EDISON

Clal Biotechnology Industries

Initiation of coverage

Israeli science, worldwide presence

Pharma & biotech

We are initiating coverage on Clal Biotechnology Industries (CBI), an Israel/Boston-based healthcare investment company with an extensive portfolio incorporating a diverse range of technologies, indications and stages of development. CBI holds direct investments in 10 companies (nine biotech and one medical device company), most importantly MediWound, a NASDAQ-listed wound care company, and Gamida Cell, which is developing a universal bone marrow transplant (BMT) product. Also, BioCanCell and Biokine have programmes in Phase III or Phase III ready. We value the company at NIS918m or NIS5.87 per share.

Year end	Revenue (NISm)	PBT* (NISm)	EPS* (NIS)	DPS NIS)	P/E (x)	Yield (%)
12/15	55.8	(209.4)	(1.44)	0.0	N/A	N/A
12/16	30.5	(454.1)	(2.89)	0.0	N/A	N/A

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

MediWound: Promoting healing

CBI has a 35% stake in, and effective control of, MediWound, a publicly traded NASDAQ-listed company with a market capitalisation of ~$124m. MediWound's lead product, NexoBrid for burn wounds, is currently on the market in the EU and Phase III results for its US trial are expected in H118. It is also developing EscharEx for the much larger chronic and hard-to-heal wound market. The company plans to initiate two Phase III trials for the product in 2018.

Gamida Cell: Improving engraftment

Another key strategic asset for CBI is Gamida Cell (18%-owned), which is developing NiCord, a product derived from umbilical cord blood (UCB) stem cells, for the treatment of high-risk haematological malignancies and rare blood disorders. NiCord is the first BMT alternative to receive FDA breakthrough therapy designation. Enrolment is underway for a Phase III study with data expected in H219. Industry pioneer, Julian Adams, PhD is chairman and CEO.

A plethora of catalysts including four IPOs

2018 is expected to be a very eventful year for CBI, with key data expected from several portfolio companies, including MediWound. In addition, NASDAQ listings are currently targeted for four investments, namely Gamida Cell, BioCanCell (44%-owned), Cadent (24%) and Neon (5%). Strategic deals for eXlthera (54%-owned) and CureTech (53%) are also planned. Both types of catalysts could provide valuation inflection points for the company.

Valuation: NIS918m or NIS5.87 per share

Using a risk-adjusted NPV analysis on its major investments and cost or carrying values for the remainder, we arrive at a valuation for CBI of NIS918m or NIS5.87 per share. Based on our calculations, MediWound, Gamida Cell and BioCanCell are the most valuable assets in the company.

15 January 2018

Price*	**NIS3.58**
Market cap	**NIS560m**

*Priced as at 12 January 2018

	NIS3.42/US$
Net cash ($m, unconsolidated) at 30 September 2017	9.9
Shares in issue	156.5m
Free float	35.2%
Code	CBI
Primary exchange	TASE
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	7.3	7.9	49.9
Rel (local)	2.2	1.7	37.4
52-week high/low	NIS4.3		NIS2.3

Business description

Clal Biotechnology Industries (CBI) is a healthcare investment company focused on investing in a variety of therapeutic, diagnostic, and medical device companies covering a full range of development phases from preclinical to post-market. The company holds 10 direct investments with interests ranging between 5% and 70%. It also has five indirect investments through its 50% stake in the Anatomy Fund, which CBI manages.

Next events

MediWound NexoBrid Phase III results	H118
MediWound EscharEx Phase III trial initiation	H118
Gamida Cell IPO	H218

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Edison profile page

Investment summary

Company description: Diverse and maturing portfolio

Clal Biotechnology Industries (CBI) is an Israel-based healthcare investment company that was incorporated in 1998 and has been publicly traded on TASE since its IPO in May 2007. As of 30 September 2017, CBI has contributed NIS1,024m ($293m) to its portfolio companies. It is controlled by Clal Industries, an Israeli investment company that invests across the industrial, healthcare, energy and technology sectors and has a 48.6% stake in CBI. Clal Industries is a subsidiary of Access Industries, an international conglomerate controlled by Leonard Blavatnik, who is currently worth an estimated $20 billion. CBI is invested in a variety of life science companies, including a wide and diverse range of technologies, indications and stages of development. CBI has direct holdings in 10 companies with applications ranging from enzymatic debridement for wound care to cord stem cell transplants for haematological malignancies to NMDA therapeutics for neuropsychiatric disorders. Additionally, CBI is managing and has 50% equity in the Anatomy Medical Technology Fund (Anatomy), which invests in medical device companies

Valuation: NIS918m or NIS5.87 per share

Using a risk-adjusted NPV analysis on its major investments (MediWound, Gamida Cell, Biokine and BioCanCell) and cost or carrying values for the remaining assets, we arrive at a valuation of CBI of NIS918m or NIS5.87 per share. Based on our calculations, MediWound, Gamida Cell and BioCanCell are the most valuable assets of the company. CBI anticipates a series of potential inflection points over the next 12-18 months. In particular, Phase III results are expected for MediWound's NexoBrid in H118. Additionally, NASDAQ listings are currently targeted for four investments, namely Gamida Cell (18%-owned), BioCanCell (44%), Cadent (24%) and Neon (5%). Licensing deals for eXlthera (54%-owned) and CureTech (53%) are also planned.

Financials: Further cash required for new investments

Due to significant ownership stakes, CBI consolidates the financials of several of its investments (MediWound, Vedantra, CureTech and the Anatomy fund) and on this basis, it had NIS193.1m ($55.2m) in cash, cash equivalents and bank deposits as of Q317. CBI's cash position at the corporate level (excluding consolidation) was NIS34.6m ($9.9m) at the end of Q317. Due to the lean nature of the firm at the corporate level, the fact that it is not required to provide additional funding to its investments and the prospect for future exits, it is unclear whether CBI itself will need to raise additional capital.

Sensitivities: Diversified clinical and financial risk

The risks usually associated with investing in development-stage healthcare companies are relevant here such as regulatory hurdles, clinical trial uncertainty, understanding mechanism of action and funding requirements. We believe, however, the risk is reduced to some extent due to the portfolio approach, its diversification across indications and the range of stages of development. Almost all of the portfolio companies will require significant future investment from other sources to develop the products through to commercialisation. It is possible that CBI may participate in future fund-raising (we do not include any further investment in our forecasts). However, attracting other investors will be crucial for some of the portfolio companies' success. Finally, it should be noted that CBI has a controlling stake in three of its direct investments; while this is usual in a portfolio company and particularly in one where a number of the companies are maturing, it is worth noting that it could have an impact on its influence in those companies where it does not have a controlling position.

Enabling investment into a wide and diverse portfolio

CBI is invested in the healthcare sector across a variety of therapeutic, diagnostic, and medical device companies covering a full range of development phases from preclinical to post-market. This diversity is a key feature of the investment thesis of this company; it enables investment into a broad company universe, which serves to increase exposure and opportunity whilst reducing investor risk through diversification. The company has indicated it focuses its investment into companies and opportunities that it believes to offer promising, proprietary solutions to unmet medical needs. CBI has established itself as a significant player in the healthcare investment space with holdings in 14 life sciences companies across two portfolios: a biotechnology focused portfolio with four key investments (Exhibit 1) and an additional five direct holdings (Exhibit 2) and the Anatomy Fund, a private medical device-focused portfolio (Exhibit 3).

Exhibit 1: CBI's key investments

Investment	Technology	% held	Founded	Status	Advantages	Targets
MediWound*	Enzyme technology for severe burns and chronic wound	35%	2001	NexoBrid: Launched in Europe; In Phase III development in the US. EscharEx: Phase II complete.	Reduces time to successful eschar removal, reduces need for surgery and need for grafting.	NexoBrid Phase III study readout in H118; EscharEx Phase III trial initiation in H118.
Gamida Cell*	Cord stem cell transplant for hematologic diseases	18%	1998	NiCord: Enrolling Phase III; CordIn: Two ongoing Phase I/II trials; Natural killer cells: Initiated Phase I.	UCB for transplantation only requires partial matching and nicotinamide technology increases the limited population and quality of stem and progenitor cells. NiCord received FDA breakthrough therapy designation.	Enrolment is underway for a Phase III study of NiCord; NASDAQ listing targeted for H218.
BioCanCell	BC-819 is a DNA plasmid for non-muscle invasive bladder cancer	44%	2004	Ongoing Phase II BC-819 and BCG combination trial	BC-819 is a 4.5 kb recombinant DNA plasmid containing H19 regulatory sequences that drives expression of the potent diphtheria toxin A (DTA) and inhibits protein translation in malignant bladder cells. Monotherapy clinical studies demonstrated promising efficacy rates.	Initiate two (monotherapy and combination therapy) pivotal clinical trials in 2018. NASDAQ listing targeted for H218.
Biokine	Cyclic peptide inhibitor of CXCR4 for AML and other malignancies	27%	2000	Phase III in stem cell mobilisation. Phase II in relapsed/ refractory AML with BioLineRx; Phase Ib/II: collaboration with Genentech, combination BKT-140/BL-8040 and Tecentriq (atezolizumab) for multiple oncology indications.	Phase I/II trials showed vigorous mobilisation of CD34+ stem and progenitor cells from the bone marrow, inducing cell death and sensitising the malignant cells to anti-cancer therapies.	Phase II mobilisation results for BL-8040 in H118. Phase II pancreatic results in H218.

