EDISON

Cellular Biomedicine Group

Clinical update

Results from AlloJoin Phase I

Pharma & biotech

In March 2018, Cellular Biomedicine Group (CBMG) announced results from the Phase I study of AlloJoin for knee osteoarthritis (KOA). The primary endpoint was safety, and the adverse event (AE) profile was similar to previous studies, with pain and swelling as the primary effects. The company did not release detailed efficacy data, but it appears that the treatment effect was sustained for 48 weeks, and it appeared to stop cartilage degradation.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/16	0.6	(18.1)	(1.34)	0.0	N/A	N/A
12/17	0.3	(20.1)	(1.40)	0.0	N/A	N/A
12/18e	0.0	(23.1)	(1.30)	0.0	N/A	N/A
12/19e	0.0	(27.8)	(1.48)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

AlloJoin safe, but not without pain

The safety data from the Phase I trial did not show any serious adverse events (SAEs), or any AEs that would preclude the use of the treatment such as inflammatory reactions or neoplasias. However, half of the patients examined in the study had grade 3 pain (no grade 4 events were observed) and two patients did not complete the study due to pain. The pain remitted after treatment in five to 14 days, although efficacy will have to be sufficient to justify this patient hurdle.

CFDA provides pathway for cell therapies

In December 2017, the Chinese FDA (CFDA) announced new guidance on the regulatory pathway for cell-based products. Cell therapies will now be regulated as drugs, which means that the company's products will likely be candidates for priority review, and have the potential for inclusion on the country's drug reimbursement lists. Also, the CFDA announced that cell therapies will only be required to have two clinical trials before approval, which significantly accelerates the company's development timeline.

Refocus exclusively on China

The company announced with its year-end 2017 update that it will be focusing its efforts exclusively on China at this time and will shelve its plan to develop AlloJoin for the US market. The outlay of resources for developing AlloJoin in the US has been very limited to this point, and we believe this decision was taken to focus resources on the increasingly amenable Chinese market.

Valuation: Increased to $353.1m or $20.76

We have increased our valuation of CBMG to $353.1m or $20.76 per basic share from $191.6m or $13.58 per basic share. This is largely driven by an increase in the probability of success for AlloJoin (to 40% from 15%) based on the recent safety data. We have also accelerated our development timelines for all of the company's products based on the recent regulatory changes. This is offset by removing the AlloJoin US program from our models.

4 April 2018

Price	**US$17.4**
Market cap	**US$296m**

Net cash ($m) at year-end FY17 + offering	52.2
Shares in issue	17.0m
Free float	55%
Code	CBMG
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(8.4)	21.7	53.3
Rel (local)	(5.7)	26.3	38.3
52-week high/low	US$21.8	US$5.3	

Business description

Cellular Biomedicine Group (CBMG) is a biotechnology company developing cell-based therapeutics with operations primarily in China. It has completed Phase II clinical trials of ReJoin, an autologous progenitor cell therapy for osteoarthritis, and Phase I for a similar allogeneic product (AlloJoin). It has also developed a CD19 CAR-T, which is currently in Phase I testing in China.

Next events

DLBCL results	Around end-H118
Adult ALL results	Around end-H118

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Encouraging clinical results from AlloJoin Phase I

On 16 March 2018, the company reported the final results from the AlloJoin Phase I clinical trial. AlloJoin is an allogeneic cell therapy composed of mesenchymal progenitor cells isolated from adipose tissue. The study enrolled 22 Chinese patients with knee osteoarthritis (KOA) and monitored them over 48 weeks. The primary endpoints of the study were safety and improvement in symptoms, as measured by the Western Ontario and McMaster Universities Arthritis Index (WOMAC). The patients were randomized onto one of three different dosing arms: 10m, 20m and 50m cells (n=7, 8, 7 respectively).

The most important data from the study at this point was safety. The adverse event (AE) profile provided by the company was largely consistent with earlier results and AE were primarily composed of pain and swelling of the knee, and no serious adverse events (SAEs) were observed. Two patients on the trial did not receive the second dose of cells because of pain following the first administration. The company provided a detailed breakdown of the grade 3 AEs (no grade 4 were observed), and they were of a similar profile (Exhibit 1). The most common grade 3 event was knee pain (seen in half of all patients). These rates are much higher than seen with other intra-articular injections. None of the AEs was reported as serious and the company stated that the pain remitted in five to 14 days following treatment. At this time, we do not consider these rates of pain necessarily limiting, considering the promises of long-term resolution in KOA symptoms which the treatment could potentially provide, although the product will have to justify this with efficacy. However, importantly, these safety results have removed several safety overhangs that could have halted development, such an inflammatory reactions or neoplasia.

