             | 7.5%        | 7.5%       | 7.5%       | 7.5%        | 7.5%       | 7.5%        | 7.5%        | 7.5%        | 7.5%        | 7.5%        | 7.5%        | 7.5%        | 7.5%        | 7.5%        | 7.5%        |             |
| Market penetration                        | -           | -          | -          | -           | -          | 20%         | 25%         | 25%         | 25%         | 25%         | 25%         | 25%         | 25%         | 25%         | 25%         |             |
| Perthoxal sales                           | -           | -          | -          | -           | -          | 208.2       | 279.7       | 300.7       | 323.3       | 347.5       | 373.6       | 401.6       | 431.7       | 464.1       | 498.9       |             |
| Adj for probability of success (30%)      | -           | -          | -          | -           | -          | 62.4        | 83.9        | 90.2        | 97.0        | 104.2       | 112.1       | 120.5       | 129.5       | 139.2       | 149.7       |             |
| Licensing revenue (35% probability)       | -           | -          | -          | 10.5        | 7.0        | 7.0         | -           | -           | -           | -           | -           | -           | -           | -           | -           |             |
| Royalty @ 7%                              | -           | -          | -          | -           | 4.4        | 5.9         | 6.3         | 6.8         | 7.3         | 7.8         | 8.4         | 9.1         | 9.7         | 10.5        |             |             |
| <b>Revenue</b>                            | -           | -          | -          | <b>10.5</b> | <b>7.0</b> | <b>11.4</b> | <b>5.9</b>  | <b>6.3</b>  | <b>6.8</b>  | <b>7.3</b>  | <b>7.8</b>  | <b>8.4</b>  | <b>9.1</b>  | <b>9.7</b>  | <b>10.5</b> |             |
| <b>3. BN006</b>                           |             |            |            |             |            |             |             |             |             |             |             |             |             |             |             |             |
| Market for anti TNF                       | 3,300       | 3,366      | 3,433      | 3,502       | 3,572      | 3,643       | 3,716       | 3,791       | 3,866       | 3,944       | 4,023       | 4,103       | 4,185       | 4,269       | 4,354       |             |
| Market growth                             | 2%          | 2%         | 2%         | 2%          | 2%         | 2%          | 2%          | 2%          | 2%          | 2%          | 2%          | 2%          | 2%          | 2%          | 2%          |             |
| Market penetration                        | -           | -          | -          | -           | -          | -           | -           | 5%          | 10%         | 10%         | 10%         | 10%         | 10%         | 10%         | 10%         |             |
| BN006 sales                               | -           | -          | -          | -           | -          | -           | -           | 189.5       | 386.6       | 394.4       | 402.3       | 410.3       | 418.5       | 426.9       | 435.4       |             |
| Adj for probability of success (10%)      | -           | -          | -          | -           | -          | -           | -           | 9.5         | 19.3        | 19.7        | 20.1        | 20.5        | 20.9        | 21.3        | 21.8        |             |
| Licensing revenue (15% probability)       | -           | -          | -          | -           | 4.5        | 1.5         | 1.5         | 1.5         | -           | -           | -           | -           | -           | -           | -           |             |
| Royalty 7%                                | -           | -          | -          | -           | -          | -           | -           | 0.7         | 1.4         | 1.4         | 1.4         | 1.4         | 1.5         | 1.5         | 1.5         |             |
| <b>Revenue</b>                            | -           | -          | -          | -           | -          | <b>4.5</b>  | <b>1.5</b>  | <b>2.2</b>  | <b>2.9</b>  | <b>1.4</b>  | <b>1.4</b>  | <b>1.4</b>  | <b>1.5</b>  | <b>1.5</b>  | <b>1.5</b>  |             |
| <b>EXPENSES (A\$M)</b>                    |             |            |            |             |            |             |             |             |             |             |             |             |             |             |             |             |
| Research and Development (5% growth p     | 0.8         | 0.8        | 0.9        | 0.9         | 1.0        | 1.0         | 1.1         | 1.1         | 1.2         | 1.2         | 1.3         | 1.4         | 1.4         | 1.5         | 1.6         |             |
| Corporate overheads                       | 0.5         | 0.9        | 0.9        | 1.0         | 1.0        | 1.1         | 1.1         | 1.2         | 1.3         | 1.3         | 1.4         | 1.5         | 1.5         | 1.6         | 1.7         |             |
| <b>Total</b>                              | <b>1.3</b>  | <b>1.7</b> | <b>1.8</b> | <b>1.9</b>  | <b>2.0</b> | <b>2.1</b>  | <b>2.2</b>  | <b>2.3</b>  | <b>2.4</b>  | <b>2.6</b>  | <b>2.7</b>  | <b>2.8</b>  | <b>3.0</b>  | <b>3.1</b>  | <b>3.3</b>  |             |
| <b>Net revenue</b>                        | -           | <b>1.3</b> | -          | <b>1.7</b>  | -          | <b>1.8</b>  | <b>15.6</b> | <b>11.7</b> | <b>18.1</b> | <b>10.6</b> | <b>12.6</b> | <b>13.7</b> | <b>12.6</b> | <b>13.0</b> | <b>13.5</b> | <b>13.0</b> |
| <b>NPV (A\$M)</b>                         | <b>32.0</b> |            |            |             |            |             |             |             |             |             |             |             |             |             |             |             |
| <b>Shares on issue (M, fully diluted)</b> | <b>74.3</b> |            |            |             |            |             |             |             |             |             |             |             |             |             |             |             |
| <b>Valuation per share</b>                | <b>0.43</b> |            |            |             |            |             |             |             |             |             |             |             |             |             |             |             |