Source: Clal Biotechnology Industries. Notes: *Material assets according to CBI. All key investments included in our rNPV.

Exhibit 2: CBI direct holdings

Investment	Technology	% held	Founded	Status	Advantages	Targets
eXlthera	Factor Xla inhibition to prevent thrombosis and stroke	54%	2012	Phase I: Safety, tolerability, PK, PD of parenteral EP-7041	Positive Phase I dose escalation readout showed EP-7041 was safe and well tolerated in healthy volunteers and also demonstrated positive PK and PD data.	Potential licensing deal for EP-7041 in H118. Phase II initiation in H218. Selection of oral candidate expected in coming months.
Vedantra	Cancer and infectious disease immunotherapy	66%	2011	Preclinical	Engineering a molecular vaccine that possesses both hydrophilic and hydrophobic properties (amph-vaccine) to exploit albumin to transport small payloads to the lymph node to initiate effective T- and B-cell responses.	Amphiphile technology-based HPV vaccine for the treatment of HPV-related head and neck malignancies expected in the clinic in H118.
Neon	Personalised neoantigen therapeutics for cancer	5%	2015	Phase I: NEO-PV-01 and OPDIVO combination therapy	Initial results published in Nature. Several collaborations in the pipeline with large pharma, academic institutions, and other clinical stage biopharmaceutical companies. Recently completed a $106m crossover Series B financing.	Initial NEO-PV-01 and OPDIVO combination results expected in H118; Potential NASDAQ listing in H218.
Cadent	Treatment of CNS disorders by targeting calcium-sensitive potassium (SK) channels	24%	2010	CD-1883 to enter the clinic in H118	CD-1883 increases the sensitivity of calcium-sensitive potassium (SK) channels that play an essential role in regular neuronal firing with the intent to restore regularity and improve motor function.	The company expects CD-1883 to enter the clinic in H118. Potential NASDAQ listing in H218.
CureTech	Pidilizumab for lymphomas and DIPG	53%	2001	Phase III ready	Positive efficacy data in Phase II trials in DLBCL, follicular lymphoma, and DIPG.	Potential new partnership for Pidilizumab H118. Pivotal trial initiation in DIPG H218.

Source: Clal Biotechnology Industries. Notes: DIPG = diffuse intrinsic pontine glioma, CXCR4 = CXC- chemokine receptor-4 pathway, AML = acute myeloid leukaemia, NMDAR = N-methyl-D-aspartate receptor.

Exhibit 3: CBI indirect holdings through 50% stake in Anatomy

Investment	Technology	Anatomy investments at fair value to CBI ($m)	Founded	Status	Advantages	Targets
FDNA	Genetic disease diagnostics with facial recognition	1.1	2011	Market	Combines computer vision, machine learning and artificial intelligence (AI) to analyse facial features, genomic data, and patient symptoms	Innovation needs to be linked to clinical outcomes
Sight Diagnostics	Computer vision point-of-care blood diagnostics system	1.0	2011	Parasight: Market; OLO: Pivotal trial	Point-of-care full complete blood count (CBC) system	OLO: Clinical validation and commercial test development. FDA approval
Colospan	Developing bypass device (CG-100) for colorectal surgery	1.6	2010	CE approved in Europe.	Prevents life threatening leakage and makes it possible to cut down the use of stomas. Positive initial clinical results	CG-100: Soft launch in Europe in 2018 for market feasibility. Recruiting approximately 137 patients to participate in the safety and efficacy trial through H219 and expects to file for FDA marketing approval following trial results.
MinInvasive	Device for arthroscopic rotator cuff repair	1.6	2011	Market	Needle-based shoulder tendon repair device that eliminates the need for suture anchors	MicroPort granted exclusive rights to distribute device in China. FDA cleared and anticipating US launch.
Pi-Cardia*	Non-implant based technology for aortic valve stenosis	1.6	2009	Clinical	Developed a low profile catheter to treat aortic stenosis without replacing the valve	Clinical validation.
Total, including $1.5m in additional investments		**8.5****				

Source: Clal Biotechnology Industries. Note: *as of year-end 2016 **Pi-Cardia is also held directly (21% stake includes direct costs of CBI and 50% stake in Anatomy).

Investment portfolio

CBI is the direct owner of private equity in four Israeli biopharmaceutical and medical device companies (Gamida Cell, Biokine, CureTech, Pi-Cardia) and four US biopharmaceutical companies (eXIthera, Vedantra, Neon, Cadent). In addition, it has two direct investments in public companies including MediWound, an Israeli market-stage wound care company listed on the NASDAQ (MDWD) with a market cap of ~$124m and BioCanCell, a clinical-stage company developing a treatment for bladder cancer, currently traded on traded on the Tel Aviv Stock Exchange (TASE: BICL). CBI operates in both Israel and the US (invested in four US-based companies) and the company believes its dual presence has facilitated access to large pharma, KOLs and capital, and will continue to do so.

The company considers certain holdings to be significant assets and defines these material companies by present or potential (next year) material value on the basis of valuation, stage of clinical development, regulatory stage, significant licensing or collaboration agreements, and investment rounds. At this time, CBI considers MediWound and Gamida Cell to be material assets, while CureTech is no longer considered a material investment. We also consider BioCanCell and Biokine to be key investments due to their stages of clinical development and clinical collaboration agreements. CBI holds a majority interest in eXIthera and Vedantra, although the investments are not considered material for the company at this time.

MediWound: Enzymatic eschar debridement

MediWound is a market-stage wound care company focused on the treatment of severe burns, chronic wound management and connective tissue disorders. The company is publicly traded on the NASDAQ with a market cap of around $124m and two primary products: NexoBrid for burn wounds and EscharEx for chronic wounds (Exhibit 4). The wound care market is segmented (by wound type, ie burns, chronic, surgical and traumatic) and key players are well-resourced with diverse product portfolios to participate within the highly competitive space.

Exhibit 4: MediWound pipeline

Product	Indication	Status	Description	Notes
NexoBrid	Adults with deep partial- and full-thickness thermal burns	Launched in Europe; US Phase III study; EU Phase III paediatric study	Eschar removal agent of proteolytic enzymes.	■ Seven Phase II and Phase III clinical studies completed ■ EU Phase III trial was completed early, after interim analysis showed statistically significant results ■ US Phase III study results H118
EscharEx	Chronic and hard-to-heal wounds	Planning for pivotal study	Proteolytic enzyme technology	■ Phase II completed ■ Initiate two Phase III trials in 2018
MWPC003	Connective tissue disease	Preclinical	Proteolytic enzyme treatment	■ Proprietary injectable bromelain solution to potentially treat connective tissue diseases, such as Dupuytren's contracture, Peyronie's disease and scar treatment

Source: MediWound presentation and Edison Investment Research

The essence of both products is the removal of eschar, or dead tissue around burns and chronic wounds. Eschar must be removed in order for the healthy tissue to heal properly and avoid infection. The process of removing eschar is called debridement, which can be achieved surgically, by scraping necrotic tissue away with a blade, or mechanically, by applying a saline-moistened dressing to the wound and leaving it to dry overnight. Surgical and mechanical debridement are both painful, have high infection rates and are non-specific, ie healthy tissue is also removed along with the eschar. Burn injuries are the fourth most common trauma worldwide, though approximately 90% of burns occur in low- and middle-income countries. In the US, 1.1 million burn injuries require medical attention annually and 50,000 of these require hospitalisation.[1]

[1] CDC

NexoBrid is a powder containing proteolytic enzymes enriched in bromelain and mixed with a gel that together remove necrotic, dead cutaneous tissue in four hours while leaving healthy tissue intact when applied to deep partial and full-thickness burns (Exhibit 4). Bromelain is a mixture of several protein digesting enzymes derived from the stems of pineapple plants. The use of bromelain for this indication is not particularly surprising as its mechanism of action is well understood and enzyme debridement is commonly used to remove necrotic tissue from wounds.

NexoBrid was launched in Europe in 2014, in Israel in 2015, and in Argentina in 2016 via direct salesforce and distribution agreements with Latin America, Asia-Pacific and the Commonwealth of Independent States (Russia, etc) for the treatment for deep partial- and full-thickness thermal burns. The product generated $0.6m and $1.6m in sales in 2015 and 2016, respectively. NexoBrid has patent protection until at least 2025 in the EU and 2029 in the US, and has EU and US orphan drug status providing market exclusivity post-approval for 10 and seven years, respectively. Furthermore, NexoBrid will be distributed in Taiwan following local regulatory approval and this process is expected to take approximately two years.

