EDISON

Pluristem Therapeutics

Clinical outlook

Progress continues

Pharma & biotech

Pluristem Therapeutics has had a productive FY18 to date. The company is advancing PLX-PAD in its Phase III study of critical limb ischemia (CLI) and Phase II study of intermittent claudication (IC), with the latter expecting results in early 2018. Additionally, the company received an orphan designation for PLX-R18 for acute radiation syndrome (ARS) currently in non-human primate studies and expanded its Phase I study for support of stem cell transplant to additional sites. We value Pluristem at $202m.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
06/16	2.8	(23.2)	(0.29)	0.0	N/A	N/A
06/17	0.0	(27.8)	(0.32)	0.0	N/A	N/A
06/18e	0.0	(42.3)	(0.40)	0.0	N/A	N/A
06/19e	0.0	(46.6)	(0.41)	0.0	N/A	N/A

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

Orphan designation for ARS

Pluristem is currently planning a pivotal non-human primate study for PLX-R18 for the treatment ARS and are in discussions with the NIH to finance the study. The company recently received an orphan designation for the program, which will entitle the company to seven years of market exclusivity (although we do not believe this is necessary), FDA protocol guidance, grants, and US tax breaks.

PLX-R18 stem cell trial expanded

The company has on ongoing Phase I clinical trial of PLX-R18 for the support of patients with insufficient hematopoietic cell recovery following hematopoietic stem cell transplant. Pluristem announced in October 2017 that it had expanded this trial to Israel following approval from the Ministry of Health. The program was previously expected to provide a readout in Q417, although it is unclear at this point if this expansion signals a delay.

Successful offering, overhang reduced to $50m

In October 2017, Pluristem completed an offering of 9.0m shares at $1.67 for gross proceeds of $15.1m. This has reduced our expected financing gap from $63m to $50m before profitability in 2020 following the expected ARS acquisition contract, although this value may increase if the company is unable to secure this contract or sell a priority review voucher from the ARS program.

Valuation: $202m or $1.87 per share

We have increased our valuation of Pluristem to $202m from $189m. This increase was driven by the new estimated net cash ($35m) following the October 2017 offering, as well as rolling forward our NPVs. Due to the new shares in the offering, however, our valuation on a per basic share basis has reduced to $1.87 from $1.94. We expect to significantly update our valuation following the release of data from the ongoing IC Phase II trial, with data expected in early 2018, as this program also has read-throughs to the CLI clinical program in Phase III.

5 February 2018

Price*	**US$1.47/ NIS5.07**
Market cap	**US$159m/ NIS548m**

*Priced as at 2 February 2018

	NIS3.51/$
Net cash ($m) at end September 2017	21.3
Shares in issue	108.1m
Free float	84%
Code	PSTI
Primary exchange	NASDAQ
Secondary exchange	TASE

Share price performance

%	1m	3m	12m
Abs	6.5	(11.4)	31.8
Rel (local)	0.9	(19.1)	6.5
52-week high/low	US$2.1	US$1.1	

Business description

Pluristem Therapeutics is a biotech company, headquartered in Israel, focused on the development of cell-based therapeutics derived from placenta. The company is advancing PLX-PAD for critical limb ischemia (CLI) in Phase III and has a Phase III study planned for hip fracture. PLX-R18 is being advanced for acute radiation syndrome and hematopoietic cell transplant.

Next events

FNF IND submission	Coming months
IC Phase II top-line results	Q2 2018

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Investment summary

Company description: Cell therapy for multiple indications

Pluristem is a biotech company incorporated in 2001 developing cell-based therapies based on tissue derived from human placenta, an ample source of mesenchymal-like cells. These placental cells are not stem cells but share many of their characteristics and secrete a large number of biologic molecules. The utility of these cells is being investigated by the company for multiple indications in two different products: PLX-PAD for vascular disorders and healing, and PLX-R18 to stimulate bone marrow growth. The company has six clinical programs, the most advanced of which is PLX-PAD for the treatment of critical limb ischemia (CLI), with an ongoing 250-person Phase III trial. The company is also investigating the cells for the treatment of intermittent claudication (IC), femoral neck fracture (FNF, the most common form of hip fracture), acute radiation syndrome (ARS), and hematopoietic cell transplant (HCT) support.

Valuation: $202m or $1.87 per basic share

We have increased our valuation of Pluristem to $202m from $189m, although it has reduced on a per share basis to $1.87 per basic share from $1.94 following the October 2017 offering. The increase in valuation was driven by an increase in net cash (to $35m pro forma) and rolling forward our NPVs. We expect to update our valuation following the release of data from the ongoing IC Phase II trial (expected early 2018) as this program has direct read-throughs into this indication as well as CLI.

Financials: Reduced cash requirement to $50m

Pluristem ended its fiscal Q118 on 30 September 2017 with an operating loss of $7.4m. R&D spending was the company's major expense at $4.7m, which is largely in line with previous quarters ($4.6m in Q417).In October 2017 the company completed an offering of common stock: 9m shares at $1.67 for gross proceeds of $15.1m. We estimate a pro forma net cash position of $35m after the offering. This has reduced our expected financing requirement to $50m ($20m in FY18, $30m in FY19) from $63m. The company announced its participation in two additional Horizon 2020 studies during the quarter, from which it expects to receive $2.4m and $600,000, respectively.