<sup>2</sup> IMS estimates the global calcitonin market for osteoporosis for 2006 as US\$437 million which converts to just under A\$600 million.

<sup>3</sup> Eli Lilly reported Forteo sales for the first nine months of 2006 as US\$422 million which represents annual sales of US\$560 million; this converts to A\$725 million.

## ORAL DELIVERY OF PEPTIDES

**Oral delivery of drugs is preferred but difficult to achieve with most peptides**

Oral delivery of therapeutic peptides has been a highly desirable yet challenging goal for bio-medical researchers for some time. Targeted at a market estimated around US\$25 billion annually oral delivery of therapeutic peptides, in most cases, is the most preferred method of drug administration as it is not only the easiest but it ensures the highest patient compliance of all delivery methods. This is particularly important when chronic diseases are treated and a particular drug has to be administered regularly over a long period of time. Most peptide drugs fall into this category.

Historically peptide drugs delivered orally showed comparatively poor plasma levels due the several barriers that they encounter in the intestinal tract. Perhaps the most important ones are the enzymatic barrier caused by proteolytic enzymes and the mucus layer covering gastrointestinal walls with transmembrane pumps providing active resistance for most peptides.

Whether a peptide can be effectively delivered orally with sufficient bioavailability is determined, besides the individual gut environment, by the peptide's solubility characteristics, its charge and size. Currently, only a few small cyclic oligo-peptides are on the market in oral formulations, including a micro-emulsion formulation of cyclosporine and desmopressin, which is in tablet form.