The safety and efficacy of NexoBrid was investigated in a Phase III European Medicines Agency (EMA) open-label randomised control trial in 156 patients (ages 4 to 55) with deep partial and full thickness burns and compared to surgical or non-surgical standard of care (SOC). The comparative study demonstrated NexoBrid's ability to reduce the time for complete debridement (2.2 days in NexoBrid vs 8.7 days in SOC from injury), reduce the number of excisions performed (24.5% in NexoBrid vs 70.0% in SOC) and percent of wound area excised (13.1% in NexoBrid and 56.7% in SOC), reduce the number of autografts performed (17.9% in NexoBrid vs 34.1% in SOC) and percent of area autografted (8.4% in NexoBrid vs 21.5% in SOC).[2] Further, NexoBrid has shown comparable efficacy to surgical debridement (the most common SOC for wounds with 70% of burns treated through surgical means) without harming viable tissues.[3,4] MediWound is evaluating the efficacy of NexoBrid compared to SOC and a gel vehicle in the 175-patient DETECT Phase III study. Initial results are expected in H118 with 12-month follow-up and a BLA submission expected in H119.

The success of NexoBrid is highly dependent on the company's ability to achieve the following critical requirements: scientific acceptance (positive clinical trial data indicating efficacy and safety), adoption (revenues growing) and reimbursement. MediWound is tackling reimbursement in Europe on a country-by-country basis. The company is seeking reimbursement on a regional level (as opposed to nationally), and is currently working with hospitals and burn centres to demonstrate the cost effectiveness. In 2015, MediWound was awarded a five-year $112m contract from the US Biomedical Advanced Research and Development Authority (BARDA) to fund continued development and procurement of NexoBrid. The BARDA contract was recently upsized by $20m and according to MediWound, total funding will be sufficient to support the upcoming US Phase III NexoBrid programmes allowing the company to pivot liquidity into the development of their second product, EscharEx, an enzymatic topical debridement for chronic wounds.

EscharEx is in Phase II studies for use in eschar removal from hard-to-heal and chronic wounds to create a clean wound bed. Chronic wounds, such as vascular leg ulcers and diabetic ulcers, affect an estimated 2.4-4.5 million people in the US.[5] On average, these ulcers last for 12 to 13 months

[2] Rosenberg, L., et al. (2015). Minimally invasive burn care: a review of seven clinical studies of rapid and selective debridement using a bromelain-based debriding enzyme (Nexobrid®). *Annals of Burns and Fire Disasters, 28*, 264-274.

[3] Rosenberg, L., et al. (2015).

[4] NexoBrid. Summary of Product Characteristics.

[5] Frykberg RG, Banks J. (2015). Challenges in the Treatment of Chronic Wounds. *Advances in Wound Care*. 4(9):560-582.

and recur in up to 60-70% of patients.[6] In 2012, chronic wounds accounted for an estimated $6-15bn in annual US healthcare costs.[7]

Wound bed preparation and cleansing is essential to tissue repair. EscharEx can be used as a precursor to many products presently on the market targeted at healing and can potentially be used in conjunction with many marketed chronic wound products. EscharEx will predominantly compete with Smith & Nephew's Collagenase Santyl Ointment, the only FDA-approved biologic enzymatic debriding agent, with demonstrated efficacy. In one study comparing the efficacy of Santyl ointment to mechanical wound debridement in 48 patients with diabetic foot ulcers, Santyl reduced wound area by a mean 45% at four weeks and 54% at six weeks and significantly outperformed mechanical wound debridement. In addition, Santyl has been shown to decrease ulcer wound area by a mean of 68% at six weeks when used in adjunct to mechanical debridement compared to mechanical debridement alone (36% at six weeks). Smith & Nephew does not specifically break out sales of Santyl, but the Advanced Wound Bioactives category, of which Santyl is a significant part, had $342m in sales in 2016.

MediWound has completed a Phase II prospective, randomised control trial in a cohort of 73 patients with diabetic foot ulcers and venous leg ulcers to evaluate the safety and efficacy of EscharEx. EscharEx did meet the primary end point of the study, which was incidence of debridement compared to a gel vehicle (p=0.047). However, the company has yet to comment on overall improved wound closure (a secondary end point).

In September 2017, MediWound announced a $22m public offering with a 30-day underwriters' option. The net proceeds from the offering and underwriting grossed approximately $25.2m. MediWound intends to use the proceeds to advance the clinical development of EscharEx. The company plans to begin two pivotal US EscharEx Phase III trials (approximately 350 patients each) in H118.

Gamida Cell: Cord stem cell transplant for blood diseases

Gamida Cell is developing cell and immune therapies to treat haematological cancers and orphan genetic diseases (Exhibit 5). Gamida Cell is predominantly active in the field of BMT, a life-saving treatment for patients with high risk leukaemia and lymphoma. Importantly, in November, it was announced that biotechnology industry pioneer Julian Adams, PhD would take over as chairman and CEO. He has held senior leadership roles at a number of biotechnology companies and most notably is known for playing a key role in the discovery and developed of Velcade (bortezomib) for multiple myeloma, which peaked at $2.6bn in sales in 2014.

According to the US Department of Health and Human Services, approximately 17,500 people in the US are diagnosed with hematologic diseases annually, where the primary course of treatment is allogeneic BMT, in which stem cells are collected from a matching donor and transplanted into the patient. A donor must "match" a minimum of 6 human leukocyte antigen (HLA) markers and only 30% of patients match with a relative. This leaves the remaining 70% in need of an unrelated donor. Patients are matched with eligible donors by HLA typing and it can take several weeks or longer to identify an appropriate donor. According to one study, the average time from donor centre-initiated HLA typing to donation is 125.4 days.[8]

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6 Frykberg RG, Banks J. (2015).

7 Markova, A., & Mostow, E. N. (2012). US Skin Disease Assessment: Ulcer and Wound Care. *Dermatologic Clinics, 30*(1), 107-111.

8 Schmidt AH, Solloch UV, Baier D, Grathwohl A, Hofmann J, et al. (2011) Support of Unrelated Stem Cell Donor Searches by Donor Center-Initiated HLA Typing of Potentially Matching Donors. PLoS ONE 6(5): e20268.

Exhibit 5: Gamida Cell pipeline

Product	Indication	Status	Description	Notes
NiCord	High-risk haematological malignancies	Phase III	Expanded cell graft derived from umbilical cord stem cells.	Enrolment is underway for confirmatory study of NiCord
CordIn	Rare genetic disease	Phase I/II	Cryopreserved stem/progenitor cell-based product of purified CD133+ cells	Two studies into use of CordIn for SCD and thalassemia and for aplastic anaemia
Natural Killer Cells	Refractory B-cell lymphoma and multiple myeloma	Phase I	Donor derived expanded NK cells	Enrolment underway for multiple myeloma and lymphomas

Source: Gamida Cell. Notes: SCD = sickle cell disease, NK = natural killer.

UCB has been utilised in clinical practice as an alternative graft source to peripheral blood for c 30 years.[9] UCB for transplantation only requires partial matching (a minimum requirement of 4 out of 6 HLA biomarkers) and has lower rates of graft-versus-host disease (GvHD).[10] However, the use of UCB for BMT requires several mixed UCB samples and is limited by the minimal number of stem and progenitor cells. Low cell dose is associated with delayed engraftment and a longer neutropenic period, which is related to higher morbidity and transplant related mortality.

The company's proprietary technology uses the small molecule nicotinamide (NAM), which is simply a form of vitamin B-3, to delay cell differentiation, increase the limited population and quality of stem and progenitor cells (CD34+/CD38-/Lin-cells) and also enhance cell functionality, ie migration, homing, engraftment.[11]

Gamida Cell's leading product, NiCord, expands UCB cell graft *ex vivo* and enriches the specific subpopulation of stem and progenitor cells to treat haematological malignancies such as leukaemia and lymphoma. Essentially, $CD133^+$ cells selected from a single unit of UCB are cultured for 21 days in nicotinamide resulting in a c 100-fold expansion of dose stem and progenitor cells, which are then cryopreserved until transplanted into patients. This expansion is a substantial advantage over a single UCB graft.

In Phase I/II data in 35 evaluable patients with acute leukaemia, myelodysplastic syndrome (MDS), and lymphoid malignancies presented at the American Society of Haematology (ASH) in December 2017, NiCord demonstrated a median time to neutrophil engraftment of 11 days and a median time to platelet engraftment of 34 days. According to case-matched data from the Center for International Blood and Marrow Transplant Research, standard UCB treatment results in a median time to neutrophil engraftment of 21 days and a median time to platelet engraftment of 46 days. These data indicate that NiCord has the potential to be the graft of choice for patients without a matched donor.

NiCord is the first and only BMT alternative to receive FDA breakthrough therapy designation, and was also granted FDA and EMA orphan drug designation. Enrolment is underway for a Phase III study of NiCord, which will take place worldwide in 12 sites. This trial is investigating the ability of NiCord to provide a UCB graft with an ample amount of cells that have fast and vigorous in vivo neutrophil and platelet producing potential to improve transplantation outcomes (as low cell dose is associated with delayed engraftment and poor outcomes). The primary endpoint for the trial is time to neutrophil engraftment following transplantation (on or before the 42nd day post-transplant) compared to a non-manipulated cord blood unit. The company intends to utilise the funds from its recent $40m fund-raising to progress its Phase III trial, which is expected to read out in H219.

Cord blood is currently used for the treatment of certain cancers (acute lymphoblastic leukaemia, acute myeloid leukaemia, Hodgkin's lymphoma), blood disorders (sickle cell anaemia, thalassemia)

[9] Ballen, K. K., et al. (2013). Umbilical cord blood transplantation: the first 25 years and beyond. *Blood, 122*(4), 491-498.