Sensitivities: Clinical risk predominates

Pluristem is subject to the typical risks associated with a clinical-stage biotechnology company. The successful demonstration of efficacy in humans for its cell-based products remains the greatest risk. Historically, cell therapies have proven to be one of the most difficult classes of therapeutics to develop, and there have been no successful programs employing stem cells or progenitor cells like those used in Pluristem's products. The company is in late-stage trials (Phase III for CLI and entering Phase III for FNF). However, the company has not successfully met any approvable endpoints for any indication, and did not perform confirmatory Phase II studies. Because of this, we consider the company's programs high risk. The company also faces significant commercial risk. The ARS clinical program is being performed largely to secure government contracts, which have a high degree of commercial uncertainty. The CLI program must compete with consistently improving minimally invasive surgical treatments and the FNF program must justify its addition to the surgical standard of care, although this may be justified based on the poor prognosis of patients. Additionally, the company must raise $50m in additional capital to reach profitability in 2020, which poses a dilution risk. If the company is unable to secure an ARS contract or sell the program priority review voucher, this number could increase by at least $30m.

Benefiting from the placenta

Pluristem has been investigating the potential therapeutic benefit of cells derived from the human placenta. The placenta is one of a small number of sources where multipotent cells can be isolated, and harbors multiple cell lineages that are useful for different purposes. Cord blood has become famous as a source of hematopoietic stem cells that can be used in lieu of bone marrow in patients who need stem cell transplant. However, epithelial and mesenchymal progenitors cells can be also be isolated from tissues within the placenta.[1] The placenta is not the only source of these cells, as various progenitors can be found in tissues throughout the body, but placenta offers a rich supply of cells of multiple lineages from tissue that would otherwise be medical waste. Although these cells are not stem cells and lack the immortality and pluripotency to meet that definition, they secrete a wide array of cytokines and growth factors and can exert a potent influence on the function of other cells in the body.

Following the isolation of placental tissue, the cells are expanded using a proprietary tissue culture technology that enables the growth of adherent cells on a 3D matrix in bioreactors. This scalable technology allows for the production of up to 150,000 therapeutic doses of cells with the company's current manufacturing facility. These cells can then be differentiated into different products by varying the culture conditions. The conditions to which the cells are exposed can determine their precise lineage as well as influence their secretion profile. However, the company has provided limited data on the precise cell population used in its preparations. Officially, it terms the cells it isolates as mesenchymal-like adherent stromal cells. The placental expanded (PLX) cells are then cryogenically preserved and can been stored for a number of years (currently validated up to three) before use.

The placenta is the only organ that is generated by the contact between two organisms with differing genetic backgrounds and immune systems. The developing fetus can be considered an allograft of foreign genetic material that must be protected from the host (the mother's) immune system. The placenta has developed a series of defense mechanisms to ensure that the molecules necessary for fetal development can be transferred while remaining immune privileged. Mesenchymal progenitor cells in the placenta may help contribute to its low immune reactivity as they secrete large concentrations of anti-inflammatory cytokines. This feature is carried through to the cultured placental cells, as although they express HLA antigens, they do not typically need to be HLA matched against patients when used as a therapy. However, we expect that, as part of the quality control and safety assurances, the HLA types of donors and individual batches will have to be tracked and recorded. We also expect some manufacturing overhead dedicated to maintaining quality and consistency as multiple tissues sources will be used.

Exhibit 1: Pluristem pipeline

Indication	Stage	Product
Critical limb ischemia (CLI)	Phase III	PLX-PAD
Intermittent claudication (IC)	Phase II	PLX-PAD
Femoral neck fracture (FNF)	Phase III ready	PLX-PAD
Acute radiation syndrome (ARS)	NHP study	PLX-R18
Hematopoietic cell transplant (HCT)	Phase I	PLX-R18

Source: Pluristem Therapeutics. Note: NHP=non-human primate.

Pluristem's lead product is PLX-PAD, developed for the treatment of peripheral artery disease (PAD). The cells are a placental cell fraction similar to mesenchymal stromal cells (MSC) derived from bone marrow, but lack the differentiation potential of bone marrow derived cells. The cytokines and growth factors secreted by these cells encourage angiogenesis and control inflammation, similar to what is seen in the developing placenta. The product is currently being investigated for

[1] Parolini O, et al. (2008) Isolation and Characterization of Cells from Human Term Placenta: Outcome of the First International Workshop on Placenta Derived Stem Cells. *Stem Cells* 26, 300-311.

critical limb ischemia (CLI), intermittent claudication (IC) and femoral neck fracture (FNF). The company previously investigated PLX-PAD for the treatment of pulmonary arterial hypertension (PAH) in a collaboration with United Therapeutics. The collaboration was terminated in December 2015. Data were only released on the first dosing cohort of the trial (0.5m cells/kg), which stated that the three patients improved by 21 meters on a six-minute walk test, although the baseline for this group was not reported, and there was no control, making the results difficult to interpret.

The company's other product in development is PLX-R18 as a treatment for hematologic disorders, specifically radiation exposure and hematopoietic stem cell engraftment. PLX-R18 is derived from a fraction of cells existing at the interface between the maternal and fetal tissue in the placenta and contains cells from both mother and child. This cell fraction secretes growth factors encouraging hematopoiesis, and the company hopes to use these properties of the treatment to encourage the recovery of bone marrow cells and the immune system after they are killed with radiation. The same process could potentially increase the chances of a successful bone marrow transplant and encourage the graft to proliferate before graft failure.