**Several strategies are pursued to make peptides orally available including Bone's formulation approach**

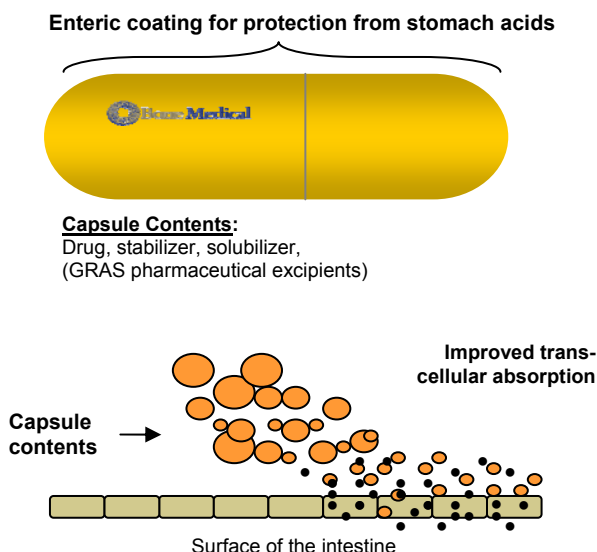
Current efforts to improve oral availability of peptide drugs include strategies such as amino acid backbone modifications, formulation approaches, chemical conjugation of hydrophobic ligand, and use of enzyme inhibitors, adhesive polymers, and absorption enhancers. Bone's in-licensed Axxcess™ technology uses a formulation approach and does not require any modification to the chemical structure of the peptide to be delivered; it contains a proprietary mixture of known pharmaceutical excipients, underpinning the potential for achieving bioavailabilities which may result in commercially viable products.

### Axxcess™ ORAL DELIVERY TECHNOLOGY

**Bone's formulation contains aromatic alcohols and solubisation aids already approved for medicinal use**

Axxcess™ is a novel combination of two known groups of pharmaceutical excipients; aromatic alcohols and solubilisation aids. These components act together enhancing absorption by altering the behaviour of intestinal cells to allow protein to cross the gut wall.

**FIGURE 1– Axxcess™ oral delivery technology**



**Bone's patents have been approved in Europe and South Africa**

Axcess™ is subject to patent applications with claims covering novel indication and pharmaceutical compositions incorporating the particular combination. Axcess™ is formulated as a dry powder in an enteric coated capsule. Capsules are simple and cost effective to manufacture while they provide added protection for the therapeutic peptides within. Approvals for granting of patents have recently been obtained for Axcess I in Europe and Axcess II in South Africa.

The Axcess™ oral delivery system does not modify the active ingredients, in Bone's case calcitonin or parathyroid hormone. The contents of the capsule are released in the jejunum in an area with neutral pH, further minimising damage to these actives.

The components of the Axcess™ oral delivery system have been approved and used in therapeutic medicine for some time. Given that the actives are also approved for the target applications this could potentially open the way for an NDA under section 505(b)(2).

## PRODUCT PORTFOLIO

Bone Medical Limited has exclusive license to three technology platforms for use in musculoskeletal conditions; Axcress™, an oral peptide delivery system, Mozaic™, a cell based drug discovery system and Vaccine™, an oral vaccination system.

**Bone's lead products are oral formulations of approved drugs calcitonin and parathyroid hormone**

Bone, using the Axcress™ technology, is currently developing oral formulations of existing treatments for bone and skeletal conditions with a particular focus on osteoporosis, where some of the leading therapeutic agents can only be delivered by nasal spray or injection, and osteoarthritis, which is a poorly-served indication. Bone's leading oral candidates (Capsitonin™ and Perthoxal™) are currently in clinical trials. Bone has used the Mozaic™ technology to identify a novel drug candidate (BN006) for down-regulation of TNF; it intends to develop this new drug in an oral formulation to treat rheumatoid arthritis. BN006 is currently in pre-clinical trials.

**Capsitonin™ and Perthoxal™ are currently in phase II clinical trials**

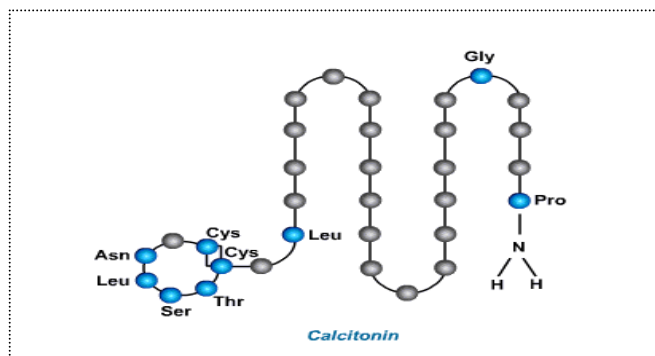
**FIGURE 2 – Product development pipeline**

