



**Buy 22 cents**

# Cbio Limited (CBZ)

**Marc Sinatra**

+61 0408 108 996

m.sinatra@lodgepartners.com.au

## Significant milestone fast approaching

### Company Data

ASX Code	CBZ
Price	\$0.22
12 month price target	\$0.82
Implied return	372%
Shares on issue	142.7m
Market capitalisation	31m

### Board of Directors

Stephen Jones	Chairman (Exec)
Jason Yeates	MD & CEO
Göran Ando	Non-Exec. Dir.
Peter Corr	Non-Exec. Dir.
John Funder	Non-Exec. Dir.
Michael Monsour	Non-Exec. Dir.
Terje Kalland	Non-Exec. Dir.
Steven Streefer	Non-Exec. Dir.

### Major Shareholders

Michael Monsour	8.0%
Himstedt & Co Pty Ltd	7.6%

### Share Price Chart



Source: Iress Market Technology

### Business Overview

Cbio is biopharmaceutical company based in Brisbane, Australia. It is focussed on commercialising its proprietary drug, Xtoll, for autoimmune and inflammatory diseases.

Cbio is closing in on completion of a significant phase IIa clinical trial in rheumatoid arthritis patients, with results due at the end of this quarter.

### Core Technology

Xtoll is very similar to the naturally occurring protein chaperonin 10. It is thought to act high-up in the regulatory cascade that leads to immune system activation and inflammation. As such, Xtoll should affect target diseases in a global manner, rather than the hit and miss nature of drugs that act lower down. Xtoll should be safer than other drugs because it suppresses the immune system rather than completely stopping components of it, like other drugs, that are required for the maintenance of normal human health.

### Xtoll Development

The phase IIa trial that Xtoll is being studied in is likely to be of sufficient size, duration and overall design to provide solid evidence of the drug's ability to safely treat rheumatoid arthritis. The data produced should also be sufficient to attract a commercial partner, pending final results, with deals in the rheumatoid arthritis space often occurring just after phase IIa trials. The last three significant deals in the space having featured upfront payments between US\$80 and US\$100 million, with milestones between US\$650 and US\$1.1 billion.

Drugs for rheumatoid arthritis often prove useful for treating other diseases and Xtoll should be no different, with data already in hand for psoriasis. Further potential applications also exist and, given the wealth of opportunities, carefully chosen and timed follow-on indications could see Xtoll become a significant treatment for many diseases.

### Valuation and Recommendation

Cbio represents a straight forward investment opportunity in an area where many are complex and poorly defined.

The company has a high calibre Board and Management team with an excellent mix of skills, and general and specific expertise. Importantly, they have already demonstrated an ability to do deals which is essential for success in the rheumatoid arthritis space.

Results from a small previous phase IIa study in rheumatoid arthritis auger well for the soon to be released results from the current study. These results are likely to prove a catalyst for a substantial re-rating of the company.

Our analysis includes no value for indications other than rheumatoid arthritis, giving tremendous possible upside to our valuation.

Cbio appears significantly undervalued based on our DCF analysis. **Consequently, we place a buy recommendation on the stock with a 12-month price target of 82 cents.**

## Background

Cbio is an Australian-based biopharmaceutical company focussed on the development of its drug Xtoll for the treatment of a range of autoimmune/inflammatory disorders, focussing initially on rheumatoid arthritis (RA).

Autoimmune disorders are disorders where the body comes under attack from its own immune system. Closely related, inflammatory diseases refer to situations where inappropriate inflammation causes problems.

Xtoll was licensed from the University of Queensland in 2000. Since that time, it has been the subject of several clinical studies in diseases such as RA, psoriasis and multiple sclerosis. Although the results from the studies have been promising, there has been a shift away from the intravenous drug delivery used in these studies to subcutaneous (SC, under the skin) delivery, particularly in the RA market. Consequently, Cbio decided to switch to SC delivery of Xtoll and, to this end, it has now completed a phase I SC delivery study and commenced a phase IIa study in rheumatoid arthritis patients. **Results of this study are due towards the end of the current quarter and a positive finding should prove a major value inflection point for the company.**

The company listed in 2010 via an initial public offer at one dollar per share which raised \$7.1 million. Since then the company has arranged a funding facility with New York-based institutional investor Springtree special opportunities fund. The facility provides for a minimum of \$5.45 million and a maximum of \$12.45 million over three years. The company can draw a minimum of \$150,000 and a maximum of \$350,000 per month through the issue of convertible notes to Springtree. The facility can be cancelled should it no longer be required. A share purchase plan raised \$402,000 dollars in June 2010 at 35 cents per share. A further \$9.3 million was raised via a rights issue at 16 cents per share that was completed in December 2010. The proceeds of the rights issue ensure that the company can complete its phase IIa RA trial. It has also already used some of the proceeds from the rights issue to repay a \$150,000 convertible note issued to Springtree.

## Valuation

We have valued Cbio using a project-based, probability adjusted, discounted cash flow model for the seven major pharmaceutical markets (US, Japan, France, Germany, Italy, Spain and the UK).

The assumptions made and values used in our model are as follows:

- 16% discount rate;
- 30% corporate tax rate;
- \$1 Australian = \$1 US = €0.78;
- 4.5 million patients with RA across relevant territories;
- \$15,000 cost per patient per year for Xtoll;
- 5% peak market penetration;
- 70%, 75% and 80% chance of phase IIa, IIb and III clinical trial success, respectively;
- Regulatory approval assumed on phase III success;
- Product out-licensed after phase IIa trials at no further cost to Cbio;
- Licensing terms: US\$40 million upfront, US\$250 milestones, 12% royalty on sales;
- 40% chance of achieving licensing deal;

### Assumptions

### Comparables

- No value attributed to other diseases Xtoll may treat.