In addition to these products there is the potential to develop other classes of therapeutic using these cells. For instance, in January 2018 preclinical data were published that showed that cells conditioned with tumor necrosis factor alpha (TNF-α) and interferon-gamma (IFN-γ) inhibited tumor growth in 26 of 59 cancer cell lines, and in a triple negative breast cancer cell line tested via mouse xenograft.[2]

The company has 18 US patents covering the manufacturing, composition, and therapeutic use of PLX cells with expiration dates between 2020 and 2033. The composition of matter patent (USPA 13/642,725) expires in 2031, before patent term extensions.

Critical limb ischemia

Pluristem is investigating PLX-PAD for the treatment of critical limb ischemia (CLI). CLI is the most severe form of PAD and is characterized by the blockage of major arteries in the lower extremities. The key diagnostic indicator for CLI is pain in the legs that occurs when at rest, due to lack of oxygen. CLI is a high-risk disease: in the US Medicare population, the rate of amputation in one year or less following diagnosis was 33.5% and the one-year mortality rate was 30.3%.[3] The disease is caused by the build-up of atherosclerotic plaques in the vessels of the legs, typically secondary to poor peripheral circulation due to diabetes, obesity, or other vascular disorders. Additional risk factors for CLI are similar to other vascular disorders and include smoking, being of male sex, high cholesterol and high blood pressure. The working group for the Trans-Atlantic Inter-Society Consensus (TASC) on the Management of Peripheral Arterial Disease estimates the incidence of CLI in the US and Europe at between 500 and 1,000 new cases per year per one million in population.[4]

The most common treatments for CLI are revascularization via a bypass or endovascular intervention (angioplasty, atherectomy, or stents). However, only half of all CLI patients are fit for these procedures.[4] We expect the medical device technology to continue to advance and provide new options in the form of drug-coated balloons and other technology, especially in difficult-to-treat, below the knee occlusions. However, there will be a persistent need for non-invasive solutions for

[2] Allen H, et al. (2017) Human Placental-Derived Adherent Stromal Cells Co-Induced with TNF-α and IFN-γ Inhibit Triple-Negative Breast Cancer in Nude Mouse Xenograft Models. *Sci. Rep.* 8, 670.

[3] Baser O, et al. (2013) Prevalence, Incidence, and Outcomes of Critical Limb Ischemia in the US Medicare Population. *Vas. Dis. Management* 10(2).

[4] Norgren L, et al (2007) Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) *J. Vasc. Surg.* 45(1), S5-S67.

patients in poor health and with occlusion in smaller vessels. Cell-based therapies have emerged as potential treatments because the growth factors secreted by multipotent cells can encourage the formation of new blood vessels. There have been a large number of clinical studies of multipotent cells for the treatment of CLI going back to at least 2002.[5] However, these studies have generally been small, and there has been little progress in the private sector (Exhibit 2), and no approvals. The most advanced trial was for Ixmyelocel-T from Vericel, which terminated early in 2013 following enrolment difficulties stemming from the trial design. The trial was terminated after a year when only 40 of the planned 594 patients had enrolled. Vericel terminated the trial after attempts to increase enrolment by increasing the number of trial sites (from 70 to over 100) and loosening the enrolment criteria (by removing the "no option" criterion) failed to accelerate the rate of new patients. The difficulties observed in this trial should serve as a precaution for the future clinical efforts to develop PLX-PAD. However, it is important to note that while the Vericel product required harvesting and then a return trip by the patient for infusion, PLX-PAD can be administered via a standard syringe in one visit. To our knowledge, currently the only other company technically with a Phase III development plan is Cesca Therapeutics. It initiated a Phase III for its SurgWerks-CLI platform in 2016, although it has not enrolled any patients, and this device appears to be deprioritized in favor of the company's MXP system, which has not entered the clinic.

Exhibit 2: Cell-based therapies for PAD

Product	Company	Stage	Auto/Allo	Lineage	Notes
Ixmyelocel-T	Vericel	Phase III	Autologous	Mesenchymal stem cells	Phase III terminated in 2013 due to poor enrolment
SurgWerks-CLI and MXP	Cesca	Phase III	Autologous	Bone marrow derived mononuclear cells	Stem cell isolation devices. Development stalled
ERC-124	Intrexon	Phase II	Allogenic	Endometrial regenerative cells	Last public clinical development in 2013
ACP-01	Hemostemix	Phase II	Autologous	Blood derived progenitor cells	
CLBS12	Caladrius Biosciences	Phase II	Autologous	CD34+ cells	
Alecmestencel-T	apceth	Phase I/II	Autologous	Mesenchymal stem cells	No progress since 2014
Biochymal	Taiwan Bio	Phase I/II	Allogenic	Mesenchymal stem cells	

Source: Evaluate Pharma, Pluristem Therapeutics documents

Pluristem reported results from two open-label Phase I studies (one in the US, n=12, one in Germany, n=15) of PLX-PAD in patients with CLI who lacked surgical options in 2011. The US study investigated the difference in safety and efficacy of a single administration of 280m cells, or the same injection given two weeks apart. The German trial investigated three different doses of cells: 200m, 300m and 600m. The primary efficacy endpoints of the trials were the fraction of patients with amputation-free survival (AFS, no amputations or death) at six months and one year.

Combined, the two studies showed 85% AFS, 100% for the US study and 73% for the German study (Exhibit 3). There is a high degree of variability for AFS reported in the literature, and the rate appears to have been increasing since the mid-1990s due to higher rates of revascularization procedures as well as better diabetes control, antiplatelet therapy, infection control and smoking cessation.[6] The largest trial to date examining AFS in CLI patients (the TAMARIS gene therapy trial) showed an AFS of 67% in the control arm.

[5] Tateishi-Yuyama E, et al. (2002) Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet* 360(9331), 427-435.