| Product/Compound               | R&D  | Pre-clinical | Phase I | Phase II | Phase III | NDA |
|--------------------------------|--|--------------|---------|----------|-----------|-----|
| Capsitonin™™ (oral calcitonin) | [Progress bar showing completion through R&D, Pre-clinical, Phase I, and Phase II] |              |         |          |           |     |
| Perthoxal™™ (oral PTH)         | [Progress bar showing completion through R&D, Pre-clinical, Phase I, and Phase II] |              |         |          |           |     |
| BN007 (collagen tolerance)     | [Progress bar showing completion through R&D]                                      |              |         |          |           |     |
| BN006 (TNF down regulator)     | [Progress bar showing completion through R&D]                                      |              |         |          |           |     |
| BN008 (osteoclast regulator)   | [Progress bar showing completion through R&D]                                      |              |         |          |           |     |
| BN005 (osteoblast regulator)   | [Progress bar showing completion through R&D]                                      |              |         |          |           |     |

### Capsitonin™

Bone's most advanced product is Capsitonin™, a novel oral formulation of synthetic salmon calcitonin (STC) in tablet or capsule format. Capsitonin™ is designed to allow for protection of calcitonin from digestion in the stomach and allow its successful delivery into the gut. Calcitonin is a natural hormone first purified in 1962 by Copp and Cheney. It is produced by cells in the thyroid gland. Salmon calcitonin is a 32-amino acid peptide hormone with calcitropic activity.

**FIGURE 3 – Synthetic salmon calcitonin**



Calcitonin controls the level of calcium in the blood by decreasing calcium absorption in the intestines, decreasing osteoclast activity in bones and decreasing calcium and phosphate reabsorption by the kidney tubules, and thereby assisting the body in absorbing calcium into bones.

Human calcitonin (such as Cibacalcin™) and synthetic salmon calcitonin (such as Calcimar™), are two types of calcitonin therapy used in an injectible form to help prevent bone loss from osteoporosis, relieve bone pain after fractures, treat hyper-calcemia and Paget's disease and reduce the symptoms of lumbar canal stenosis, a painful narrowing of the spinal canal.

### Market for Capsitonin™

**Calcitonin accounts around 10% of the osteoporosis market, although sales are expected to increase with the availability of an oral formulation**

Currently the most significant market for calcitonin, and hence an oral formulation, is osteoporosis. Over 200 million women suffer from the condition worldwide and it is expected that this number will continue to increase. Up to 70% of those treated for the disease use bisphosphonates<sup>4</sup> as they contribute to greater increase in bone density than calcitonin and are available in oral form. Global sales of calcitonin for the osteoporosis market are estimated around US\$437 million in 2006, although according to Datamonitor calcitonin sales for the treatment of osteoporosis are expected to decrease by 3.2% annually due to the availability of more effective treatments.

The total annual global calcitonin market across a range of indications, including osteoporosis and Paget's disease and including injectible and nasal forms, is estimated at around US\$700 million.

However, it is important to note that when Novartis launched Miacalcin, a nasal spray calcitonin, it rapidly took 50% of the market due to its easy administration. Therefore an oral formulation could largely replace injectible forms and gain rapid growth into the US\$437 million calcitonin market for osteoporosis.

In addition, calcitonin may be approved for other indications in the future. Of particular interest is the potential for the use of calcitonin to treat osteoarthritis. Osteoarthritis is a degenerative joint disease that mainly affects the cartilage; it is associated with ageing and typically affects those joints that have been subject to continual physical stress during life, such as the knees, hips, fingers and lower spine. According to the WHO, approximately 10% of men and 18% of women over 60 have symptomatic osteoarthritis. There are no approved pharmaceutical products capable of treating the underlying causes of the disease and osteoarthritis is typically treated symptomatically. The use of calcitonin in patients suffering from osteoarthritis and related pain is now being studied by Novartis.

### Side effects of calcitonin treatment

There are no known long-term serious side effects related to any form of calcitonin therapy. Allergies to synthetic salmon calcitonin are known but they are rare.