**Based on our model, we have valued Cbio at a market capitalisation of \$102 million.** Unfortunately, It is difficult to find comparable companies with which to reality check this valuation. The main issue is that with one drug being studied for one indication, few companies are as focussed as Cbio. Chelsea Therapeutics (NASDAQ:CHTP), like Cbio, has a novel drug for RA currently in a phase IIa trial and has a market capitalisation of US\$364 (AU\$364) million. So does Galapagos NV (Euronext: GLPG) which has a market capitalisation of €319 (AU\$411) million. 4SC AG (Frankfurt: VSC) has a novel drug in phase IIb trials and has a market capitalisation of €161 million (AU\$208 million). All of these companies, however, have more than one drug in development. In the case of Galapagos, it has three other RA drugs in development, in addition to its drug in the phase IIa trial, and a licensing deal with GlaxoSmithKline. Given the difference between Cbio and these companies, the most we can probably conclude based on this comparison is that our valuation looks reasonable.

Possible licencing/go it alone combination strategy

## The Commercial Opportunity

**Cbio represents a relatively straightforward commercial opportunity.**

The company's overall strategy is to license Xtoll after phase IIa studies for major indications, such as RA, while looking to develop Xtoll further for niche indications, such systemic erythematous lupus, possibly to marketing approval and beyond. This is a tried and tested strategy for small drug development companies, allowing them to off-load risk and maximise shareholder returns while operating within the capabilities they possess.

Such a strategy for the RA indication is likely to realise royalties on sales of between 10%-15% for products licensed after phase IIa studies, total milestone payments of anywhere between \$300 million and \$1 billion and an upfront payment of \$50-\$150 million dollars. Obviously, the quality of the phase IIa results will dictate the precise nature and figures of any licencing deal. Deals for niche indications would be smaller (if Cbio chooses to licence at all). This is balanced against the likelihood that Cbio will be able to take Xtoll further into development for these indications, reducing development risk and improving its negotiating position.

Demonstrated capacity to deal with larger companies

**Cbio has already demonstrated an ability to do deals with larger pharmaceutical companies.** In 2008, Cbio entered into an option agreement with Novo Nordisk A/S for the rights to Xtoll in exchange for a \$2 million option fee and a further \$1 million dollar payment related a recruiting milestone in the current phase IIa trial, which has been passed. More details regarding this agreement are discussed later.

Getting in position to do a very good licencing deal

Importantly, the phase IIa study that Cbio is conducting with Xtoll for RA is of a significant size (n=150). A trap that companies can fall into is to try and only do just enough to justify a compound's movement from phase IIa to IIb trials. The issue, however, is that this just transfers risk to the much more expensive phase IIb trial. Potential partners will recognise this and their willingness to pay in any licencing deal will be decreased. The nature of Cbio's current RA trial, however, should leave little doubt in the mind of potential licensees as to the prospects of Xtoll going forward, such that a positive result from the current phase IIa should put Cbio in a position to do an excellent licencing deal.

Cbio's immediate future is dependent upon how well it has and continues to run the phase IIa RA trial. Cbio has significant previous experience in running clinical trials and the quality of results that those trials provided suggest that the current phase IIa carries little execution risk. Having said that, even small errors in clinical trial execution can have major implications for the future of a drug. Drug development companies cannot afford to relax given the significance that clinical trials play in their success or failure.

Capital constraints have left the identification and development of Xtoll for additional indications still to be settled and this is an area that Cbio needs to address going forward to maintain momentum and avoid the creation of a gap in its pipeline. Several possible indications exist, such as psoriasis and systemic erythematous lupus (SLE). Factors to consider in choosing a second indication will include the market, partnering possibilities, the

clinical utility of Xtoll for the indication, capital requirements and how far into development Cbio will be able to take Xtoll for the particular indication. Generally, the further into development a company can take a compound for an indication the better will be the licensing deal they eventually negotiate. **Given the likely wide-ranging utility of Xtoll for multiple diseases, Cbio should be able to identify a highly suitable follow-on indication to RA for Xtoll.**

Licencing soon to become of the focus for Cbio

It is possible that Cbio may choose to license Xtoll as a whole, rather than on an indication by indication basis. This would leave Cbio needing to in-license a second compound that fits well with its autoimmune/inflammatory focus. Given the wide apparent utility of Xtoll, however, the better route appears to be to develop it for additional indications rather than look to a new compound. The infrastructure required to develop Xtoll for additional indications will be less than that for a new compound and Cbio already has significant demonstrated expertise with the putative drug.

**Overall, the commercial opportunity presented by Cbio is sound and their strategy well-tailored to the opportunity.** The RA opportunity is now largely down to execution risk in terms of the clinical trial and subsequent licensing of the drug, insofar as variables that Cbio can control go. Once a licensing deal is done, focus will shift to developing Xtoll for new indications. The addition of these new indications has the potential to add significant value to the company and the Xtoll franchise.

## Products in Development and Their Markets

As mentioned earlier, Cbio's main development project is Xtoll for patients with RA.

### Xtoll – Chaperonin 10

Xtoll is an altered form of a protein that occurs naturally and is thought to perform a number of roles in humans. It belongs to a family of molecules known as chaperonins (also termed heat-shock proteins), Xtoll itself is a slightly modified form of chaperonin 10 (Cpn10). Cpn10 is thought to be the same molecule as early pregnancy factor (EPF), so named because it is produced early in pregnancy. However, some doubt exists as to whether they are, in fact, the same molecules. Nonetheless, it was the ability of EPF to influence the immune system, which gave rise to the thought that it and, subsequently, Cpn10 could be used to treat autoimmune/inflammatory diseases.

Cpn10's likely mechanism of action in treating such diseases is not well understood. The protein is found both in and outside of cells, with the Cpn10 found outside of cells thought to influence the immune system.