[6] Benoit E, et al. (2012) Improved amputation-free survival in unreconstructable critical limb ischemia and its implications for clinical trial design and quality measurement. *J. Vasc. Surg.* 55, 781-789.

Exhibit 3: CLI amputation and survival studies

Author	Trial	Year	No.	Amp	Death	AFS
Jivegård	Spinal cord stimulation	1995	26	50%	31%	N/A
Lepäntalo	Retrospective clinical review	1996	105	46%	54%	28%
Claeys	Spinal cord stimulation	1996	41	20%	29%	N/A
Klomp	Spinal cord stimulation	1999	60	48%	23%	40%
Spincemaille	Spinal cord stimulation	2000	18	50%	28%	N/A
Amann	Spinal cord stimulation	2003	39	46%	0%	54%
Marston	Wound care only	2006	86	38%	0%	62%
Brass	CIRCULASE (PGE1 analog)	2006	190	11%	10%	81%
Nikol	TALISMAN (NV1FGF gene therapy)	2008	56	34%	23%	48%
Hiatt	TAMARIS (NV1FGF gene therapy)	2010	259	21%	15%	67%
Powell	Intramuscular hepatocyte GF	2010	6	33%	17%	N/A
Pluristem	PLX-PAD US Study	2010	12	N/A	N/A	100%
Pluristem	PLX-PAD German Study	2011	15	N/A	N/A	73%

Source: Pluristem Therapeutics, Benoit et al[6]

It should be noted, however, that Pluristem studies were not powered for statistical significance and carry the inherent biases associated with open-label studies. Additionally, patients in the US study were relatively mild in terms of CLI: before the start of the trial, patients had transcutaneous partial oxygen ($TcPO_2$) concentrations of 45.5mmHg, with is at the low end of the normal range (depending on location of measurement, the low end is 45-55 mmHg).[7] Patients in the German study had $TcPO_2$ concentrations of 12.6 at induction, by comparison. The company did not report any safety issues from the studies, and noted that there were no immune reactions or neoplasms as a result of the treatment.

Pluristem currently has an ongoing pivotal Phase III CLI trial in the US and EU. The trial is currently enrolling up to 246 patients who are otherwise unsuitable for revascularization, and will measure the time to amputation or death as the primary endpoint. The company has stated that it expects a single trial to be sufficient to support approval, and it has consulted with both the FDA and EMA regarding the pathway. In part, this is enabled by the large safety database that will be provided by the ongoing intermittent claudication clinical trial. The program has fast-track in the US and has an adaptive pathway designation in the EU, which may entitle it to early provisional approval (after 123 events). Additionally the program received fast-track status from the FDA in September 2017. All of these special programs ensure an increased level of interaction with the regulatory agencies and guidance. The company also has plans to initiate a 75-person study in Japan, through a subsidiary co-owned by Sosei. This is also expected to be the only trial needed for approval, as in Japan, regenerative products face a lower bar of statistical evidence for approval (statistical safety and a signal of efficacy). We should note that the decision to progress to a Phase III trial without a confirmatory Phase II study and without statistically demonstrating a treatment effect is exceptionally aggressive and the program is high risk.

The drug is also available in the US through the FDA's Expanded Access (approved January 2018) program for CLI patients with severe disease that cannot participate in the Phase III. This program allows access to the treatment for patients outside of the clinical trials, and the potential for reimbursement to the company at cost. The FDA makes this determination on the basis that there is evidence of safety and effectiveness and a lack of other treatments. We believe that this designation is indicative of the innocuous safety profile of the treatment and the program may provide further support for the safety database.

Intermittent claudication

Pluristem is also developing PLX-PAD for the treatment of intermittent claudication (IC), a milder form of PAD than CLI. IC is characterized by pain in the legs that occurs with exertion, but goes

[7] Dowd GSE, et al. (1984) Measurement of transcutaneous oxygen pressure in normal and ischaemic skin. *J. Bone Joint Surg.* 65-B(1) 79-83.

away with rest, as opposed to CLI. IC can progress to CLI without treatment (although CLI can also occur de novo, without any prior history of claudication). The incidence of IC is substantially higher than CLI, with a prevalence of 1% to 5% of the US general population.[8] Also, unlike CLI, the prognosis for patients with IC is generally positive, as the disease can resolve itself spontaneously, without the need for intervention. The first line of treatment recommended by TASC is encouraging increased activity, which can improve pain, and this is followed by medical treatment if the issue does not resolve itself. There are currently several approved medications for PAD that are used to treat IC: Pletal (cilostazol, Otsuka), Praxilene (naftidrofuryl, Merck Serono) and pentoxifylline. In addition, painkillers or drugs to treat the underlying atherosclerotic risk factors can be prescribed. All of these drugs are genericized and typically retail for less than $2 per day. Revascularization is rare for these patients, but is increasing in frequency.[4]

The company is currently engaged in a 170-person, Phase II study of PLX-PAD for intermittent claudication (IC). The trial is a double-blind, randomized, placebo-controlled study measuring the maximum walking distance of IC sufferers on a treadmill a year after two injections of PLX-PAD. The trial was initiated in 2012 and had initial enrolment difficulties, although the company announced enrolment was complete in early 2017. We expect the trial to be complete and to provide top-line results in H118.