### Competition

Currently two nasal spray forms of calcitonin are available: Miacalcin® Nasal by Novartis, Fortical® Nasal by Unigene. Although nasal formulations are generally preferred to injectible forms by patients, they are not as reliable in delivering a specific dose. One other oral calcitonin, co-developed by Novartis and Emisphere, is in development and is currently in phase II clinical trials.

### Clinical development status of Capsitonin™

In 2005 a phase Ib/IIa clinical trial has been completed on 8 postmenopausal female volunteers in an open label safety and tolerability study of Capsitonin™. Preliminary efficacy and activity was also measured. Nasal Miacalcin™ was used as active comparator against Capsitonin™, which was administered in two doses; 1,250 IU and 2,500 IU. Serum calcitonin, serum CTX<sup>5</sup> and blood calcium were used as key biomarkers.

The study results showed that:

- Biomarkers showed a reduction of serum CTX levels, which represented a reduction in bone destruction
- In a small number of patients calcitonin was measured in the blood
- Blood calcium levels were also reduced
- Although in a small number of patients, Capsitonin™ exerted statistically significant biological effect, and therefore calcitonin was delivered orally

**TABLE 3 – Current and planned trials**

| Objective                   | Location            | Expected date | completion |
|-----------------------------|---------------------|---------------|------------|
| Optimum formulation (human) | Brazil              | January 2007  |            |
| Dose finding (human)        | Australia (Qpharm)  | March 2007    |            |
| Toxicology (pre-clinical)   | Australia (Firefly) | March 2007    |            |

### Perthoxal™

**Perthoxal™** is a synthetic parathyroid hormone (PTH) in an oral capsule form. Parathyroid hormone increases bone formation and has been used in the treatment of osteoporosis since 2002. PTH is a very important regulator of the calcium/phosphate balance in the blood.

In its natural form parathyroid hormone is secreted by the parathyroid glands as a polypeptide containing 84 amino acids. It acts to increase the concentration of calcium in the blood in three ways; it enhances the release of calcium from the large reservoir contained in the bones, enhances reabsorption<sup>6</sup> of calcium from renal tubules and it also enhances the absorption of calcium in the intestine by increasing the production of vitamin D and up-regulating the enzyme responsible for converting vitamin D to its active form, which affects the actual absorption of calcium by the intestine. PTH also acts to decrease the concentration of phosphate in the blood, primarily by reducing reabsorption in the proximal tubules of the kidney. The decreased phosphate enhances bone demineralization.

### Market for Perthoxal™

PTH is the latest osteoporosis treatment approved by the FDA and has only been widely available to severe osteoporosis patients since 2002. Forteo® (teriparatide), the first injectible PTH on the market, was launched by Eli Lilly. The injectible PTH market is currently estimated at US\$560 million annually and is still growing. Datamonitor's report on osteoporosis in January 2004 predicted that the PTH market will grow to US\$1.5 billion by 2011.

**Perthoxal™ is an oral parathyroid hormone formulation**

**Oral PTH market is rapidly increasing and expected to reach US\$1.5B by 2011**

## Side effects of PTH

As a relatively new drug for osteoporosis PTH is observed very keenly by regulators for side effects. During the clinical trials of PTH a small number of subjects (under 10%) experienced mild symptoms; however this number was only slightly higher than the placebo group. So far teriparatide has been used in over 300,000 people with one case of osteosarcoma reported in July 2006, which coincides with the background incidence rate is one in 250,000.

## Competition

**Competition is intense to get into the PTH market, delivery by nasal sprays or via oral formulations are explored by Novartis, Emisphere, Unigene and NPS Pharma**

Novartis licensed **Emisphere**'s oral parathyroid hormone candidate early this year after Eli Lilly was found by the courts to have breached its option agreement with Emisphere in relation to the licensing of the same compound and its delivery technology. The deal is worth around US\$30 million in milestone payments, plus royalties on sales of the product. The drug is currently in phase II clinical trials.