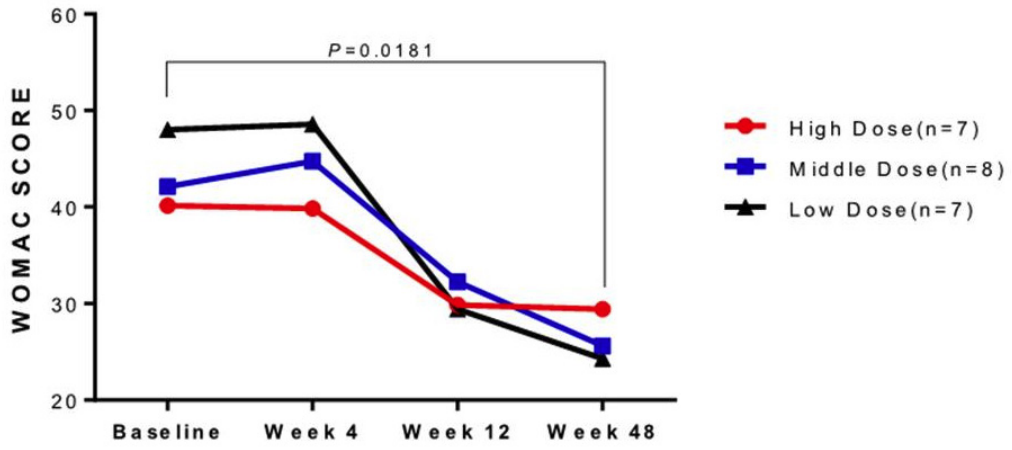
Exhibit 1: Grade 3 and higher AE

	A (high dose)				B (mid dose)				C (low dose)			
	N	Extent (Grade)	Duration (days)	Outcome	N	Extent (Grade)	Duration (days)	Outcome	N	Extent (Grade)	Duration (days)	Outcome
Knee pain	4	Moderate (3)	13	Remission	4	Moderate (3)	14	Remission	3	Moderate (3)	5	Remission
Knee localized edema					1	Moderate (3)	2	Remission	1	Moderate (3)	20	Remission
Hydrarthrosis					1	Moderate (3)	1	Remission	1	Moderate (3)	1	Remission
Arthrophlogosis					1	Moderate (3)	8	Remission				

Source: Cellular Biomedicine Group

The efficacy data provided by the company are limited by the fact that they are not placebo controlled and the company did not provide detailed numbers on treatment effects (instead opting to provide charts alone, Exhibits 2 to 5). The trial reported an improvement in patients' WOMAC scores of an estimated 10-20 points, and the improvement was statistically significant with the combined arms compared to baseline (p=0.0181, Exhibit 2). The WOMAC scale is a 24-item questionnaire measuring the impact of arthritis on daily function, such as pain while walking or the ability to rise from bed or go shopping. It is subdivided into three subparts: WOMAC A for pain, WOMAC B for stiffness, and WOMAC C for function. Historically, intra-articular saline injections show reduction in WOMAC scores of approximately 25-30% at week 12.

Exhibit 2: Improvement in WOMAC from AlloJoin

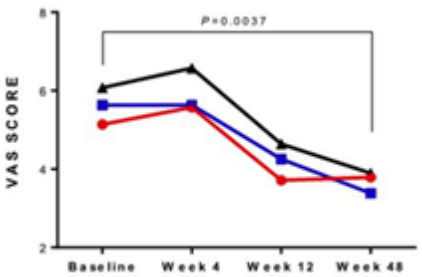


Source: Cellular Biomedicine Group

We find it encouraging that the trial was able to demonstrate an improvement in WOMAC in such a small number of patients and to maintain its effect for such a prolonged period. The widely used intra-articular hyaluronic acid (HA) injection product, Synvisc-One (Hylan G-F 20, Sanofi), showed a 37% improvement over baseline in the WOMAC A pain subscale at 26 weeks (31% for placebo),[1] although the total WOMAC was similar to saline.[2] The recently approved Zilretta (Flexion), an extended-release formulation of the steroid triamcinolone, improved WOMAC scores by approximately 50% in each category, although these effects peak at weeks 4-8 and are similar to placebo (~25%) by week 28.[3]