Hip injury

Pluristem has investigated the use of PLX-PAD as an agent to aid in the regrowth of muscle following surgery on the hip. The goal of this treatment is to improve muscle healing following surgery. Initial studies focused on treatment following total hip replacement (THR) surgeries for osteoarthritis, but the current clinical pathway is focused on aiding recovery following THR for femoral neck fracture (FNF). The femoral neck is the region of the femur immediately before the ball-and-socket joint into the hip. Fractures of this type are common in the elderly, especially osteoporotic women. Each year, 63.3 women and 27.7 men per 100,000 have FNF.[9]

FNF is most commonly treated surgically, with either fixation and repair of the fracture with implants, or with hip replacement. Pharmacologic treatments associated with FNF surgery are limited to prophylactic antibiotics and postoperative analgesics. Forteo (teriparatide, Lilly) can be given following surgery to improve bone density. There currently are no treatments in the same niche as PLX-PAD designed to improve muscle healing and the degree of medical need for such a therapy is unclear at this time. However, the addition of this procedure to surgery may be justified on the basis of the poor prognosis of these patients. FNF is associated with a mortality risk, although the effect is highly variable based on the study and corrective procedure (4.2-20%).[10] The exact extent that PLX-PAD can improve on outcomes remains to be elucidated.

PLX-PAD has been studied in a single Phase I/II study in patients following elective THR, which reported results in January 2014. It should be noted that this indication is different to current hip injury indication and included patients that opted for THR as a treatment for osteoarthritis. These patients have a significantly higher quality of life and lower morbidity than patients following hip fracture. The randomized, double-blind study measured the contractile force of patients' gluteal muscle (the muscle damaged during surgery) six months following a single dose of PLX-PAD. The increase in muscle volume was measured via MRI as a secondary endpoint. The 20 patients in the

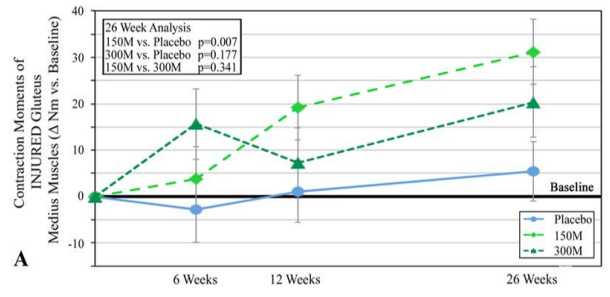
[8] McDermott MM (2006) The magnitude of the problem of peripheral arterial disease: Epidemiology and clinical significance. *Clevland Clin. J. Med.* 73(s4), s2-s7.

[9] Koval KJ and Zuckerman JD (1994) Overview and evaluation and treatment of femoral-neck fractures. *J. Am. Acad. Orthop. Surg.* 2(3), 141-149.

[10] Bhandari M, et al (2003) Internal Fixation Compared with Arthroplasty for Displaced Fractures of the Femoral Neck. *J. Bone Joint Surg.* 85(9) 1673-1681.

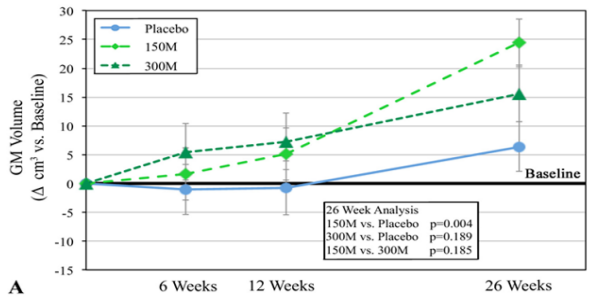
trial were split between a 150m cell dose (n=7), a 300m cell dose (n=6), and placebo (n=7). The trial demonstrated a significant increase in both the contractile force of approximately five times that of placebo for the 150m cell dose (p=0.0067), and increase in muscle volume for this dose of approximately 300% (p=0.004). There is some difficulty in interpreting how these results will translate into functional improvement because the baseline was not reported for either of these metrics. Although there was a trend towards improvement in both metrics for the higher 300m dose, the results were lower than seen for the 150m cell dose and not significant. The reason for this discrepancy is probably that the 300m cell dose was administered in the same volume as the 150m cell dose (ie double the concentration), possibly negatively affecting the survivability of the cells. The company did not report any adverse reactions in the trial, including immune responses, but subclinical immune reactions are common with biologics, and contribute to the "bell shaped" activity curves that are often seen, and provide an upper limit of the effective dose.

Exhibit 4: Muscle contractile force following THR



Source: Pluristem Therapeutics. Note: Dotted lines show treatment with different cell concentrations of PLX-PAD.

Exhibit 5: Muscle volume following THR



Source: Pluristem Therapeutics. Note: Dotted lines show treatment with different cell concentrations of PLX-PAD.

The company announced on 26 September 2017 that it had received "positive feedback" from the FDA and EMA regarding a proposed Phase III clinical trial for FNF. The trial will enrol 180 patients across the US and Europe who will receive an injection of 150m PLX-PAD cells during an arthroplasty procedure. The study will be randomized, double blind and placebo controlled. The primary endpoint will be change in the Short Physical Performance Battery (SPPB) at six months following injury. The SPPB is a series of simple physical tests of the lower extremities that mimic the physical requirements of daily activity and it is typically used to assess geriatric patients. The battery is semi-quantitative and composed of three sections measuring different aspects of function: balance, gait speed, and getting into and out of a chair. The company announced that it will be submitting an IND for the FNF clinical program in the coming months following the announcement, shortly after which we expect the Phase III trial to be initiated.