**Unigene** licensed its oral PTH product to GlaxoSmithKline in 2002 in a transaction with a value of US\$150 million before royalties. The product is currently in phase I clinical development by GSK.

**NPS Pharmaceuticals** has developed an injectible PTH product (licensed to Nycomed in Europe) and submitted an NDA for its approval to the FDA. It is also developing, in partnership with GlaxoSmithKline, calcilytics in phase I clinical trials. Calcilytics are claimed to be orally active, small molecules targeted at bone and mineral disorders, such as osteoporosis. NPS claims that calcilytics antagonize calcium receptors on parathyroid glands resulting in a transient release of the body's own stores of parathyroid hormone (PTH). In this way, calcilytics may have the potential to produce the same therapeutic effect as injectible PTH.

**Nastech Pharmaceutical Company Inc.** announced in June this year that in a preliminary phase I clinical trial of its nasal spray form parathyroid hormone provided comparable exposure levels to the approved subcutaneous product, Forteo®, in elderly subjects. The product has been licensed to Procter & Gamble; the full terms of the transaction have not been disclosed but Nastech has disclosed expected revenues in 2006 from the deal to be up to \$32 million with a total lifetime value of up to \$577 million.

## Clinical development status of Perthoxal™

**Perthoxal™ is currently in phase II clinical trials with results in early 2007**

A phase I study was completed in 2005 using Perthoxal™. It was an open label trial for safety and tolerability while preliminary pharmaco-dynamic effects were observed using injectible PTH as control. Two different formulations of Perthoxal™ were administered to 18 post-menopausal female volunteers measuring serum calcium concentration as a key biomarker. Both formulations were shown to be safe and a biological response in the key endpoint was detected with a similar profile to the injected version with one formulation of Perthoxal™.

**TABLE 4 – Current and planned trials for Perthoxal™™**

| Objective           | Location           | Expected completion |
|---------------------|--------------------|---------------------|
| Optimum formulation | Brazil             | early 2007          |
| Dose finding        | Australia (Qpharm) | June 2007           |

It is expected that results of the next Perthoxal™ clinical trial will be available in early 2007.

## BN006 - TNF $\alpha$ down-regulator

**BN006 is a group of candidate compounds in development for rheumatoid arthritis**

Bone's third drug candidate, BN006, is in pre-clinical development for the treatment of rheumatoid arthritis. It was derived utilizing the Mozaic™ drug discovery technology, Bone's second in-licensed platform for the development of treatments for bone and joint diseases.

BN006 acts to reduce cellular production of tumor necrosis factor alpha (TNF $\alpha$ ), an important cytokine<sup>7</sup> involved in local inflammation. TNF $\alpha$  was first isolated in 1975 by Carswell as a soluble factor released by host cells that caused necrosis of a transplanted tumor. Although TNF $\alpha$  does cause the necrosis of some tumors, it may stimulate the growth of others which means the name itself is a misnomer.

**FIGURE 3 – TNF $\alpha$  3D structure**



TNF $\alpha$  is a 185 amino acid glycoprotein peptide hormone, and it is released by white blood cells, the endothelium and several other tissues in the course of damage, such as infection.

TNF $\alpha$  promotes the inflammatory response, which in turn causes many of the clinical problems associated with autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and psoriasis.

These disorders are sometimes treated by inhibiting TNF $\alpha$  with a monoclonal antibody such as infliximab (Remicade) or adalimumab (Humira), or with circulating receptor fusion proteins such as etanercept (Enbrel).

These drugs have been associated with serious side effects such as elevated risk of contracting tuberculosis or causing latent infections to become active.

Bone has used its access to the Mozaic™ technology to identify drug candidates that are potentially orally available and that can regulate TNF $\alpha$  release without ablating it entirely, thereby overcoming deficiencies of the current antibody-based products. The result is a family of new lead molecule known as BN006. In contrast to antibody-based treatments, BN006 does not interact with TNF $\alpha$  itself but with the cells that produce TNF $\alpha$  in order to reduce the amount they generate.