Strong rationale behind Xtoll for superior efficacy and safety

Cpn10 and another chaperonin, termed chaperonin 60 (Cpn60), are thought to interact with each other and a series of receptors found on the surface of cells, called toll-like receptors (TLRs). The binding of Cpn60 alone to TLRs is thought to trigger inflammatory activity, but when Cpn10 binds Cpn60 this activity is inhibited. The net result is that the activity of pro-inflammatory molecules, like tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), increase, while that of anti-inflammatory interleukin-10 (IL-10) decreases in the presence of Cpn60, while this activity is reversed when Cpn10 is added.

The potential utility of using Xtoll to treat RA becomes clear when one considers that drugs targeting TNF- $\alpha$  represent the vast majority of sales in the RA market. It is hoped that by acting higher up in the inflammatory cascade, Xtoll will have a more even effect on dampening the immune systems response in RA than targeting molecules further downstream, such as TNF- $\alpha$ . The rationale is that by targeting molecules further downstream, specific functions of the immune system may be almost completely shut down. While this can be positive in terms of limiting the autoimmune disease, it is also likely to mean that normal protective functions of the immune system involving that target molecule may also be shut down. This leads to side-effects and the vast majority of drugs used to treat RA have significant side effects. With those drugs that target TNF-  $\alpha$ , for example, queries exist regarding increased cancer and infection risk.

**It needs to be remembered that although the immune system is the source of autoimmune diseases, it is also an indispensable part of the body's defence against**

**other diseases and that new treatments for autoimmune diseases need to be mindful of this.**

### About Rheumatoid Arthritis

RA is a disease where the immune system attacks the joints of an individual. Specifically, the immune system attacks a membrane, termed the synovium, which covers joints and contains the synovial fluid within it. RA is caused by white blood cells which migrate to the joint causing inflammation. This, in turn, causes the joint to swell and the synovium to thicken. Sooner rather than later, the synovium invades and damages the bone and cartilage on either side of the joint. Next, the muscles, tendons and ligaments that support the joint stop working properly.

Symptoms of RA vary considerably from patient to patient and include pain and stiffness for more than 30 minutes after a long rest, inflammation and poor function of joints. Some less obvious symptoms, such as fatigue and fevers, can also be associated with RA. Diagnosis of RA is made through a medical history, physical exam and a range of diagnostic tests, such as testing for the presence of rheumatoid factor. For the later stages of the disease, x-rays can be used to assess damage to the joints and gauge disease progression.

The ultimate cause of RA is unknown, but the disease is thought to be multi-factorial, with genetics, the environment and others factors playing a role in its development.

### Treatment of Rheumatoid Arthritis

Treatment of RA is designed to reduce pain and inflammation and inhibit the damage caused by the disease. While a range of lifestyle changes and medical devices can be used to treat the disease, including surgery (e.g. joint replacement), pharmaceuticals form the mainstay treatment.

Three classes of RA drugs one for each line of treatment

While RA was initially treated by non-steroidal anti-inflammatory drugs, such as ibuprofen, and corticosteroids in short bursts, more successful strategies have shown that early aggressive treatment with a class of drug termed, disease modifying anti-rheumatic drugs (DMARDs) yield better results. These drugs are so named because they are thought to modify the normal course of RA, slowing disease progression. Methotrexate, a drug which is also used in cancer treatment, is the mainstay small molecule DMARD (smDMARD) and also features in most combination therapies. Other smDMARDs include hydroxychloroquine and sulfasalazine. Methotrexate remains the preferred smDMARD due to its effectiveness, generally low-level side effects and its low cost. Nonetheless, side effects of methotrexate still mean patients taking it require regular blood tests for anaemia and liver function tests due to the drug's toxicity. Patients who are intolerant or unresponsive will often be tried on one or more smDMARDs or on a combination of smDMARDs.

Anti-tumour necrosis factor (anti-TNF) drugs are part of a group of biologic DMARDs (bDMARDs). They form the second line of RA therapy should smDMARDs perform poorly. They are termed bDMARDs because they are created by biological processes and include antibody-based drugs. TNF is considered a key molecule in the inflammation process and biologic drugs which bind and inhibit TNF have proven very useful in treating RA. Such drugs include infliximab, etanercept and adalimumab. The main drawback of these drugs is cost, although there are also some concerns regarding the development of cancers and infections with long term use, as mentioned previously.

More use of drugs outside of their traditional line of therapy

**TNF inhibitors, however, do not work for all patients and these patients may then receive a third-line treatment consisting of a bDMARDs aimed at a target other than TNF.** Four drugs of this nature have been approved in the US; anakinra, rituximab, abatacept and tocilizumab.

While the use of drugs to treat RA has been neatly classified into first, second and third-line therapies, the real situation is not that simple. Anti-TNF drugs may be used alone or in conjunction with smDMARDs as a first line therapy, although rarely. Similarly, novel bDMARDs can be used as a second-line therapy, while smDMARDs can end up being used at any line in combination therapies.

High incidence of RA

### Rheumatoid Arthritis Market Size

The National Arthritis Data Workgroup estimates that 1.3 million Americans or 0.6% of the

population has RA (2008). These numbers are down on those previously published primarily due to more restrictive classifications being used to define RA, although there is a feeling among the medical community that the actual prevalence of RA is also falling (National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 2009). Worldwide, the prevalence of RA is generally put at 1% of the population, but these figures have probably been compiled using the old classification system.

Large market with biologic treatments like Xtoll dominating

While RA does affect all sexes, races and ages, more women have RA than men (two to three times more) and the frequency of RA increases with age (NIAMS, 2009), with patients generally reporting being first affected by the disease between 30-60 years of age (The Johns Hopkins Arthritis Centre website, accessed 2010).