Radiation exposure

The company is investigating using PLX-R18 cells for the treatment of individuals following severe radiation exposure. Acute radiation syndrome (ARS) is a cluster of health effects following exposure to high doses of ionizing radiation. This radiation can cause damage to DNA, which can have devastating effects on rapidly dividing cells, such as those in the gastrointestinal tract and bone marrow. The effects on the hematopoietic cells of the bone marrow typically result in a decrease in red blood cells, platelets and immune cells, leading to difficulty in healing, which can further complicate any other injuries sustained during a traumatic exposure event, as well as hemorrhage and severe anemia. PLX-R18 is being tested for radiation exposure because the combination of growth factors secreted by these cells encourages the proliferation of hematopoietic cells and can potentially aid in maintaining immune cell populations.

Potential exposures include industrial accidents as well as nuclear weapons devices. The US federal government therefore has a vested interest in maintaining stockpiles of agents that can be

deployed quickly following such an event, and stockpiles of radiation treatments are maintained by the Strategic National Stockpile (SNS), managed by the Centers for Disease Control and Prevention. The SNS currently stockpiles Neupogen (filgrastim, Amgen) for the treatment of ARS, among other more basic medications such as chelators and potassium iodide. Neupogen is stockpiled for similar applications to PLX-R18 to aid in restoring the immune system following radiation exposure, although this is not an approved indication and Neupogen only affects white blood cells (PLX-R18 helps to regenerate white cells, red cells and platelets). Also, platelet infusion is required on top of Neupogen treatment, which may be difficult in the case of a nuclear event. SNS acquired a quantity of Neupogen for $155m in an initial contract in 2013. Subsequently, the SNS has acquired a smaller amount of the similar but longer-lasting Neulasta (pegfilgrastim, Amgen) for $37.7m in 2016. PLX-R18 has the potential advantage of encouraging the growth of a broader array of hematopoietic cells, besides just neutrophils, as is the case with Neupogen and Neulasta. However, we lack significant insight into the government contracting and procurement process outside its prior history. If the company is able to secure a contract, we would expect potential future procurements to replace expired product.

Exhibit 6: Development stage ARS treatments

Product	Target	Company	Latest developments
Entolimod	TLR5 agonist	Cleveland BioLabs	Pre-EUA dossier filed
HemaMax	Interleukin-12	Neumedicines	Large animal
Recilisib	DNA repair modulator	Onconova	NHPs

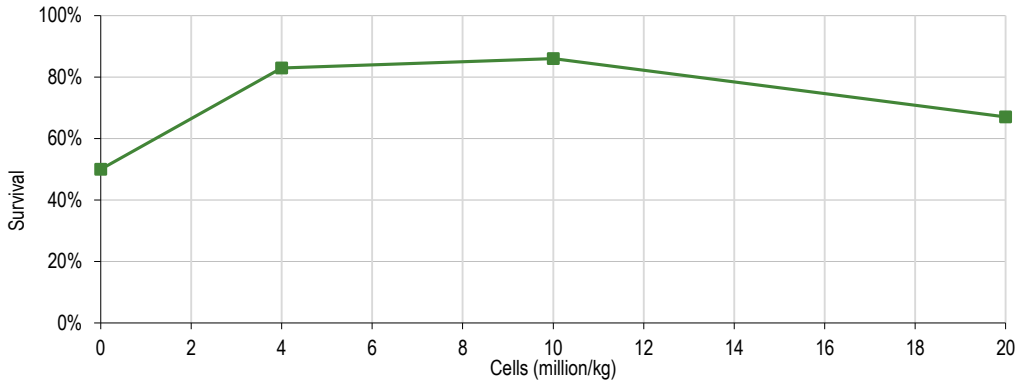
Source: Pluristem Therapeutics reports, Evaluate Pharma

Previous research

Pluristem reported the results from its non-human primate (NHP) study of PLX-R18 for the treatment of acute radiation syndrome (ARS) in early May 2017. The product is being developed for ARS via the FDA animal rule, which allows for approval based on animal studies for conditions such as ARS that cannot be feasibly studied in human clinical trials, so this NHP study is an important component of the approval package. Studies in NHPs are important to establish safety and as the basis for the human dose equivalent, as these animals provide the closest approximation to human subjects, and the purpose of this study was to determine the optimal dose.

The 48 animals were separated into four dosing arms (4, 10, 20 million cells per kilogram, and control) and were either irradiated or left intact. The study saw a trend towards increasing survival in the active arms of the trial: 83%, 86% and 67%, respectively, compared to 50% for the control (Exhibit 7). This “bell shaped” response, in which higher doses can have lower efficacy, is not uncommon with biologics, and these data provide an important insight into the correct dose with which to proceed in future studies. Unfortunately, these data were not powered for statistical significance.

Exhibit 7: Survival of non-human primates with ARS following PLX-R18 dosing



Source: Pluristem Therapeutics

Importantly, the company also reported that there were no safety issues seen in the non-irradiated group (although detailed safety information was not released), and that leukocyte counts were not increased in these animals. This means that the treatment can potentially be administered before determining the degree of radiation exposure without concern for adverse reactions. The company also stated that PLX-R18 led to improvement in an array of hematopoietic cells, although further details were not provided.

These results compare favorably to Neupogen (albeit in NHP instead of humans), which is the currently stockpiled treatment for hematopoietic recovery from ARS. Neupogen showed an improvement in survival to 79% from 59% in the control arm from a study of 46 NHPs (p=0.023).[11] On a placebo adjusted basis, Neupogen provided only a 20% improvement in survival compared to 36% for the optimal dose of PLX-R18. Moreover, PLX-R18 could provide a safer and more convenient dosing strategy than Neupogen, if PLX-R18 continues to show a benign safety profile. Neupogen has the potential to induce leukocytosis if overdosed, and requires blood tests every three days to ensure normal white blood cell counts. A drug that can be dosed without risk like PLX-R18 may be beneficial, especially in emergency radiation exposure situations. Finally, Neupogen only improves neutrophil cell counts, whereas the company stated that PLX-R18 improved multiple lineages, which would be a significant improvement over the former, although we would like to see data from NHP to back up these claims.