The key advantages of BN006 can be summarised as follows:

- It is intended to be orally bioavailable, to be taken in tablet or capsule form.
- It does not completely eliminate TNF $\alpha$  from the system and thus promise a better side-effect profile than the currently available antibody-based products.
- It can be manufactured inexpensively using a relatively simple synthetic process.

### Market for BN006

Rheumatoid arthritis affects an estimated 2.5 million people in the United States alone. In developed countries the incidence of rheumatoid arthritis is between 0.5% and 1% of the population and expected to grow as the proportion of most likely sufferers, that is over 65 years old women, is expected to grow.

In recent years treatment has been primarily by TNF $\alpha$  inhibitors such as the monoclonal antibody Remicade or Humira, or with circulating receptor fusion proteins such as Enbrel. While these injectible drugs reduce swelling caused by inflammation and may even prevent bone damage, they also have debilitating side effects in a significant number of patients. They are also very expensive with annual cost of treatment for Humira for example exceeding US\$16,000.

There is a clear, unmet medical need for a safe and effective treatment of rheumatoid arthritis, the target disease for BN006, particularly in oral form.

### Competition for BN006

Bone's BN006 is in a pre-clinical development stage and it is therefore difficult to ascertain what future competition may exist for the treatment of rheumatoid arthritis at the time it becomes licensable, or indeed market ready. However it is certain that any new drug will have to compete with the currently accepted treatments for efficacy, while it will have to demonstrate better safety and tolerability characteristics.

Besides the above listed monoclonal antibody therapies and receptor fusion proteins there is also a strong R&D drive among traditional small molecule drug developers to find new, early target for inhibiting the disease.

### Development status

Utilizing its in-licensed Mozaic technology Bone identified BN006 as the most promising of its drug candidates and it is currently being tested in pre-clinical trials for efficacy and safety.

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<sup>4</sup> Bisphosphonates (previously referred to as biphosphonates or diphosphonates) are a group of agents which are analogues of pyrophosphate. When administered either orally or parenterally they are adsorbed onto hydroxyapatite crystals in bone mineral and, because their structure renders them resistant to enzyme degradation, they act principally by inhibiting bone resorption, although some effect on bone formation probably also occurs.

<sup>5</sup> CTX (serum C-telopeptide of type 1 collagen) is an accepted marker for calcitonin activity in the blood. Calcitonin causes significant decrease in serum CTX levels.

<sup>6</sup> Bone reabsorption is the normal destruction of bone by osteoclasts, which are indirectly stimulated by PTH.

## BOARD AND MANAGEMENT

Bone is lead by Executive Chairman, Mr Paul Hopper. Mr Hopper is responsible for capitalization, corporate governance and business development. Bone's Chief Scientific Officer is Dr. Roger New; his responsibilities include research and development, formulation, and management of product development. Bone's VP of clinical and regulatory affairs is Dr. Tony Lockett, while commercial operations are managed by Mr Tim Earle.

### Mr Paul Hopper (Executive Chairman) BA (UNSW), A.S.I.A., FAICD

Mr Hopper was appointed as Executive Chairman on 7 November 2005. He is based in San Diego, USA, and has 25 years experience in the public capital markets primarily in the healthcare and biotechnology sectors. Mr Hopper was Director of MedAire Limited between November 2003 to March 2004 and Managing Director of Australian Cancer Technology Limited between August 2003 and February 2005. Mr Hopper's international experience includes senior board positions with Innovate Oncology, Inc, and Evolve Oncology, Inc.; both listed biotechnology companies involved in the development of oncology products. Mr Hopper was Director of Advanced Biotherapy, Inc. a pioneer in developing antibodies to interferon gamma and is currently a consultant to US based merchant banks Cappello Group, Inc and BIO: IB. He has served on numerous public and private boards, including as CEO of Alpha Healthcare Limited, as Director of The Australian Private Hospitals' Association and was Chairman of Singapore based Your Health Group.