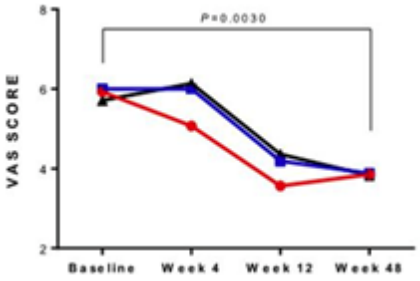
The company additionally provided data on knee pain (as measured on the visual analogue scale, VAS, Exhibits 3 and 4), and these values appear similar to Synvisc and placebo (improvement of 2.0 and 2.1 units respectively).[4]

Exhibit 3: VAS for pain in left knee



Source: Cellular Biomedicine Group

Exhibit 4: VAS for pain in right knee



Source: Cellular Biomedicine Group

The company also provided new data on the regrowth of cartilage using the product. Previously, the company reported that ReJoin increased cartilage volume by 104 mm^3 in the Phase I/IIa trial and 302mm^3 in the Phase IIb trial, as assessed by MRI. This is an important and unique property of this

[1] Chevalier X, et al. (2010) Single, intra-articular treatment with 6ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. *Ann Rheum Dis* 69, 113-119.

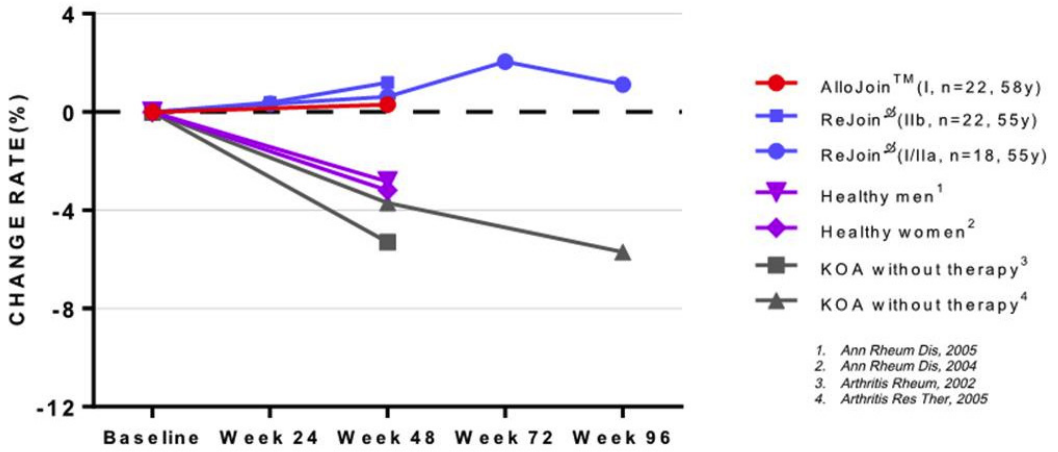
[2] FDA Summary of Safety and Effectiveness.

[3] Kelley AD, et al. (2017) An intra-articular, extended-release formulation of triamcinolone acetonide as a cost-effective therapy for treating osteoarthritis of the knee. ISPOR 21st Annual Meeting

[4] Karlsson J, et al. (2002) Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. *Rheumatol* 41, 1240-1248.

technology because other treatments for KOA may provide symptomatic relief but do not alter the course of the disease. In this instance the company provided data showing that AlloJoin altered the rate of change in cartilage volume, instead of absolute amounts. The 19 patients on the trial evaluable for cartilage volume had a small positive rate of cartilage gain, similar to ReJoin (albeit smaller). This is in comparison to the steady loss seen in healthy subjects and KOA patients in the historical controls.

Exhibit 5: Rate of change in cartilage volume



Source: Cellular Biomedicine Group

In general, we view the efficacy results as encouraging. It is difficult to draw conclusions without more specific data to compare to historical controls, but this is tempered by the prolonged period the effect was seen and the apparent effects on maintaining cartilage.

China to regulate cell therapies as drugs

There have been a number of significant changes to Chinese regulations, which are expected to affect the company. In December 2017, the CFDA released guidance on the development and regulatory pathway for cell-based therapeutics. This document provides significant clarity on the regulatory framework under which CBMG's products (and others) will be evaluated. Notably, cell-based therapeutics will be regulated as drugs. This has several immediate impacts. CBMG's products should qualify for priority review as innovative drugs, which should expedite filing timelines significantly. The company will need to file a clinical trial application (CTA) for each product, like other drug companies, but this should also be expedited. We also expect this regulation to put increasing scrutiny on the CAR-T and stem cell industries in China, by requiring manufacturing inspections, although we do not see this as a limitation for CBMG, because the company has consistently focused its efforts on maintaining its manufacturing quality to international standards. Finally, cell therapy products have a more direct pathway to reimbursement as drugs. There are a series of national drug reimbursement lists in China that are periodically updated, and cell therapies are entitled to inclusion on these lists, which insures some level of reimbursement (varying by province and resources).