The company will need to perform an additional NHP study that is adequately powered for statistical significance to receive approval for ARS treatment. Additionally, a human safety database must be established, although data from other trials using PLX-R18 (such as the Phase I trial in hematopoietic stem cell transplant patients) can be used. Finally, a human/animal dose conversion study must be performed, which simply requires pharmacokinetic and pharmacodynamic comparisons between humans and animals. The development program to this point has been conducted by the NIH and, as such, there has no cost to the company at this stage. The company is in ongoing discussions with the NIH to finance the pivotal animal study (which has not started yet).

In August 2017, the company announced that the US Department of Defense (DOD) also has an interest in studying the therapy. The proposed DOD pilot study would test PLX-R18 after radiation exposure as in previous studies, but will also test whether the product can encourage hematopoietic recovery when administered before radiation exposure. This will support the potential use of the product for the US military's unique needs to protect personnel from potential or imminent radiation exposure. This program, if successful, could provide additional revenue streams to the company in the form of DOD acquisition contracts.

An additional upside to the program is that it would qualify Pluristem to receive a priority review voucher (PRV) from the FDA. These vouchers are issued by the FDA to encourage certain development programs such as underserved indications and they allow the voucher holder to shorten the FDA period of review from 10 to six months. PRVs are not attached to a particular company and can be freely traded, and we fully expect Pluristem to sell any vouchers it acquires. In the recent 21st Century Cures Act, the agency expanded the PRV program to include products that are potentially important to national security, and agents used in the event of radiological threats expressly fall under this definition. Therefore, the company should be able to apply for such a voucher in the event that the product gains approval. The most recent voucher sale was for $125m from Sarepta Therapeutics to Gilead in February 2017. These vouchers have been less expensive lately (from a peak of $350m) and we expect prices to continue to trend lower with the recent expansion.

[11] Neupogen label.

In other regulatory news, in October 2017 the company announced that PLX-R18 had received orphan drug designation from the FDA. This would entitle the company to seven years of market exclusivity if it is approved, as well as FDA protocol guidance, grants, and US tax breaks. The main benefit we see to Pluristem is in increased agency interaction, which has few downsides, but the other factors are less impactful as we model the current IP as sufficient, the program is currently funded by the NIH, and the company already receives significant incentives based on its Israeli domicile.

Stem cell transplant programs

Pluristem is also investigating PLX-R18 for a series of indications associated with stem cell transplant. The most advanced program from these studies is an ongoing Phase I clinical investigation of PLX-R18 to support the engraftment of hematopoietic stem cells following transplant. The same factors secreted by PLX-R18 cells that encourage the proliferation of hematopoietic cells following radiation also encourage the growth and differentiation of transplanted cells. There were approximately 22k hematopoietic cell transplants (HCTs) reported in the US in 2015.[12] A majority of these (~60%) were autologous transplants of the patient's own cells. Cord blood transplants make up the minority with less than 1,000 procedures per year. The company previously stated that interim results from the clinical trial would be available in H217, although it recently expanded the trial sites in the study, which may result in a delay. There is also an ongoing preclinical study sponsored by the New York Blood Center to investigate the efficacy of PLX-R18 as an adjuvant for cord blood transplantation.

The company tested the capacity of the therapy to improve the transplant of human cord blood into mice.[13] Human CD45 was tracked in the mice as a marker for mature lymphocytes, indicating the quality of graft. The concentration of CD45 positive cells in the blood arm rose significantly faster in the PLX-R18 treated arm to approximately 3-4 times the concentration in the control arm ($p<0.001$), but normalized significantly (to <2 times control) by week 8. An earlier study in 2007 examined a different PLX cell fraction (PLX-I) in a similar system examining the number of human CD45 cells in mice following a cord blood transplant that were preconditioned with either radiation or chemotherapy.[14] The number of CD45 cells in the radiation preconditioned arm was 133% higher compared to control ($p=0.01$) and 357% higher in the chemotherapy preconditioned arm ($p<0.05$). The company initiated a 30-person Phase I clinical study of PLX-R18 to treat incomplete recovery following HCT in the US.

The company also recently announced in November 2017 that it would be collaborating with Tel Aviv Sourasky Medical Center to investigate PLX-PAD for the treatment of steroid refractory chronic graft versus host disease (GvHD). GvHD is a complication associated with allogeneic HCT, in which the transplanted white blood cells have an immune response against the host. Incidence estimates for the chronic form of the disease vary significantly from study to study from 6% to 80% of allogeneic transplants.[15] Of these patients, 30-50% are well controlled with steroids.[16] This

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[12] Center for International Blood & Marrow Transplant Research.

[13] Metheny L, et al. (2016) Intramuscular Injection of PLX-R18 Improves Human Engraftment in NSG Mice Following Transplantation with CD34+ Umbilical Cord Blood. *Biol Blood Marrow Transpl.* 22(3), S148

[14] Burger O, et al. (2007) Human Placental Derived Mesenchymal Stromal Cells (MSC) Grown in 3D-Culture (PLX-I), Promotes Engraftment of Human Umbilical Cord Blood (hUCB) Derived CD34+ Cells in NOD/SCID Mice. *Blood* 10(11) abstract #1416.