### Dr Roger New (Director and Chief Scientific Officer)

Dr New has thirty years experience in research and development in field of drug delivery, is a world-recognised expert in liposomes and author of seminal reference book "Liposomes - A Practical Approach" published by OUP. He was the first to demonstrate efficacy of liposomal amphotericin and coordinated the first Phase I/II trials of liposomal doxorubicin. During his career he devised three new systems for oral delivery of insulin, giving first positive human results ever observed in Type I diabetics. Dr New is a honorary professor at several foreign academic institutions and a consultant advisor to IRCD. He is also a member of the UK Government Expert Mission on Biotechnology to China. He has many patent applications filed and granted in areas of pharmaceuticals, diagnostics and microbiology and he is the inventor of Mozaic, Axxess and Vaxcine patents/applications.

### Mr Leon Ivory (Director)

Mr Ivory has been involved in corporate finance, funds management and venture capital for 35 years in New Zealand, Australia, Europe and North America. He established Broadlands Finance in Australia, and was its Chief Executive Officer. Broadlands Finance operated successfully as an investment bank and was sold to NZI Bank for \$45 million. Leon Ivory also co-founded Western Capital, a venture capital organization which subsequently evolved into one of Australia's first public biotechnology companies. He served as a director of a number of public companies including Auspharm International Limited, Arbuthnot Latham Bank Ltd (London), Foreign Commerce Bank (Zurich) and VRI BioMedical Limited.

### Dr Barry Walker (Director)

Barry R. Walker, M.D., F.A.C.P. received his BA from Yale University in 1958. He graduated from the College of Physicians and Surgeons at Columbia University after which he completed a medical internship and residency at Temple University Hospital. Dr Walker completed his NIH Fellowship in renal-electrolyte diseases at the University of Pennsylvania. He is board certified in internal medicine, a fellow and member of numerous scientific organizations and a co-founder of the American Society of Hypertension for which he served as Vice President and Chairman of the Board. Dr Walker has been an Adjunct Associate Professor of Medicine at the Hospital of the University of Pennsylvania and the Leonard Davis Institute of the Wharton School, University of Pennsylvania. He also co-authored over one hundred peer reviewed publications.

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<sup>7</sup> **Cytokines** are a group of protein like signaling compounds that are used extensively for inter-cell communication, very much like hormones and neurotransmitters.

While Senior Vice President for Clinical Research and Development at Wyeth-Ayerst Research, he was responsible for establishing and supervising research and development, bio-statistics, data and financial management in the United States, Canada, South America, Japan and Europe. Other management responsibilities have included strategic planning for all aspects of corporate research and development including mergers and acquisitions. During the past fifteen years Dr Walker has been a consultant for venture capital and investment firms (Deutsch Bank, Morgan Stanley, Philadelphia Ventures and Liberty Ventures) on matters of technology assessment and due diligence. He has consulted with major pharmaceutical, biotech and medical device firms in the areas of regulatory, reimbursement issues and new product strategic planning. He is currently the Senior Vice President of Regulatory and Clinical Development for a biotech company, Yaupon Therapeutics, Inc. He was appointed to the Board on the 16 November 2005.

### **Mr Ed Daquino (Chief Financial Officer)**

Ed has completed the Advanced Diploma of Accounting & has more than 16 years experience as Company/Financial Accountant for large private companies in the retail, manufacturing, mining & construction industries. He served three years as Finance Director of a construction company before joining Bone Medical in September 2005.

### **INTELLECTUAL PROPERTY**

Bone has exclusive global rights for the use of the Axcress™, Mozaic™ and Vaxcine™ technologies to develop a range of treatments for musculoskeletal disorders. Bone's two leading drug candidates, Capsitonin™ and Perthoxal™ are using the Axcress™ oral delivery technology. BN006 was selected as a candidate with Mozaic™.

The Axcress™ oral delivery technology is protected by three patents in relation to the use of aromatic alcohols for the enhancement or oral delivery of peptides, the pharmaceutical composition of the Axcress™ system and for the methods for solubilisation.

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