Additionally, in an interesting departure from the standard protocol for drugs, which requires a Phase I, II and III, the CFDA announced that cell therapy products will only need to go through two clinical Phases: an early phase (focused on safety, dosing, and pharmacokinetics and pharmacodynamics) and a confirmatory phase. We believe that this is in part an effort to accelerate the development of this segment of healthcare, and that it will be reflected in the timeline for CBMG.

In other regulatory news, the CFDA, as well as other healthcare agencies, was reorganized into a larger market regulatory body. We expect this reorganization to increase governmental pressure on the agency, but that most of its regulatory functions will remain intact.

CBMG realigns to focus exclusively on China

The company announced with its year-end 2017 results that, after a strategic review, it has decided to focus its development efforts exclusively on China. Previously, the only program with a US presence was AlloJoin, although the company had not started US clinical trials. US development efforts to date have been limited to the establishment of a cell line for future trial use. We hypothesize that the recent results and the new regulatory pathway in China have increased confidence in the company's ability to gain traction there, and that the decision was made to simplify operations and maintain focus.

Valuation

We have increased our valuation of CBMG to $353.1m or $20.76 per basic share from $191.6m or $13.58 per basic share. This is largely driven by an increase in the probability of success for AlloJoin (to 40% from 15%) based on the safety data from the recently reported clinical trial results. Additionally, we have advanced our clinical trial timelines based on the new regulatory framework. We expect each product to require only two trials and to receive priority review status. This has advanced our timeline for ReJoin by approximately one year, and 18 months for the remaining products. Finally, we have increased net cash to reflect the recent financing. These factors are offset by removing the US commercialization of AlloJoin from our model and an increase in the negative NPV from AlloJoin/ReJoin cannibalism (due to the increased probability of success). The company has stated that it intends to release top-line results from the ongoing CAR-T studies around the end of H118, and we expect to update our valuation at that time.

Exhibit 6: Valuation of Cellular Biomedicine Group

Development program	Region	Prob. of success	Launch year	Peak sales ($m)	Margin	rNPV ($m)
DLBCL	China	20%	2022	181	63%	53.6
ALL	China	20%	2022	102	62%	28.9
ReJoin	China	40%	2021	144	31%	41.8
AlloJoin	China	40%	2022	431	58%	209.9
AlloJoin/ReJoin cannibalism	China					(33.2)
Total						$300.9
Net cash and equivalents (YE17+offering) ($m)						$52.2
Total firm value ($m)						$353.1
Total shares (m)						17.0
Value per basic share ($)						$20.76
Options						1.9
Value per diluted share ($)						$19.79

Source: Cellular Biomedicine Group reports, Edison Investment Research

Financials

The company reported a loss of $24.8m for 2017, which was lower that 2016 ($29.2m) despite R&D expenses increasing from $11.5m to $14.6m. This increase in R&D spending was driven largely by the advancement of the CAR-T and KOA clinical programs, and we expect it to continue to increase in later years ($15.9m in 2018). The company ended the period with $21.6m in cash following a $14.5m private placement at the very end of the year. This was subsequently followed by a $30.6m private placement at the beginning of February. We expect this cash to provide a runway into 2019, although we expect the company to need $90m in additional capital before profitability in 2022 ($20m in 2019 and $70m in 2021).