[10] Macmillan, M. L., et al. (2008). Acute graft-versus-host disease after unrelated donor umbilical cord blood transplantation: analysis of risk factors. *Blood, 113*(11), 2410-2415.

[11] Peled, T., et al., (2012). Nicotinamide, a SIRT1 inhibitor, inhibits differentiation and facilitates expansion of hematopoietic progenitor cells with enhanced bone marrow homing and engraftment. *Experimental Hematology, 40*(4).

and bone marrow failure syndromes (such as severe aplastic anaemia) as well as metabolic disorders and immunodeficiencies. Using NAM technology and UCB, Gamida Cell is developing CordIn to treat aplastic anaemia (AA), sickle cell disease (SCD), and thalassemia. AA is a blood disorder with variable worldwide incidence. A review compared annual national incidences of AA in China with 7.4 per million, 4 per million in the US and 2.34 per million reported in the EU.[12] Likewise, SCD is a common genetic blood disorder that affects approximately 100,000 Americans, the majority of whom are African American, and millions of people worldwide.[13] Individuals with SCD in the US contribute to up to $1.6bn in healthcare utilisation.[14] The company expects to report CordIn Phase I/II in patients with SCD and thalassemia results around the end of 2018. An additional Phase I/II in patients with AA was recently initiated and is expected to be completed in 2021.

Furthermore, Gamida Cell is developing donor derived natural killer (NK) cells for blood and solid cancers such as B-cell lymphoma and multiple myeloma. The market for multiple myeloma treatments is significant as there are approximately 30,000 new cases per year in the US alone.[15] Revlimid, a leading treatment of multiple myeloma, in addition to myelodysplastic syndromes, marketed by Celgene, had $6.97bn in sales in 2016. NK cells are a type of lymphocyte, or white blood cell, that play a central role in lysing infected or transformed cells and therefore offer an innovative approach to cancer treatment. Advances in cell processing and engineering, and improved methods of characterisation, purification and expansion have led to increased interest in using NK cells for cancer immunotherapy.[16] Companies such as NantKwest, Affimed, and Celgene are working to develop NK cells for cancer immunotherapy. In a mouse model, NK cells expanded with NAM demonstrated higher retention in bone marrow, spleen and peripheral blood than untreated NK cells. The results were presented at ASH in December 2017 and, based on these preclinical findings, the company has initiated a Phase I trial with the University of Minnesota in 24 adult patients with multiple myeloma and lymphomas. The primary end point of the trial is the safe maximum tolerated dose of NAM-NK cells and the study is expected to readout in H119. The company has stated that NAM-NK cells can be manufactured cost effectively and can potentially be distributed as an off-the shelf product, and if validated this offers a significant opportunity for the company because historically NK cell expansion into a clinically significant quantity has presented challenges as NK cells only represent a minor portion of peripheral blood mononuclear cells.[17]

BioCanCell: A DNA plasmid to treat bladder cancer

BioCanCell is a clinical-stage biopharmaceutical company founded in 2004 upon the discovery of the H19 gene, a controlling element for fundamental malignant cell processes such as carcinogenesis and metastasis. BioCanCell's technology and clinical platform targets non-muscle invasive bladder cancer (NMIBC). Bladder cancer is the sixth most common cancer worldwide and has the highest per patient medical cost of any cancer.[18] There will be an estimated 79,000 new cases diagnosed in the US in 2017.

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12 Young, N. S., & Kaufman, D. W. (2008). The epidemiology of acquired aplastic anemia. *Haematologica, 93*(4), 489-492.

13 Lanzkron S, Carroll CP, Haywood C. Mortality Rates and Age at Death from Sickle Cell Disease: U.S., 1979–2005. *Public Health Reports*. 2013;128(2):110-116.

14 Arnold, S.D. et al. (2015). Allogeneic hematopoietic cell transplantation for children with sickle cell disease is beneficial and cost-effective: A single-center analysis. Biology of Blood Marrow and Transplantation, 21(7), 1258-1265.

15 NCI

16 Shook, D. R., and D. Campana. Natural killer cell engineering for cellular therapy of cancer. *Tissue Antigens*, vol. 78, no. 6, 2011, pp. 409–415.

17 Fujisaki, H., et al. (2009) Expansion of highly cytotoxic human natural killer cells for cancer cell therapy. *Cancer Research, 69(9),* 4010-4017.

18 *World J Urol*. 2009 Jun; 27(3); 295-300.

Patients who present with NMIBC undergo initial tumour transurethral resection followed by Bacillus Calmette-Guérin (BCG) therapy. BCG was the first intravesical immunotherapy for urothelial carcinoma treatment approved by the US Food and Drug Administration (FDA) in the 1980s and has remained the mainstay following tumour resection. Yet, patients experience recurrence rates of 15-61% and 31-78% after one and five years, respectively.[19] Even with optimal combination BCG and chemotherapy, almost 50% of patients will experience invasive cancer or develop new cancers of the upper urinary tract and approximately 30% of these cancers are treated with a cystectomy (surgery to remove the urinary bladder). Nearly three decades later, the FDA approved a series of immunotherapies to treat bladder cancer (Exhibit 6).

Exhibit 6: Immunotherapy drugs for bladder cancer

Drug	Company	FDA approval
Opdivo (nivolumab)	Bristol-Myers Squibb	February 2017
Tecentriq (atezolizumab)	Genentech	April 2017
Keytruda (pembrolizumab)	Merck	May 2017
IMFINZI (durvalumab)	AstraZeneca	May 2017
Bavencio (avelumab)	EMD Serono	May 2017

Source: FDA, Edison Investment Research

BioCanCell is developing BC-819 (DTA-H19), a 4.5 kb recombinant DNA plasmid containing H19 regulatory sequences that drives expression of the potent diphtheria toxin A (DTA) and inhibits protein translation in malignant bladder cells. Pre-clinical analysis of BC-819 demonstrated an 85.2% uptake into bladder cancer cells after a single *in vitro* transfection.

In an open label 18-patient Phase I/II single-arm trial, intravesical infusion of BC-819 into the bladder showed a 12-month recurrence free rate of 44% and 24-month recurrence-free rate of 29%. A desirable safety profile and no dose-limiting toxicity was observed. Mild to moderate bladder discomfort, painful and urgent urination, urinary tract infection, diarrhoea, hypertension and weakness were among the most common adverse events reported. In an open label 39-patient Phase II single-arm trial, the intravesical infusion of BC-819 into the bladder demonstrated 12-month and 24-month recurrence-free rates of 46% and 33%, respectively, and in an ongoing 38-patient Phase II combination trial of the intravesical infusion of BC-819 with BCG demonstrated a 12-month recurrence-free rate of 68% while the 24- month recurrence rate has yet to be reported. The combination of BC-819 and BCG demonstrated a similar safety profile to that of BC-819 monotherapy. It is important to note that all three trials are single- arm (non-comparative) with small sample sizes making it difficult to compare to the current standard of care.

BioCanCell is preparing to initiate two pivotal clinical trials in 2018. BC-204 will be an open label Phase II single-arm trial in 140 patients who are unresponsive to BCG therapy and the primary end point is durable response rate (either partial or complete) at 12 months and is expected to begin in H118. BC-301 will be an open label Phase III trial in approximately 495 patients of BC-819 in combination with BCG in versus BCG alone and is expected to begin in H218. The BC-301 trial has been granted a special protocol assessment (SPA) by the FDA and the primary end point is median time to recurrence. The BC-301 trial will be the first comparative study and we expect the results to elucidate the clinical value of BC-819 for NMIBC.

In addition, BioCanCell is developing BC-821, a modification of BC-819, which contains a second promoter with an IGF2-P4 regulatory sequence. The IGF2 protein is involved in cell proliferation and differentiation and is overexpressed in a variety of human tumours. Therefore, the IGF2-P4 promoter is functional during tumour development. DTA expression via two different control elements can potentially enhance cell-killing and increase the chance of activation of one of the promoters. *In vitro* and *in vivo* studies showed BC-821 is four times more potent than BC-819. BC-819 patents will expire in the US and in the rest of the world in 2017 and 2018, respectively;

[19] Van der Heijden, A. G., & Witjes, J. A. (2009). Recurrence, Progression, and Follow -Up in Non–Muscle-Invasive Bladder Cancer. *European Urology Supplements, 8*, 556-562.

however, BC-819 and BC-821 are considered biologics and are eligible to receive 12 years of market exclusivity in the US and eight to 11 years of market exclusivity in the EU and Japan.

A recent tender offer to take the company private was rejected by shareholders. Management had previously indicated the potential for an uplisting on the NASDAQ market, which has been friendlier to gene therapy-related companies, in H218. That remains an option, although others are also under consideration.

Biokine: Mobilising stem cells for AML

Biokine is a privately held clinical-stage biopharmaceutical company investigating the overexpression of the CXC-chemokine receptor-4 (CXCR4) pathway in cancer, ie tumour progression, angiogenesis, metastasis, and survival.[20] CXCR4 is overexpressed in many haematological malignancies such as acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), and NHL. The company's lead programme, BKT-140, is a cyclic peptide CXCR4 antagonist and was licensed to BioLineRx in 2012. BKT-140/BL-8040 is being developed for the treatment of acute myeloid leukaemia (AML), an aggressive blood cancer that originates in bone marrow. The NIH estimates that there will be over 21,000 new cases of AML in 2017 in the US and only 26.9% of patients will survive five years or more after initial diagnosis.