**GlobalData (2010) estimated the global 2009 RA market at US\$9 billion with a forecast market of US\$14.3 billion in 2017.** This represents a compound average growth rate of 6%. Small molecule DMARDS account for only 2% of total sales, with bDMARDS (which include TNF inhibitors) accounting for more than 75% of sales in 2008 (Stoll and Yasothan, 2008). NSAIDs and corticosteroids make up the remainder (Stoll and Yasothan, 2008).

Small (n=23) initial phase IIa study

### Xtoll for Rheumatoid Arthritis

Xtoll has been studied in a randomised, double-blind, multi-centre phase IIa study of 23 patients with moderate to severe RA. Patients were randomised into three cohorts receiving Xtoll intravenously twice weekly for twelve weeks at doses of 5mg (n=8), 7.5mg (n=8) or 10mg (n=7). There was no control group. Patients taking NSAIDs, corticosteroids and stable doses of sDMARDS were included. Patients who had taken bDMARDS within three months of the study start were excluded. Primary outcome measures were disease activity score (DAS28) and the American College of Rheumatology response score (ACR). The DAS28 is a score between two and ten based upon examination of 28 joints, a diagnostic test and an estimate of the disease activity by the patient. The ACR response score is a method of assessing improvement in core disease measures, where ACR20, ACR50, and ACR70 indicate a 20%, 50% and 70% improvement, respectively.

Very solid initial results despite trial design issues

DAS28 score improved significantly for all dose levels when day 14 measurements were compared to baseline. Further improvement was seen out to day 84, again for all dose levels. In terms of ACR scores, regardless of the cohort, 13 patients achieved an ACR20, six ACR50 and four ACR70. In general, there were no differences in the response rates between the different doses. This was probably due to the small numbers in each cohort. Measurements also showed significant decreases in TNF $\alpha$  and IL-6 when the cohorts were combined, which would be expected if Xtoll were having the desired effect. Overall, three patients dropped out of the study; one whose RA was uncontrolled at day 28, one who had cellulitis and one who was lost to follow-up.

The results of this study provide some evidence of safety and efficacy. The small number of patients and the lack of a control arm are significant drawbacks, though. These drawbacks make definitive conclusions difficult in terms of efficacy, since the small numbers mean considerable variation may exist around disease scores and placebo effects are common in these types of studies (i.e. patients demonstrating disease improvement despite not receiving the test drug). The number of patients in this study who achieved an ACR70, however, is difficult to explain by a placebo effect alone; a point the authors of the study made to support the efficacy of Xtoll. Another drawback of the study is that its duration was short compared to the time an RA patient would normally spend on a drug, leading to the need for longer term data to be produced, both for efficacy and safety determinations to be made.

As mentioned earlier, Cbio expects to complete its more definitive phase IIa study towards the end of the current quarter. This study is titled "a multicentre, randomised, double-blind, placebo-controlled, parallel group, phase IIa clinical trial to assess the efficacy and safety of Cpn10 administered as twice weekly subcutaneous injections in subjects with rheumatoid arthritis".

Impeccable large scale phase IIa study design

**The design of this trial addresses the three major issues with the previous phase IIa study.** Firstly, a much larger number of subjects, n=150, will be enrolled in the trial with 50 patients per cohort – 25mg, 75mg and placebo. Secondly, the inclusion of a placebo (control) cohort will allow the size of the placebo effect to be measured and compared against the test cohorts. The size of this trial and the inclusion of a control arm should allow much more

definitive conclusions regarding the efficacy of Cpn10. In addition, the trial duration is twice as long as the previous study, 24 weeks versus 12. This will allow the longer term safety of Cpn10 to be assessed, as well as longer term efficacy. Responders in this study will also be invited to enrol in an open label, non-controlled, longer term study (72 weeks) to further assess the safety and efficacy of Cpn10.

Other than the size and duration of the current study, it also differs from the previous Ila study in the method of delivery of the drug. The original Ila study used an intravenous route of administration, while the current study uses a SC route of delivery, as previously mentioned. The latter is a much more commercially acceptable form of delivery and should allow the patient to self-administer the drug at home. The subcutaneous method of delivery also explains the increases in the doses of Cpn10 used in the current study compared to the past Ila study, with bioavailability being greater for intravenous administration.

**The design of the current Ila study is solid and should yield a persuasive set of results one way or another. Given the results of the original Ila study, it seems much more likely than not that the current study will produce positive results.**

### **Competition in the Rheumatoid Arthritis Market**

Small molecule DMARDs look likely to dominate the first-line of RA therapy until such time as generic versions of TNF inhibitors become available, since one of the primary advantages of off-patent smDMARDs is cost. Methotrexate costs about \$500-600 per year per patient, while TNF inhibitors run at about US\$20,000 a year per patient. Even after generic TNF inhibitors become available, smDMARDs are still likely to play a significant role. Small molecule DMARDs have been used for a very long time and their performance characteristics, including side-effects, are very well understood and, consequently, doctors feel comfortable using them. They also work well in combination with bDMARDs, which will help them maintain market share well into the foreseeable future.

**How drugs are given is becoming more important**

Similarly, the TNF inhibitors are very well entrenched as a second-line therapy. The three main TNF inhibitors, etanercept, infliximab and adalimumab were launched for RA in 1998, 1999 and 2002, respectively. Consequently, TNF inhibitors have also been around for some time and doctors are quite comfortable using them.

Competition within the TNF inhibitors is now primarily targeted at the method and frequency of drug delivery. Infliximab is given by intravenous infusion, which takes about two hours, every eight weeks. Etanercept and adalimumab are administered by subcutaneous injection; etanercept one to two times a week and adalimumab once every two weeks. Two newer TNF inhibitors, however, golimumab and certolizumab pegol are given subcutaneously once a month and once every four weeks, respectively (i.e. patients receive one more injection of certolizumab per year). While these new drugs have not been on the market long enough to truly judge the weight doctors and patients will place on decreased dosing frequency, it is an area to watch. One trend that is emerging is that managed care providers do prefer subcutaneous injections to intravenous infusions due to the lack of an infusion administration fee.