Exhibit 7: Financial summary

$'000s	2016	2017	2018e	2019e
31-December	US GAAP	US GAAP	US GAAP	US GAAP
INCOME STATEMENT				
Revenue	627.9	336.8	0.0	0.0
Cost of Sales	(860.4)	(162.2)	0.0	0.0
Gross Profit	(232.5)	174.6	0.0	0.0
EBITDA	(15,716.2)	(19,245.4)	(19,913.7)	(24,139.7)
Normalised operating profit	(18,351.2)	(22,231.4)	(23,357.6)	(27,462.1)
Amortisation of acquired intangibles	(4,611.7)	0.0	0.0	0.0
Exceptionals	0.0	0.0	0.0	0.0
Share-based payments	(5,452.4)	(5,345.2)	(5,345.2)	(5,345.2)
Reported operating profit	(28,415.3)	(27,576.6)	(28,702.8)	(32,807.3)
Net Interest	78.9	133.6	215.7	(296.6)
Joint ventures & associates (post tax)	0.0	0.0	0.0	0.0
Exceptionals	132.1	1,955.1	0.0	0.0
Profit Before Tax (norm)	(18,140.2)	(20,142.6)	(23,141.9)	(27,758.6)
Profit Before Tax (reported)	(28,204.3)	(25,487.9)	(28,487.1)	(33,103.9)
Reported tax	(4.1)	(2.5)	0.0	0.0
Profit After Tax (norm)	(18,140.2)	(20,142.6)	(23,141.9)	(27,758.6)
Profit After Tax (reported)	(28,208.4)	(25,490.3)	(28,487.1)	(33,103.9)
Minority interests	0.0	0.0	0.0	0.0
Discontinued operations	(1,000.6)	727.2	0.0	0.0
Net income (normalised)	(18,140.2)	(20,142.6)	(23,140.9)	(27,756.6)
Net income (reported)	(29,209.0)	(24,763.1)	(28,487.1)	(33,103.9)
Basic average number of shares outstanding (m)	14	14	18	19
EPS - basic normalised ($)	(1.34)	(1.40)	(1.30)	(1.48)
EPS - diluted normalised ($)	(1.34)	(1.40)	(1.30)	(1.48)
EPS - basic reported ($)	(2.16)	(1.73)	(1.60)	(1.77)
Dividend ($)	0.00	0.00	0.00	0.00
Revenue growth (%)	(74.9)	(46.4)	N/A	N/A
Gross Margin (%)	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Normalised Operating Margin	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	27,936.4	36,635.4	36,177.5	35,841.1
Intangible Assets	21,771.4	20,098.5	20,098.5	20,098.5
Tangible Assets	4,117.7	12,973.3	12,515.5	12,179.1
Investments & other	2,047.3	3,563.5	3,563.5	3,563.5
Current Assets	40,692.1	24,526.9	33,299.3	26,106.5
Stocks	0.0	0.0	0.0	0.0
Debtors	452.7	1,105.8	1,105.8	1,105.8
Cash & cash equivalents	39,252.4	21,568.4	30,340.8	23,148.0
Other	987.0	1,852.7	1,852.7	1,852.7
Current Liabilities	(2,364.0)	(3,676.1)	(4,532.5)	(4,762.0)
Creditors	(216.2)	(225.3)	(1,081.7)	(1,311.2)
Tax and social security	(28.9)	(28.9)	(28.9)	(28.9)
Short term borrowings	0.0	0.0	0.0	0.0
Other	(2,119.0)	(3,422.0)	(3,422.0)	(3,422.0)
Long Term Liabilities	(370.5)	(183.6)	(183.6)	(20,183.6)
Long term borrowings	0.0	0.0	0.0	(20,000.0)
Other long term liabilities	(370.5)	(183.6)	(183.6)	(183.6)
Net Assets	65,894.0	57,302.5	64,760.6	37,002.0
Minority interests	0.0	0.0	0.0	0.0
Shareholders' equity	65,894.0	57,302.5	64,760.6	37,002.0
CASH FLOW				
Op Cash Flow before WC and tax	(15,716.2)	(19,245.4)	(19,913.7)	(24,139.7)
Working capital	(255.4)	(1,434.6)	856.4	229.5
Exceptional & other	103.9	2,086.6	215.7	(296.6)
Tax	0.0	0.0	0.0	0.0
Net operating cash flow	(15,867.7)	(18,593.4)	(18,841.7)	(24,206.8)
Capex	(2,733.4)	(10,192.9)	(2,986.0)	(2,986.0)
Acquisitions/disposals	0.0	0.0	0.0	0.0
Net interest	0.0	0.0	0.0	0.0
Equity financing	43,285.6	10,826.5	30,600.0	0.0
Dividends	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.0	0.0
Net Cash Flow	24,684.4	(17,959.8)	8,772.4	(27,192.8)
Opening net debt/(cash)	(14,884.6)	(39,252.4)	(21,568.4)	(30,340.8)
FX	(316.6)	275.8	0.0	0.0
Other non-cash movements	0.0	0.0	0.0	0.0
Closing net debt/(cash)	(39,252.4)	(21,568.4)	(30,340.8)	(3,148.0)

Source: Cellular Biomedicine Group reports, Edison Investment Research

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