BKT-140/BL-8040 Phase I/II trials demonstrated vigorous mobilisation of CD34+ stem and progenitor cells from the bone marrow, which therefore causes malignant cells to become sensitive to anti-cancer therapies. The studies also found that BKT-140/BL-8040 inhibits the growth of haematological malignancies by inducing apoptosis (cell death). The US FDA granted orphan drug designation to BKT-140/BL-8040 for the treatment of AML and stem cell mobilisation. Sanofi's MOZOBIL (plerixafor), a CXCR4 inhibitor, is the only FDA-approved stem cell mobiliser on the market and is used in combination with a granulocyte stimulating factor (G-CSF) to traffic hematopoietic stem cells to the peripheral blood for collection and autologous transplantation to treat multiple myeloma and non-Hodgkin's lymphoma. However, plerixafor cannot be used in patients with leukaemia. BioLineRx is investigating BKT-140/BL-8040 in combination with the current standard of care for AML, cytarabine, in a 194-patient Phase II study that is expected to readout interim data in H118. Additionally, BioLineRx has begun a Phase III trial of BKT-140/BL-8040 in combination with G-CSF for hematopoietic stem cell mobilisation for autologous transplantation in patients with multiple myeloma, which is scheduled to read out in H219. BKT-140/BL-8040 is also being investigated in significant collaborations with leading pharmaceutical companies and institutions.

In 2016, BioLineRx initiated a single-arm Phase II trial with Merck to evaluate BKT-140/BL-8040 in combination with KEYTRUDA (pembrolizumab), the anti-PD-1 therapy, in 30 patients with metastatic pancreatic adenocarcinoma. The patients are first treated with subcutaneous (SC) injections (1.25mg/kg) of BKT-140/BL-8040 monotherapy for one week followed by combination therapy (200mg 30-minute intravenous infusion of pembrolizumab plus SC injections of 1.25mg/kg BKT-140/BL-8040) three times a week for three weeks. The primary end point of the trial is objective response rate, which is determined by CT or MRI imaging evaluation of lesions and is expected to read out in mid-2018. A clinical research collaboration between Merck and the MD Anderson Cancer Center is investigating the combination of BKT-140/BL-8040 with KEYTRUDA and with various other treatments for pancreatic cancer.

Additionally, BioLineRx announced the initiation of several Phase Ib/II trials with Genentech to investigate the combination of BKT-140/BL-8040 with Tecentriq (atezolizumab), the anti-PDL1 immunotherapy, in 60 patients with intermediate to high-risk AML, in 185 patients with pancreatic adenocarcinoma, and in 357 patients with gastric cancer.

[20] Teicher, B. A., & Fricker, S. P. (2010). CXCL12 (SDF-1)/CXCR4 Pathway in Cancer. *Clinical Cancer Research, 16*(11), 2927-2931.

Although the collaborations with Merck, Genentech and the MD Anderson Cancer Center for pancreatic cancer, gastric cancer and NSCLC are motivating, we do not include these indications in our valuation at this time. Our analysis of Biokine is solely dependent on the AML trials. However, we expect to update our valuation as the trials progress.

eXIthera: Inhibiting FXIa in blood coagulation

eXIthera Pharmaceuticals is a US biotech company developing small molecules to inhibit Factor XIa, a plasma serine protease, for the prevention of thrombosis and stroke. Blood coagulation involves both thrombosis and haemostasis, which are intrinsic and extrinsic pathways, respectively. Thrombosis contributes to the global disease burden of ischemic heart disease, ischemic stroke, and venous thromboembolism.[21] To illustrate, every year over 795,000[22] people in the US have a stroke, whereas an estimated 87%[23] of all strokes are ischemic and more than 130,000 of those incidences are fatal.[24] Stroke costs the US $33bn annually, including the costs of medicine, healthcare services and missed days of work.[25]

Current antithrombotic therapies are classified as either anticoagulants, which target either thrombin, Factor Xa or both serine proteases involved in the coagulation cascade, or antiplatelet agents which inhibit the formation of blood clots and decrease platelet aggregation. Common anticoagulants include antithrombin activators (heparins), vitamin K antagonists (warfarins), direct inhibitors of thrombin (Pradaxa [dabigatran etexilate]), and Factor Xa inhibitors (Xarelto [rivaroxaban] and Eliquis [apixaban]) and common antiplatelet agents include ADP antagonists (clopidogrel, ticagrelor), COX inhibitors (aspirin), glycoprotein IIb/IIIa inhibitors (tirofiban, abciximab), and phosphodiesterase inhibitors (dipyridamole). Although antithrombotic therapies on the market today are effective and cost efficient, several are dose limiting, irreversible (clopidogrel), require monitoring as they can cause severe bleeding (abciximab), and have serious food-drug and drug-drug interactions (heparin, warfarin).[26] According to IMS Health, antithrombotics are expected to have sales of approximately $26 billion in 2018, with Xarelto, a Factor Xa, expected to sell over $6.4 billion of that, according to Evaluate Pharma.

Coagulation is triggered by either the extrinsic pathway (haemostasis) or the intrinsic pathway (thrombosis), which feed into a shared pathway that results in the production of thrombin and consequently fibrin formation. Recent studies suggest that Factor XIa plays a significant role in thrombosis but a minor role in haemostasis and thus provides an alternative to current blood thinners that have limited dissolution between the two pathways. Previous studies from other groups have demonstrated that individuals with high levels of Factor XIa were more likely to develop venous thromboembolism, myocardial infarction and stroke,[27, 28, 29] whereas Factor XIa

[21] ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to the global disease burden. *J Thromb Haemost* 2014; 12: 1580-90.

[22] Centers for Disease Control and Prevention (CDC).

[23] Benjamin EJ, Blaha MJ, Chiuve SE, et al. on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics - 2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e229-e445

[24] CDC.

[25] Mozaffarian D, et al. Heart disease and stroke statistics - 2015 update: a report from the American Heart Association. *Circulation* 2015;131(4): e29–322.

[26] Al-Horani, R. A., & Desai, U. R. (2016). Factor XIa inhibitors: A review of the patent literature. *Expert Opinion on Therapeutic Patents, 26*(3), 323-345.

[27] Meijers JC, et al. (2000) High levels of coagulation factor XI as a risk factor for venous thrombosis. *N. Eng. J. Med*. 342: 696-701.

[28] Doggen CJ, et al. (2006) Levels of intrinsic coagulation factors and the risk of myocardial infarction among men: opposite and synergistic effects of factors XI and XII. *Blood* 108: 4045-4051.

[29] Yang DT, et al. (2006) Elevated factor XI activity levels are associated with an increased odds ratio for cerebrovascular events. *Am J. Clin. Pathol*. 126: 411-415.

deficiency studies demonstrated antithrombotic activity and reduced ischemic stroke and venous thrombosis.[30] [31]

eXlthera is developing EP-7041 to inhibit Factor XIa as a novel anticoagulant. The company presented data from a double-blind Phase I safety, efficacy and dose evaluation trial of EP-7041 in 60 healthy adults at the American Heart Association Scientific Sessions in November 2017. EP-7041 demonstrated a rapid and predictable increase in activated partial thromboplastin time (aPPT, a standard clinical measure of anticoagulation activity) and did not affect prothrombin time (PT, a measure of clotting time via the extrinsic pathway). The pharmacokinetics and pharmacodynamics of EP-7041 suggest it has potential to be effective for use in hospitals and would directly compete in the heparin market. eXlthera is also developing an oral therapeutic. eXlthera faces the uncertainties of a crowded market and its future success is highly dependent on its ability to identify a partner to advance studies of EP-7041, as the company expects upcoming trials to include thousands of patients. CBI is currently targeting a licensing deal in H118 with Phase II beginning by the end of 2018.

Vedantra: Endogenous immune response for HPV and malaria

Vedantra Pharmaceuticals, a preclinical immunotherapy company based in Cambridge, MA, is developing vaccines to engage the immune system to target cancer and infectious disease. Gamida Cell's Julian Adams was appointed as executive chairman in January 2017.

Vedantra is developing two technologies to stimulate the adaptive immune system to safeguard against diseases such as cancer and malaria by directly delivering antigens or protein fragments to antigen-presenting cells (APCs) of the lymph node. It is using its lead technology to engineer a molecular vaccine that possesses both hydrophilic and hydrophobic properties (amph-vaccine) to exploit albumin to transport small payloads to the lymph node to initiate effective T- and B-cell responses.[32] The company plans to advance an amphiphile-technology-based HPV vaccine for the treatment of HPV-related head and neck malignancies into the clinic in H118. In March 2017, Vedantra announced a non-exclusive research collaboration with Neon Therapeutics, also a portfolio company of CBI, in which the companies will explore the combination of Vedantra's amph-vaccine platform and Neon's neoantigen research to develop cancer therapeutics.