There are four bDMARDs on the market for RA which target molecules other than TNF. These drugs target IL-1 (anakinra), the CD20 molecule on the surface of antibody producing B-cells (rituximab), the CD28 molecule on immune system T-cells (abatacept) and IL-6 (tocilizumab). Currently, the main role of these drugs is in treating individuals who have failed to respond to TNF inhibitors, as stated earlier. In the future, though, they are likely to offer doctors the ability to further tailor RA treatments for individual patients and the lines between first, second and third line treatments may become even more blurred. Abatacept is already thought to be taking market share from infliximab, due to its shorter infusion time, similar claimed efficacy to the other TNF inhibitors and, very importantly, its different mode of action to TNF inhibitors (Stroll and Yasothan, 2009). If one TNF inhibitor doesn't work for a patient, the others are unlikely to. Hence, having drugs with alternate modes of action allow doctors to more quickly find a suitable drug regimen for patients.

**Xtoll will initially compete as a third line therapy**

There are several promising drugs in later stage clinical trials (phase II and III) for RA. Pfizer has tasocitinib, a smDMARD janus kinase 3 (JAK3) inhibitor, in phase III trials, while Rigel/Astra Zeneca have fostimatinib, a smDMARD inhibitor of spleen tyrosine kinase, also in phase III trials. Eli Lilly/Incyte have LY3009104, a smDMARD inhibitor of janus kinases 1 & 2,

in phase II studies, while 4SC AG has vidofludimus, a smDMARD inhibitor of interleukin-17 (IL-17), also in phase II studies. Bristol-Meyers Squibb (BMS)/Alder Biopharmaceuticals appear to have the only significant biologic in late stage development for RA. BMS-945429 is a monoclonal antibody which targets IL-6, as does Roche/Chugai's recently approved Tocilizumab. It is in phase II trials.

Xtoll is unlikely, at least initially, to compete with the traditional first-line smDMARDs or TNF inhibitors, given how entrenched they are in clinical practice. Its main source of competition is likely to come in the form bDMARDs aimed at targets other than TNF, as well as the newer smDMARDs and bDMARDs currently in development.

Many lucrative niches in the RA Market

Table 1 compares Xtoll to the non-TFN bDMARDs and newer smDMARDs either on the market or in the later stages of development.

Given that the dosing regimen of Xtoll is not too onerous, it looks like it will compete with those drugs delivered by infusion or SC largely on the basis of safety and efficacy.

In terms of efficacy, it needs to be remembered that not all patients will respond to each of the drugs listed nor will those who respond to the same drugs necessarily have equivalent responses to each drug. **The point being that despite a market that is starting to look crowded, niches capable of sustaining even more drugs are likely to exist and, as can be seen in the cases of rituximab and abatacept, the rewards can be very significant, although it must be noted that that rituximab is used to treat a wide range of diseases, not just RA.**

Table 1. Comparison of Xtoll with likely competitor products

Name	Trade Name	Company	Target	Delivery	Dosing	Stage	'09 Sales - Million US\$
<b>Marketed</b>							
Anakinra	Kineret	Amgen	IL-1	SC	Daily	N/A	60
Rituximab	Rituxan	Roche/Biogen	CD20	IV	2 infusions/6 months	N/A	5,600
Abatacept	Orencia	BMS	CD28	IV	30min infusion/4 weeks	N/A	602
Tocilizumab	Actemra	Roche/Chugai	IL-6	IV	1hr infusion/4 weeks	N/A	N/A
<b>In development</b>							
<i>Cpn10</i>	<i>Xtoll</i>	<i>Cbio</i>	<i>?Cpn60</i>	SC	<i>Twice weekly</i>	<i>Ph. II</i>	<i>N/A</i>
Tascocitinib	N/A	Pfizer	JAK1	Oral	Twice daily	Ph. III	N/A
Fostamatinib	N/A	AZ/Rigel	SVK	Oral	Once/twice day	Ph. III	N/A
LY3009104	N/A	E. Lilly/Incyte	JAK1&2	Oral	Once/twice day	Ph. II	N/A
SC12267	N/A	4SC AG	IL-17	Oral	Once daily	Ph. II	N/A
BMS945429	N/A	BMS/Alder	IL-6	IV	1hr infusion/2 weeks	Ph. II	N/A

Safety will help establish Xtoll over time

**Safety is where Xtoll could make good inroads into the market.** As stated earlier, it is hoped that by acting higher up in the inflammatory process that Xtoll will dampen the immune system rather than essentially knocking out one component of it. Thus, the full immune system should remain functional, giving Xtoll a limited side effect profile. The difficulty with demonstrating superior safety, however, is that adverse events (a negative health issue that arises while the patient is enrolled in the study) are generally fairly rare, may occur years after the patient has started taking the drug and they cannot necessarily be linked to the drug's use. The net result is that demonstrating superior safety is generally extremely costly and time consuming. It often takes many years for a drug to gain a reputation as extremely safe. Nonetheless, other RA drugs are prone to side-effects and, although a strong safety profile probably won't cause sales to rise rapidly, its effect on sales over a number of years could be very significant.