The company's second technology involves encapsulating active agents with adjuvants in interbilayer-crosslinked multilamellar vesicles (ICMVs) to provide an alternative approach to lipid nanoparticle carriers. Vedantra's preclinical studies demonstrate that a lipid shell with crosslinked adjacent phospholipid bilayers preserves *in vivo* particle stability (for about 30 days), improves protein retention and delivery kinetics versus traditional drug-delivery vehicles, ie polylactic-co-glycolic acid (PLGA) nanoparticles, multilamellar vesicles (MLVs), dehydration-rehydration vesicles (DRVs), and liposomes.[33] The ICMV manufacturing process is validated by an external GMP CMO.

The company is using the ICMV platform to advance preventive vaccines to drive endogenous immune responses to target malaria. Vedantra's malaria research programme is currently in a preclinical monkey study supported by the Bill and Melinda Gates Foundation.

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30 Salomon O., et al. (2008) Reduced incidence of ischemic stroke in patients with severe factor XI deficiency. *Blood* 111:4113-4117.

31 Salomon O *et al.* (2011) Patients with severe Factor XI deficiency have a reduced incidence of deep-vein thrombosis. *Thromb. Haemost.* 105: 269-273.

32 Lui, H., et al., (2014). Structure-based programming of lymph-node targeting in molecular vaccines. *Nature, 507*, 519-522.

33 Moon, J., et al., (2011). Interbilayer-crosslinked multilamellar vesicles as synthetic vaccines for potent humoral and cellular immune responses. *Nature Materials, 10*, 243-251.

Neon: Personalised neoantigens for cancer

Neon Therapeutics is a clinical immuno-oncology company headquartered in Cambridge, Massachusetts, developing patient-specific vaccines and autologous T-cell therapies to treat cancer. Since Neon's inception in 2015, it has raised a total of $161m in private financing and an IPO is targeted for H218. The work of several co-founders from the Dana-Farber Cancer Institute, the Broad Institute and Massachusetts General Hospital is the foundation of Neon's technology. There have been significant advances in the development of checkpoint inhibitors, specifically PD-1 (Keytruda [pembrolizumab], Opdivo [nivolumab]) and PD-L1 (Tecentriq [atezolizumab], Bavencio [avelumab], Imfinzi [durvalumab]) antibodies and, along with recent developments, there is now a considerable need for the development of cancer vaccines to potentiate checkpoint inhibitors specifically for solid cancers.

Neon's lead therapeutic, NEO-PV-01, is a personalised cancer vaccine and is developed using mass spectrometry DNA and RNA sequencing, which is used to analyse the relationship between peptide antigens and cell surface proteins, and RECON, which is a cloud-based bioinformatics system used to identify somatic mutations and determine which mutations are likely to express immunogenic neoantigens, which are human leukocyte antigen (HLA) bound peptides that arise from tumour-specific mutations. NEO-PV-01 is manufactured for each individual patient. Neon has several collaborations in the pipeline with large pharma, academic institutions and other clinical-stage biopharmaceutical companies. NEO-PV-01 is currently being investigated in a 90-patient Phase Ib trial for use in combination with Bristol-Myers Squibb's Opdivo (nivolumab), a PD-1 immune checkpoint inhibitor, for the treatment of metastatic melanoma, non-small cell lung cancer and bladder cancer. The study is expected to be completed by the end of 2018 with data likely in H119, although interim results are likely before that. The primary end point of the trial is the rate of severe adverse events (and adverse events) that lead to treatment discontinuation. In December, the company announced a clinical trial combination with Merck to evaluate NEO-PV-01 in combination with KEYTRUDA (pembrolizumab) Merck's PD-1 immune checkpoint inhibitor.

In June of this year, the Dana-Farber Cancer Institute demonstrated the feasibility, safety and immunogenicity of a vaccine (five priming and two boosters) that targets up to 20 predicted personal tumour neoantigens per patient in six patients with melanoma. Of six vaccinated patients, the four who entered the study with stage IIIB/C melanoma experienced no recurrence at 25 months post vaccination, while the two patients who entered the study with previously untreated stage IVM1b melanoma did demonstrate disease recurrence and were then treated with anti-PD-1 therapy and subsequently experienced tumour regression.[34] In addition, Neon and Apexigen, a clinical-stage biopharmaceutical company, are collaborating in a Phase I clinical trial investigating the combination of NEO-PV-01 and Apexigen's APX005M, a CD40 agonist antibody that stimulates the anti-tumour immune response.

Furthermore, Neon is developing NEO-PTC-01, a personal autologous T-cell therapy using immunogens in co-culture with T-cells and monocyte-derived dendritic cells from patients to stimulate autologous T-cells to target neoantigens, and trials are expected to begin in 2018. Lastly, Neon is developing a programme to identify foreign peptides that can be used in tumour-specific and pan-tumour indications. Shared targets can be utilised in several product formats such as off-the-shelf vaccines, antibody approaches, and T-cell receptor-based therapies to target patients' neoantigens, which can increase tumour specificity and minimise toxicities.

Cadent: Modulating CNS targets

Cadent Therapeutics, formerly Luc Therapeutics, is a private biopharmaceutical company, based in Cambridge, MA, developing drugs to target movement and cognitive disorders.

[34] Ott, P. A., & Wu, C. J., et al. (2017). An immunogenic personal neoantigen vaccine for patients with melanoma. *Nature, 547*, 217-222.

In March 2017, Cadent announced the acquisition of Ataxion Therapeutics, a preclinical spin-off division of Saniona focused on the treatment of ataxia. The merged company is working to advance its preclinical therapeutics programme for CD-1883, a positive allosteric modulator (PAM), to treat spinocerebellar ataxia (SCA), an orphan genetic disorder characterised by cerebellum dysfunction or degeneration that causes difficulty co-ordinating movements, and essential tremor (ET), a neurological disorder characterised by involuntary and rhythmic shaking, most commonly of the hands and forearms. CD-1883 increases the sensitivity of calcium-sensitive potassium (SK) channels that play an essential role in regular neuronal firing with the intent to restore regularity and improve motor function. The company expects CD-1883 to enter the clinic in H118.

The company is also targeting the N-Methyl-D-aspartate receptor (NMDAR) system for the treatment of serious psychiatric diseases. NMDARs are glutamate-gated ion channels and are critical to central nervous system development, the production of rhythms for breathing and locomotion, and underlying synaptic plasticity, cognition and memory.[35] Hyperactivity or hypofunction of the NMDAR system, which is the primary receptor for all excitatory neurotransmission that exists as multiple subunits with distinct properties, contributes to nervous system disorder pathophysiology such as depression, schizophrenia, pain and chronic neurodegenerative diseases.[36] The company's development programmes in this area target depression and schizophrenia. Although the mechanisms of the NMDAR system are established, it is particularly complex to develop any psychiatric drug and there are always side effects.

Major depressive disorder (MDD) is one of the most common mental disorders in the US with an estimated 16.1 million adults in the US experienced at least one major depressive episode in 2015.[37] Medications approved for MDD affect different neurotransmitters, primarily serotonin, norepinephrine and dopamine. In 2016, Lilly's Cymbalta generated revenues of $269m in the US and $661m outside the US. Zoloft and Effexor generated worldwide revenues of $304m and $278m, respectively, for Pfizer in 2016. More recently, psychiatrists have administered low doses of Ketamine and Esketamine (an enantiomer of Ketamine), NMDA antagonists, intravenously to patients who are unresponsive to antidepressants (Exhibit 7).

Exhibit 7: Antidepressants: On the market, off-label, and in development

Classification	Drug	Company	Status	Administration
SSRIs	Prozac (fluoxetine)	Eli Lilly	Market	Oral
	Celexa (citalopram)	Allergan	Market	Oral
	Paxil (paroxetine)	GlaxoSmithKline	Market	Oral
	Zoloft (sertraline)	Pfizer	Market	Oral
SNRIs	Effexor (venlafaxine)	Pfizer	Market	Oral
	Cymbalta (duloxetine)	Eli Lilly	Market	Oral
TCAs	Elavil (amitriptyline)	AstraZeneca	Market	Oral
	Tofranil (imipramine)	Novartis	Market	Oral
	Pamelor (nortriptyline)	Novartis	Market	Oral
MAOIs	Nardil (phenelzine)	Pfizer	Market	Oral
	Parnate (tranylcypromine)	GlaxoSmithKline	Market	Oral
NaSSAs	Remeron (mirtazapine)	Merck	Market	Oral
NDRIs	Wellbutrin (bupropion)	Valeant	Market	Oral
NMDAs	Ketamine	(generic)	Off-label	Intravenous
	JNJ-54135419 (Esketamine)	Janssen	Phase III	Intranasal
	GLYX-13 (Rapastinel)	Allergan	Phase III	Intravenous

Source: Edison Investment Research. Note: SSRI = Selective serotonin reuptake inhibitor, SNRI = Serotonin-norepinephrine reuptake inhibitor, TCA = Tricyclic antidepressant, MAOI = Monoamine oxidase inhibitor, NaSSA = Noradrenergic and specific serotonergic antidepressant, NDRI = Norepinephrine-dopamine reuptake inhibitor, NMDA = N-methyl-D-aspartate.

35 Blanke, M. L., & VanDongen, A. M. (2009). *NCBI*. Boca Raton, FL: CRC Press/ Taylor & Francis.

36 Zhou, Q., & Sheng, M. (2013). NMDA receptors in nervous system diseases. *Neuropharmacology, 74*, 69-75.

37 NIH.

Ketamine, (or Special K), is a derivative of phencyclidine (PCP or angel dust, a noted hallucinogen of the 1960s) with anaesthetic properties. Ketamine was used widely as an emergency anaesthetic during the Vietnam War, although the drug became popular for its hallucinogenic effects and, due to continued abuse, the drug was listed as a schedule III controlled substance in the US.

For depression, the intravenous (IV) infusion of ketamine provides fast-acting symptom relief and is offered in ketamine clinics, which have opened in New York, New Jersey, North Carolina, California and Oregon, whereas current medications can take several weeks to start working. A meta-analysis of seven clinical trials, involving a total of 147 patients, analysed the efficacy of ketamine in the treatment of MDD. The review illustrated rapid antidepressant effects of a single intravenous infusion of ketamine with 52.6% responding 24 hours post-infusion (compared to just a 7.0% response in the placebo arm) and symptom remission in 29.8% of patients (compared to 0% in placebo).[38]

In October 2015, Cadent and Novartis entered into a licence and collaboration agreement to advance their subtype selective negative allosteric modulating NR2B-containing NMDA receptors to treat depression. Under the financial terms of this agreement, Cadent is entitled to a $6m upfront payment, up to a total of $180m for development milestones, up to a total of $200m for sales milestones and royalties of up to 10% of total annual sales. In October 2017, Cadent received a milestone payment of $15m from Novartis for the initiation of the Phase I trial in treatment-resistant depression. Although in its infancy, the collaboration with Novartis makes Cadent an interes ting holding for CBI. A NASDAQ listing is targeted for H218.

CureTech: Monoclonal antibody to treat lymphomas and DIPG

CBI holds 53% majority interest in CureTech, a private Israeli biotechnology company developing antibodies and peptide therapeutics to modulate the immune system to treat cancer. The company's lead therapeutic, pidilizumab (CT-011), is a monoclonal antibody with demonstrated immune-mediated, anti-tumour effects with a relatively ambiguous mechanism of action.

In 2006, Teva Pharmaceuticals entered into a collaboration with CureTech for the development of pidilizumab. At the time, it was suggested that the drug was a PD-1 checkpoint inhibitor. After investing approximately $108.5m to support research and development costs over seven years, Teva terminated the partnership in 2013 after restructuring the company (Teva) with a focus on other indications. In 2014, Medivation, since acquired by Pfizer, licensed exclusive rights to pidilizumab from CureTech for an upfront payment of $5m (in addition to $85m in development and regulatory milestone payments and $245 sales based milestone payments) with the intention of entering the checkpoint inhibitor market. However, it has since been revealed that pidilizumab is not primarily a PD-1 inhibitor and that it primarily binds to DLL1, thereby eliminating cis-inhibitory effects and inducing gene transcription associated with Notch1 in lymphocytes and secondari ly binds to a hypoglycosylated/nonglycosylated form of PD-1 present on subpopulation of T cells.

Pidilizumab preclinical analysis and ongoing clinical trials have demonstrated efficacy in lymphoma patients and children with DIPG. The Phase II open-label, non-randomized pidilizumab intravenous (IV) treatment of DLBCL demonstrated a 72% and 84%, progress ion-free survival and overall survival, respectively, 18 months after autologous transplant in 72 patients. Additionally, treatment was associated with quick and continuous increases in circulating lymphocytes.[39] Pidilizumab is also being investigated in an ongoing Phase II open-label trial in 30 patients with stage III and stage IV DLBCL subsequent to initial remission. The primary end point of the trial is response to

[38] New port, D. J., et al. (2015). Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression. *American Journal of Psychiatry, 172*(10), 950-966.

[39] Armand, P., et al., (2013). Disabling Immune Tolerance by Programmed Death-1 Blockade w ith Pidilizumab After Autologous Hematopoietic Stem-Cell Transplantation for Diffuse Large B-Cell Lymphoma: Results of an International Phase II Trial. *Journal of Clinical Oncology*, *31*(33), 4199–4206.

pidilizumab where response is defined as a 50% increase in lymphocyte subsets and the secondary outcome measures include toxicity, overall survival and PFS. In a 29-patient Phase II trial of pidilizumab and rituximab in follicular lymphoma patients, complete remission was noted in 52%, partial remission in 14%, with an overall response rate of 66%; tumour regression was observed in 86%.[40] Preliminary Phase I/II data presented at the International Symposium on Paediatric Neuro-Oncology (ISPNO) in June 2016 demonstrated median event-free survival of 9.3 months and overall survival of 16.5 months in nine children with DIPG. Three patients remained progression-free at 16.3, 22 and 24 months after diagnosis, one of whom experienced a partial response.

In October of this year, the agreement between CureTech and Pfizer was terminated, as it appeared that Pfizer had little interest in the asset. CureTech re-acquired pidilizumab back from Pfizer for $20m in milestones, continue developing the drug and also find an alternate partnership with a synergistic biotechnology company. A partnership is targeted for H118. However, it has also been announced that CureTech will no longer be considered a material portfolio company, hence, at this time we are not including it in our valuation.

Anatomy portfolio

The Anatomy Medical Technology Fund (Anatomy) was formed as a limited partnership between CBI (50%) and two Israeli institutional investors including the Migdal Insurance Company (30%) and the Harel Insurance Company (20%). Anatomy operates under an incentive programme of the Israel Ministry of Finance and Ministry of Industry, Trade & Labour, which encourages financial institutions to invest in high-technology industry. The limited partners are committed to investing a total of NIS150m in the fund. Since the fund's launch in January 2012 through year-end 2016, the limited partners have invested NIS66m (NIS33m by CBI). Campus Bio, a fully owned subsidiary of CBI, acts as general partner and CBI's Ofer Goldberg is the managing director. The private fund supports five Israeli medical device companies, which focus on surgical technologies and diagnostics in which CBI is indirectly invested, including MinInvasive, Colospan, Pi-Cardia, Sight Diagnostics and FDNA. CBI is also directly invested in Pi-Cardia. The value of the private fund to CBI is determined by 50% of the price at which Anatomy purchased its stakes in the five companies as provided by the company.

Valuation

We arrive at a valuation for CBI of NIS918m or NIS5.87 per share based on a risk-adjusted NPV analysis on its major investments (MediWound, Gamida Cell, Biokine and BioCanCell) and cost or carrying values for the remaining direct holdings as well as 50% of the price at which Anatomy purchased its stakes in the five companies (see Exhibit 8 and Exhibit 9). We are able to assign probability of success in the range of 30-80% due to the advanced stages of development of the key portfolios.

We assign our highest probability of success to MediWound's NexoBrid at 80% in the US (and 100% in the EU as it is already on the market). By our measure, MediWound is the highest value portfolio company ($226m total valuation, $79.2m for CBI's share, compared to a current market cap of $124m), due to a number of factors including near-term revenue generation along with the growing acceptance of NexoBrid in hospitals and burn centres throughout the EU. MediWound is the only company with a marketed product. However, it should be noted that the wound care market is complex as it is segmented by wound type and key players are equipped with diverse product

[40] Westin, J. R. et al., (2014). Safety and Activity of PD1 Blockade by Pidilizumab in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma: a Single Group, Open-label, Phase 2 Trial. *The Lancet Oncology*, *15*(1), 69–77.

portfolios to participate in the highly competitive space. We expect the company to require a great deal of clinical development and a strong commercial partner to enter this space.

CBI anticipates a series of potential inflection points over the next 12-18 months: BioCanCell fund-raising (and potential privatisation) and concurrent start of pivotal Phase II and Phase III trials, Gamida Cell top-line data for the NiCord Phase III trial for haematological malignancies and MediWound NexoBrid Phase III results. We also expect to update our valuation with the announcement of new deals and as the early stage direct holdings advance through the clinical pipeline.

Exhibit 8: Valuation assumptions

Company	Assumptions
MediWound	NexoBrid entering the US market in 2019, achieving almost 30% penetration among burn-related hospitalisations, with peak sales of $91m priced at $4,000, biologic exclusivity through 2030 and with an 80% probability of success as it is entering Phase III. We have assumed 8% peak market share and $19.6m in peak sales in the EU, priced at $4,000, where NexoBrid is already on the market, although EU sales thin to date. Data exclusivity in the EU runs out in 2022 and NexoBrid's IP protection expires in 2025. We have assumed a 2019 launch for EscharEx with total peak sales of $443.7m (priced at $1,250) with 8% market penetration in both the diabetic foot ulcer and venous leg ulcer markets with a 50% probability of success. With patents filed in 2017, patent protection should continue until 2037.
Gamida Cell	NiCord market launch in 2020 in the US and EU with a 10% market share in the US and 7% in the EU of BMTs for leukaemia (AML, ALL, CML, CLL) and with a 50% probability of success. This leads to peak sales of $437m, priced at $100k. Data exclusivity protection should run through 2031 in the US and 2029 in the EU.
Biokine	BL-8040 launch in 2023 in the US and EU with approximately 20% peak market share in both regions and peak sales of $1,286m, priced at $120k in the US and $100k in the EU, with a 30% probability of success. It is important to note that as BL-8040 was licensed to BioLineRx, and in turn will be out-licensed to a partner, Biokine will likely have an effective royalty of 8-12% (40-60% of the expected 20% royalty that BioLineRx will receive). Orphan drug exclusivity should protect the compound until 2029 in the US and 2032 in the EU.
BioCanCell	2022 launch in the US and EU for BC-819 with a 10% peak penetration in the addressable market (intermediate to high-risk non-muscle invasive bladder cancer patients who recur following BCG) with a 30% chance of success and $530m in peak sales. Priced at $60,000 in the US and $40,000 in the EU.