Oral small molecule DMARDs will change market, but not quickly

The appearance of any of the wave of new oral smDMARDs in development on the market could change the dynamics of the RA market at the third-line treatment level considerably. An oral method of delivery alone, however, will not be enough to ensure success of a drug. Efficacy and, in particular, safety will still play dominant roles in the minds of doctors when prescribing RA drugs. The fact that these potential new oral drugs are aimed at as yet untried targets and that small molecule drugs may lack the specificity of many biologics, doctors will be very wary of any undesirable effects these new oral drugs may have. **Consequently, while these new oral drugs may change the dynamics of the RA treatment market, this change is unlikely to be explosive or revolutionary.**

Phase II is the time to do deals

One aspect where Xtoll probably has a significant advantage is in production cost. Most biologics must be produced using mammalian cells and, if possible, produced using human cells. The reason for this is that human proteins produced in non-mammalian cells don't look human to the human immune system. Consequently, the immune system attacks them. Eventually, this will lead to a situation where the drug is blocked from working by the immune system. Producing proteins in mammalian cells is more difficult and more expensive than producing them in bacterial cells. However, Xtoll, although a protein, doesn't seem to elicit much of an immune reaction, if any, when produced in bacterial cells. Cheaper drugs tend to appeal to both insurers and patients and, to a lesser extent, regulatory bodies for obvious reasons.

### Deals in the Rheumatoid Arthritis Space

Over the four months from November 2009 to February 2010, three significant deals were done in the RA space. A summary of these deals is given in table 2. As can be seen the deals were all done while the compounds were in phase II development, with the better deal negotiated by Rigel probably due to the later stage of development of fostamatinib.

These figures provide some actual indication of the deal Cbio could strike for Xtoll, although, as stated before, the specific numbers will be dependent on data from the current phase IIa trial. This is important since Cbio's clear aim is to licence at a similar development point and the data from the table tells us that this is the time point that potential licensees are active.

As an aside, it should be noted that an upfront payment of \$90 million represents a multiple of three times Cbio's current market capitalisation, which makes the company look significantly undervalued.

Table X Significant recent deals involving RA drugs.

Drug	Licensee	Licensor	Stage	Upfront	Milestones	Territories
BMS945429	Alder Biopharma.	BMS	Ila	85	764	Global
LY3009104	Incyte Corp.	Eli Lilly	Ila	90	665	Global
Fostamatinib	Rigel Pharma.	AstraZeneca	Iib	100	1,100	Global

RA is a market for big companies and the Novo deal demonstrates Cbio can deal with these companies

One thing that is clear by looking at the RA drugs on the market, in development and deals done is that the later stage game is for major players – with names like Johnsons & Johnson, Pfizer, AstraZeneca, Bristol-Myers Squibb and Roche all present. There are probably two reasons it is a game for major players. The first is that phase III programs for RA drugs require the testing of 1500-2000+ patients. At a cost of US\$100,000 per patient, out of pocket expenses for a phase III program are likely to be between US\$150 and US\$200+ million. The second is that given the competitive nature of the market, a strong marketing and sales force is required to draw doctors' attentions to a drug. Both the capital and sales and marketing resources required to tackle the RA market are probably beyond even the best funded and staffed small drug development companies.

RA drugs often have many applications

**From this point of view, the interest shown in Xtoll by Novo Nordisk, which is currently building a presence in treating autoimmune and chronic inflammatory diseases, provides a reasonable level of reassurance as to the opportunity Xtoll presents.** The deal struck between Cbio and Novo saw Cbio grant Novo Nordisk an exclusive right to negotiate a licensing deal for Xtoll in exchange for an option fee of US\$2 (AU\$2) million and a further US\$1 (AU\$1) million on achieving a recruiting milestone in the current phase IIa trial. Cbio is under no obligation to enter into a licensing agreement with Novo, other than granting the company 120 days to exclusively negotiate a licence. Importantly, the deal also includes a requirement that Cbio undertake a work plan, which includes the current phase IIa trial, specified by Novo. While this work plan could be a double-edged sword to a certain extent in that it limits Cbio's freedom, the work plan devised by Novo with all its resources is likely to be highly beneficial to the development of Xtoll and beyond any plan that Cbio could have devised on its own.

### Other Indications

Many drugs used to treat RA are also used to treat other autoimmune diseases. Infliximab, for example, was first approved for the treatment of Crohn's disease (adult) in 1998. Subsequently it has been approved for RA, ulcerative colitis, Crohn's disease (paediatric), plaque psoriasis, psoriatic arthritis and ankylosing spondylitis. Xtoll may well have similar broad utility, although the ultimate indications for use are likely to be different.

#### Results of Xtoll in psoriasis justify further trials

Cbio has run phase IIa trials of Xtoll for chronic plaque psoriasis (the most common form of psoriasis, characterised by silvery scales) and multiple sclerosis (MS).

The double-blind chronic plaque psoriasis study involved 24 patients which were randomised into three groups of eight destined to receive 5mg, 7.5mg or 10mg of Xtoll intravenously twice a week for 12 weeks. According to the authors, disease activity decreased in all patient groups, with seven out of the eight patients in the 10mg group showing a response. When patients were assessed by the Psoriasis Area Sensitivity Index (PASI), median percent change in PASI scores decreased significantly by day 14 ( $p=0.01$ ) and further by day 84 ( $p=0.02$ ). When assessed by a second method, the Physician Global Assessment (PGA) score, score improved significantly by day 56 ( $p=0.02$ ) and further improved by day 84 ( $p=0.03$ ). Two inflammation markers, including TNF $\alpha$ , were shown to be significantly decreased. As with RA, marked placebo effects are often seen in psoriasis studies and, as with the original RA study, the lack of a control arm makes it difficult to draw any conclusions with the usual scientific rigor required. **Nonetheless, the results of Xtoll in this study could certainly justify the commencement of a larger scale phase IIa study as has been done in RA.**