Source: Edison Investment Research

Exhibit 9: Clal Biotechnology Industries valuation table

Product	Setting	Status	Launch	Peak sales ($m)	Probability of success	Royalty rate	rNPV ($m)	% owned by Clal B	Clal B rNPV ($m)
MediWound	Burns	Market and Phase III ready	Nexobrid: Market, EscharEx: Phase III	375	Nexobrid US 80%, Europe 100%, EscharEx 50%	Nexobrid: 100% EscharEx: 20%	226	35%	79.2
Gamida cell	Leukaemia (AML, ALL, CML, CLL)	Phase III	2020	437	50%	100%	374	18%	67.3
Biokine	AML	Phase III	2023	1,286	30%	40% of what BioLineRx receives from a sublicense (assume 20%)	38	27%	10.3
BioCanCell	Bladder cancer	Phase II and Phase III ready	2022	530	30%	100%	126	44%	55.5
Neon								5%	5.0
Vedantra								66%	9.1
eXlthera								54%	10.3
Cadent								24%	7.1
Anatomy portfolio									8.5
Portfolio total ($m)									252
Cash-unconsolidated (as of 30 September 2017) ($m)									10
Overall valuation									262
NIS/$ conversion rate									3.5
Overall valuation (NISm)									918
Shares outstanding (m)									156.5
Per share (NIS)									5.87

Source: Edison Investment Research, Clal Biotechnology Industries reports

Financials

Due to significant ownership stakes, CBI consolidates the financials of several of its investments (MediWound, Vedantra, CureTech and the Anatomy fund) and on this basis, it had NIS193.1m ($55.2m) in cash, cash equivalents and bank deposits as of Q317. CBI's cash position at the corporate level (excluding consolidation) was NIS34.6m ($9.9m) at the end of Q317.

Total consolidated revenues of NIS42.4m ($12.1m) were generated through the sales of MediWound's NexoBrid in Europe, Israel and Argentina, licensing agreements and rent in addition to a gain of NIS10.5m ($3m) from the decrease of equity interest in associates and a NIS19.1m ($5.5m) gain from the disposal of subsidiaries or loss of control in 9M17.

Significant investment was made into the development of underlying technologies and products of CBI's material assets as indicated by R&D spend of NIS24m ($6.9m) in 9M17 (NIS42m ($12m) in FY16). General and admin costs as of Q317 were NIS64m ($18.3m), which include payroll and related expenses, management fees, and marketing and advertising expenses on a consolidated basis.

CBI's operating profit was NIS1.8m ($0.51m) in the nine months to 30 September 2017, up from a post-tax loss of NIS51.6 ($14.7m) for the first half of the year (and up from a post-tax loss of NIS155m ($44.3m) for Q316). This increase was driven by a gain of NIS12.3m ($3.5m) attributed to non-controlling interests over a reported loss of NIS10.5m ($3m) attributed to CBI's shareholders.

We outline historical financials in Exhibit 10; however, we are not providing forecasts at this time.

Exhibit 10: Financial summary

NIS'000s	2015	2016
Year end 31 December	IFRS	IFRS
PROFIT & LOSS		
Revenue	55,759	30,484
Cost of Sales	(42,549)	(46,967)
Gross Profit	13,210	(16,483)
R&D expenses	(54,094)	(42,011)
SG&A expenses	(82,747)	(81,107)
EBITDA	(175,382)	(434,812)
Operating Profit (before GW and except)	(179,999)	(451,764)
Intangible Amortisation	0	0
Exceptionals	0	0
Operating Profit	(179,999)	(451,764)
Other	(35,553)	(11,850)
Net Interest	6,197	9,510
Profit Before Tax (norm)	(209,355)	(454,104)
Profit Before Tax (FRS 3)	(209,355)	(454,104)
Tax	14,023	60,104
Profit After Tax (norm)	(195,332)	(394,000)
Profit After Tax (FRS 3)	(195,332)	(394,000)
Average Number of Shares Outstanding (m)	135.8	136.2
EPS - normalised (NIS)	(1.44)	(2.89)
EPS - FRS 3 (NIS)	(1.44)	(2.89)
Dividend per share (NIS)	0.0	0.0
BALANCE SHEET		
Fixed Assets	1,225,127	927,359
Intangible Assets	1,035,753	741,543
Tangible Assets	17,077	16,536
Other	172,297	169,280
Current Assets	307,645	191,351
Stocks	6,691	3,248
Debtors	18,784	16,415
Cash	256,105	171,022
Other	26,065	666
Current Liabilities	(66,785)	(68,277)
Creditors	(14,782)	(8,507)
Short term borrowings	0	0
Short term leases	0	0
Other	(52,003)	(59,770)
Long Term Liabilities	(373,520)	(297,938)
Long term borrowings	0	0
Long term leases	0	0
Other long term liabilities	(373,520)	(297,938)
Net Assets	1,092,467	752,495
CASH FLOW		
Operating Cash Flow	(156,274)	(52,529)
Net Interest	23,298	0
Tax	(14,023)	(60,104)
Capex	0	0
Acquisitions/disposals	27,971	(395)
Financing	22,499	23,123
Dividends	0	0
Other	146,116	5,447
Net Cash Flow	49,587	(84,458)
Opening net debt/(cash)	(207,517)	(256,105)
HP finance leases initiated	0	0
Other	(999)	(625)
Closing net debt/(cash)	(256,105)	(171,022)

Source: Company accounts, Edison Investment Research

Contact details	Revenue by geography
Azrieli Center, Triangle Building 45th floor, Tel Aviv 67023 Israel +972-3-6121616 http://cbi.co.il/	N/A

Management team

CEO: Ofer Gonen	Medical Director: Gilad Rosenberg
Mr Gonen has been with CBI since 2003. He manages the company's life sciences investments, business development, US-based operations and investment support for CBI's portfolio companies. Ofer serves as an executive chairman and board member of several companies, including Gamida Cell and MediWound. Prior to joining CBI, he was the general manager of Biomedical Investments as well as a technology consultant to various Israeli venture capital funds, and an academic aide to the Governor of the Bank of Israel.	Dr Gilad Rosenberg joined CBI's team in 2016, bringing CBI a vast experience and knowledge in clinical development and assessment of innovative science. Prior to that, Dr Rosenberg was vice president of clinical development at D-Pharm, medical director for Merck, Sharp and Dohme's Israeli subsidiary. Dr Rosenberg graduated cum laude from the Rappaport Faculty of Medicine of the Technion, Israel Institute of Technology and received post-graduate training in neurology at the Hadassah Medical Center, Jerusalem. Dr Rosenberg also holds an MSc in neuroscience, with distinction, from the University of Oxford.
CFO: Assaf Segal	**Vice President: Ofer Goldberg**
Assaf Segal has 15 years of experience in providing economic consulting, corporate finance, and transaction support services to leading Israeli and global companies in the biomedical sector as well as in the high-tech, financial, and other sectors. Before joining CBI in 2015, Mr Segal was a partner at Variance Economic Consulting and held managerial positions at Kesselman Corporate Finance – PwC and Amdocs (NASDAQ: DOX). Mr Segal serves as a board member of MediWound (NASDAQ: MDWD). He holds an MBA (finance and information systems) and BA in economics and statistics, both from the Hebrew University in Jerusalem.	Mr Goldberg gained extensive experience in the different aspects of the biotech industry while being actively involved with healthcare-related companies ranging in stage from inception to commercialisation. Ofer leads CBI's strategic planning and portfolio management. He also manages Anatomy Medical Technology Fund, CBI's medical device investment arm. Ofer serves as an executive chairman and board member of several biotech and medical device companies, including BioCanCell (TASE: BICL), Colospan and Sight Diagnostics. He holds an MA in Economics and Finance from Tel Aviv University and a BSc in Physics and Mathematics from the Hebrew University of Jerusalem.

Principal shareholders	(%)
Clal Industries and Invest	48.61
Teva Pharmaceutical Industries	15.93
Yelin Lapidot	7.17
Meitav DS Investments	6.53

Companies named in this report

Affimed (AFMD), BioCanCell (BICL), Biokine, BioLineRx (BLRX), Cadent, Celgene (CELG), Colospan, CureTech, Gamida Cell, Genentech (DNA), Eli Lilly (LLY), eXlthera, Johnson & Johnson (JNJ), Medivation (MDVM), MediWound (MDWD), NantKwest (NK), Neon, Pfizer (PFE), Pi-Cardia, Sanofi (SNY), Seattle Genetics (SGEN), Sight Diagnostics, Smith & Nephew (SNN), Spectrum Pharmaceuticals (SPPI), Novartis (NVS), Valeant (VRX), Vedantra

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