The MS trial was a randomised, double-blind, placebo controlled trial in which 50 patients with relapse-remitting or secondary progressive MS were studied. Relapse-remitting MS is a form of the disease in which the patients can relapse with new symptoms and/or worsening of old symptoms. These periods of relapse are followed by periods of remission. Secondary progressive MS sees steady progression of neurological damage with or without relapses and remissions. It is essentially the stage of MS which follows the relapse-remitting stage. In the study, 20 subjects received 5mg Xtoll weekly, 19 subjects alternated receiving 10mg of Xtoll one week and placebo the next week for the study duration. Eleven subjects received weekly placebo alone. All treatments were given via a two minute intravenous infusion and the treatments were administered over 12 weeks. Unfortunately, the study did not produce any statistically significant improvements in clinical outcome measures. There was a trend to fewer new lesions. The study did, however, reaffirm the safety of Xtoll. While the authors offer a variety of reasons why the study did not show any significant differences and suggest that a much larger phase IIb study should be undertaken using a higher dose of Xtoll, it seems to us that there is probably lower hanging fruit that Cbio could pick without entering into a costly clinical trial without sufficient evidence of Xtoll's likely efficacy.

As Cbio's phase IIa RA study is wrapped up, they need to be ready to start developing Xtoll for a second indication. Which indication is chosen needs to be made based on the economic realities at the time. A capital raising of sufficient size or the upfront payment from an Xtoll RA licencing deal may put them into a position to look at taking Xtoll quite a ways down the track towards a niche indication, such as ankylosing spondylitis. Alternatively, given the results in hand for chronic plaque psoriasis, funding a larger scale phase IIa trial for that indication with an eye towards a second licencing deal may also be appealing. In an ideal world, Cbio would probably do both like the major pharmaceutical companies would.

In moving toward multiple indications, Cbio may face the situation where sales for one indication at one price point may cannibalize sales for another indication at a higher price point. While this is still some way down the track, unless the products are sufficiently differentiated now, it is likely to occur and it is something Cbio needs to have in the back of its mind. Sales of the cancer drug Avastin are currently cannibalizing sales of age-related macular degeneration (AMD) drug Lucentis. Both drugs are very similar and target the same molecule. While Avastin is not approved for AMD, its price is much lower than that of Lucentis, making it an appealing off-label treatment for AMD.

## Intellectual Property

**Cbio boasts an excellent intellectual property portfolio. It consists of 11 patent families containing 43 granted and 85 patents pending and provides very robust protection of Xtoll (Cpn10).**

Extensive intellectual property protection

Family 1 relates to the detection of Cpn10 in biological fluids and covers a method for using Cpn10 to promote cell growth or for suppressing the immune system. Patents in this portfolio expire in 2014.

Family 2 relates to Cpn10 antagonists (substances that inhibit Cpn10) and their use to decrease cell growth or heighten the immune system. It also covers a method for detecting anti-Cpn10 antibodies, which is useful when examining the recipients of Xtoll for evidence of an immune reaction to the drug. Patents in this family expire between 2014 and 2017.

Family 3 relates to a method of treating MS patients with Cpn10. This family of patents expires in 2020.

Family 4 relates to the use of Cpn10 in the treatment of graft versus host disease. It also includes a composition of matter patent relating to a chemical form of Cpn10 in which an alanine residue has been substituted at the end of the protein (the current form of Xtoll). Patents in this family expire between 2023 and 2024.

Patent family 5 relates to the use of Cpn10 for regulating the TLR family and the immunomodulatory substances they induce. This family of patents is likely to expire in 2025 pending their approval.

Patent family 6 relates to the use of Cpn10 for regulating specific TLRs and covers methods for treating disease. This family of patents is likely to expire in 2026 pending their approval.

Patent family 7 relates to a range of modified versions of Cpn10 and their use in treating various forms of disease. This patent family is also likely to expire in 2026 pending their approval.

Patent family 8 relates to the use of Cpn10 or its modified forms for the treatment of hypersensitivity type diseases, a broader disease class encompassing autoimmune and other diseases. This family of patents is also likely to expire in 2026 pending their approval.

Patent family 9 relates to the use of Cpn10 to modulate the activity of immune system antigen presenting cells. This family of patents is likely to expire in 2027 pending their approval.

Patent family 10 relates to modified forms of Cpn10 which have a greater net positive charge than standard Cpn10 and which Cbio believes will serve to enhance Cpn10's ability to affect pattern recognition receptor (PRR) signalling. PRR signalling is important in innate immunity and can cause the release of a variety of pro-inflammatory molecules. This provides protection for an alternative signalling pathway than through TLRs. This family of patents is likely to expire between 2028 and 2029 pending their approval.

Xtoll will receive 12-year data exclusivity and patent extension under US legislation

Patent family 11 relates to Cpn10 variants and comprises a single provisional patent. Little further information is available.

As a biologic, **Xtoll will receive 12-years data exclusivity in the US.** While this doesn't mean that companies cannot commercialise Xtoll clones, it does mean that they will not be able to use data generated during the trials of Xtoll to support an application for approval of their own drug. The upshot being that any company wanting to commercialise an Xtoll like drug will need to do a full set of preclinical and clinical studies to gain approval. This would be an expensive exercise for what would essentially be a generic drug. Cbio will also be eligible to have some or all of its patents extended for up to 5-years under the US patent restoration act, which compensates companies for the time drugs spend in regulatory review.

Board of a very high calibre

## Board and Management

**Cbio has an exceptionally strong and well-rounded board.** Overall, it contains a nice mix of individuals with varying backgrounds unified by a history of medical science

commercialisation. Specifically, board members have significant expertise in research and discovery, drug development, regulatory affairs, pharmaceutical business development, capital raising, venture capital and public company management.

The members of the Board are as follows.

Executive Chairman Stephen Jones has a background in corporate recovery and reconstruction, and public company capital raisings. He is currently a non-executive director of Injet Digital Aerosols Ltd and Australia Biofund Investment Limited (Hong Kong), as well as Chairman of the Australian Technology Innovation Fund Limited. Previously he has been a director of numerous life science companies, including Analytica Limited, Psiron Limited and Bresagen Limited.

Managing Director Jason Yeates has been with Cbio since 2004, quickly moving up the ranks to be appointed Managing Director in 2007. Mr Yeates has a wealth of international business experience. Previously Mr Yeates held the positions of Asia-Pacific Finance Director MCI limited and a similar position at Asia Global Crossing Limited. He has also held previous roles at Harrods, Paramount/Universal and the Rutland Trust.

Non-Executive Director Dr Göran Ando is currently Vice Chairman of the Boards of Novo Nordisk A/S. Dr Ando has held previous positions as R&D Director of the Glaxo Group and President of R&D at Pharmacia. Other positions have included CEO of Celltech Group and Chairman of Novoxel S.A. Dr Ando also acts as an advisor to a number of companies investing and operating in the medical science space. Dr Ando is medical graduate of Linköping Medical University in Sweden.

Non-Executive Director Dr Peter Corr is co-founder and Managing General Partner of Celtic Therapeutics, a drug development focussed venture capital firm. After a long and distinguished career in academia, Dr Corr successfully transitioned to business. He has held positions of Senior Vice President Discovery Research at Monsanto Searle and President Pharmaceutical Research and Development at Warner Lambert/Parke Davis. More recently he has held the following positions a Pfizer: President, Worldwide Development; Executive Vice President, Global Research and Development; Senior Vice President for Science and Technology. Dr Corr has also served on a number of company and not-for-profit boards.

Non-Executive Director John Funder is a highly distinguished academic who is currently Professor of Medicine at Monash University, Senior Fellow at Prince Henry's Institute of Medical Research and a Professorial Associate at the Centre for Neurosciences, University of Melbourne. Professor Funder also holds a number of honorary positions, been a member of a number of advisory panels and has played a prominent role in healthcare in Victoria, Australia.

Non-Executive Director Dr Michael Monsour is a medical practitioner who operates a company that provides management support and software solutions for medical practitioners. Dr Monsour is the Chairman of Injet Digital Aerosols and a Director of Australia Biofund Investment Limited (Hong Kong) and the Australian technology Innovation Fund Limited. He is also the Chairman of Analytica Limited.

Non-Executive Director Dr Terje Kalland is currently Senior Vice President of the Biopharmaceuticals Research Unit and a member of senior management at Novo Nordisk. Prior to this Dr Kalland was Chief Scientific Officer at Biovitrum AB in Sweden. He has also previously been responsible for oncology research at Pharmacia. He currently holds a number of Board positions and has both a medical degree and a PhD.

Non-Executive Director Steven Streeter has an institutional stockbroking background and has held senior positions with a number Australia's revered broking houses. He is currently Executive Director Equities at Novus Capital and is a Non-Executive Director of Australia Biofund Investment Limited (Hong Kong) and the Australian Technology Innovation Fund Limited.

**Disclaimer**

In accordance with section 949A of the Corporations Act 2001, any recipient of the information contained in this document should note that information is general advice in respect of a financial product and not personal advice. Accordingly the recipient should note that: (a) the advice has been prepared without taking into account the recipient's objectives, financial situations or needs; and (b) because of that, the recipient should, before acting on the advice, consider the appropriateness of the advice, having regard to the recipient's objectives, financial situation and needs.

Although Lodge Partners Pty Ltd ("Lodge") consider the advice and information contained in the document is accurate and reliable, Lodge has not independently verified information contained in the document which is derived from publicly available sources. Lodge assumes no responsibility for updating any advice or recommendation contained in this document or for correcting any error or admission which may become apparent after the document has been issued. Lodge does not give any warranty as to the accuracy, reliability or completeness of advice or information which is contained in this document. Except in so far as liability under any statute cannot be excluded, Lodge, its employees and consultants do not accept any liability (whether arising in contract, in tort or negligence or otherwise) for any error or omission in this document or for any resulting loss or damage (whether direct, indirect, consequential or otherwise) suffered by the recipient of this document or any other person.

Lodge, its employees, consultants and its associates within the meaning of Chapter 7 of the Corporations Act 2001 may receive commissions from transactions involving financial products referred to in this document and may hold interests in financial products referred to in this document.

**General Securities Advice Warning**

This report is intended to provide general securities advice. In preparing this advice, Lodge did not take into account the investment objectives, the financial situation and particular needs of any particular person. Before making an investment decision on the basis of this advice, you need to consider, with or without the assistance of a securities adviser, whether the advice is appropriate in light of your particular investment needs, objectives and financial circumstances.

**Explanation of Lodge Partners recommendation system:**

Recommendations are assessments of each Lodge Partners Analyst's view of potential total returns over a 1 year period.

Expected total Return is measured as (capital gain (or loss) + dividend)/purchase price

We have divided our recommendations into three main categories:

**Buy:** Expected Total Return in excess of 15% over a 1 year period.

**Hold:** Expected Total Return between 0% and 15% over a 1 year period.

**Sell:** Expected Total Return less than 0% over a 1 year period.

**Analyst Verification**

I verify that I Marc Sinatra, have prepared this research report accurately and that any financial forecasts and recommendations that are expressed are solely my own personal opinions. In addition, I certify that no part of my compensation is or will be directly or indirectly tied to the specific recommendation or financial forecasts expressed in this report.

**Contact Lodge Partners:**

Melbourne

Level 5, 60 Collins St  
Melbourne Vic, 3000

Phone: +61 3 9200 7000

Fax: +61 3 9200 7077

[www.lodgepartners.com.au](http://www.lodgepartners.com.au)

Sydney

Level 30, 9 Castlereagh St  
Sydney NSW 2000

Phone: +61 2 8224 5000

Fax: +61 2 8224 5055