[15] Filipovich AH, et al. (2005) National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Group Report. *Biol. Blood Marrow Transpl.* 11, 945-956.

[16] Le Blanc K, et al. (2008) Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. *Lancet* 371, 10-16.

corresponds to approximately 3,500 patients in the US at the high end of estimates. The rationale behind using PLX-R18 is that the anti-inflammatory properties of these cells could potentially mitigate some of the immune response and protect patients. However, the therapy would have to compete with a range of other immunosuppressive therapies that are used in the second line. The company currently has a planned Phase I/II study, which we consider largely exploratory at this stage.

Sensitivities

The largest risks to Pluristem are clinical in nature. Historically, cell therapies have had one of the lowest success ratios of any class of therapeutic, and progenitor or stem cells have never been approved. The PLX system may have some advantages over other cell-based systems because of the readily available source of cells and what appears to be a compatible immunogenicity profile, but the clinical data supporting the safety and efficacy of the therapy are very limited for all of the indications being examined. The company has completed only a handful of small clinical trials, and the total number of patients who have received the therapy is very small. In addition, the clinical development plan for the company has few risk hedges and involves moving directly into Phase III for the CLI and FNF development programs, without supporting Phase II trials for these indications. The company did perform a Phase I/II trial in THR, however, which is a different but related indication to FNF. To date, the company has not achieved any statistically significant results for an approvable endpoint in any of its programs.

The most commercially uncertain program is the PLX-R18 for ARS, which depends on obtaining government contracts. This commercial risk is offset by the lack of development costs for the program. We expect increasing competition in the CLI market as medical devices advance their ability to perform revascularizations below the knee. There is potential for commercial resistance to PLX-PAD for FNF because the additional expense on top of hip replacement must be justified. This effect may be offset if the treatment improves long-term outcomes (and thus total payer spending) in this vulnerable population. There may also be adoption issues of PLX-PAD for IC, which does not present the same immediate threat to health that CLI does and can generally be managed with exercise. We expect that the company will require $50m in additional capital, in addition to any development grants, to reach profitability in 2020. This value may increase dramatically if the company is unable to secure a procurement contract for PLX-R18 at that time.

Valuation

We have increased our valuation of Pluristem to $202m from $189m. This increase was driven by the new estimated net cash ($35m) following the October 2017 offering, as well as rolling forward our NPVs. Due to the new shares in the offering, however, our valuation on a per basic share basis has reduced to $1.87 from $1.94. Otherwise, our assumptions remain unchanged. We do not include the recently initiated GvHD program in our valuation as we see it as exploratory at this point, but we may add it if the company presents promising results. Additionally, we have not included the DOD ARS program in our valuation, but may add this in the future as well. The largest near-term inflection point will be the results from the Phase II IC clinical trial in early 2018, which will have implications for this program as well as CLI.

Exhibit 8: Valuation of Pluristem

Development Program	Prior data	Clinical stage	Prob. of success	Launch year	Launch pricing ($)	Peak sales ($m)	Patent/exclusivity protection	Royalty/ margin	rNPV ($m)
CLI, US	2x Phase I	Phase III	10%	2021	22,500	235	2036	63%	43.28
CLI, Europe	2x Phase I	Phase III	10%	2021	13,500	247	2036	59%	41.07
CLI, Japan	2x Phase I	Phase I/II	20%	2021	22,500	76	2036	27%	9.55
CLI, development costs									-18.39
FNF (US and Europe)	Phase I for THR	Phase III ready	15%	2021	22,100	171	2036	55%	17.25
ARS	Primate Studies	Pivotal primate study	10%-20%	2020	N/A	155/ contract	2036	77%	35.79
IC, US	N/A	Phase II	7.5%	2022	11,500	443	2036	57%	37.16
IC, Europe	N/A	Phase II	7.5%	2022	6,900	466	2036	50%	32.96
IC, Japan	N/A	Phase II	15%	2022	11,500	144	2036	20%	7.01
IC, development costs									-35.93
HCT (US and Europe)	Mouse Studies	Phase I	5%	2023	29,300	239	2036	61%	8.13
Unallocated costs									-11.03
Total									166.83
Net cash and equivalents (FQ118 + offering) ($m)									35.02
Total firm value ($m)									**201.85**
Total basic shares (m, after offering)									108.1
Value per basic share ($)									**1.87**
Dilutive warrants (m)									8.45
Diluted firm value ($m)									213.68
Value per diluted share ($)									1.83

Source: Edison Investment Research, Pluristem company reports

Financials

Pluristem ended its fiscal Q118 on 30 September 2017 with an operating loss of $7.4m. R&D spending was the company's major expense at $4.7m, which is largely in line with previous quarters ($4.6m in Q417). In October 2017 the company completed an offering of common stock: 9m shares at $1.67 for gross proceeds of $15.1m. We estimate pro forma net cash of $35m after the offering. This has reduced our expected financing requirement to $50m ($20m in FY18, $30m in FY19) from $63m. This financing requirement is contingent on the company either receiving an ARS government contract or selling the program's priority review voucher in 2020. If neither of these occurs, we expect the company to require at least $30m in additional cash. The company's cash needs are partially offset by grants it has received. The company quotes that it is participating in grants totalling $27m. However, it is only entitled to a fraction of this cash. For instance, the company is part of consortiums that are provisionally entitled to three different Horizon 2020 grants totalling $24.6m: $8m, $8.7m, and $7.9m individually. However, the company is only entitled to a fraction of these amounts: approximately $2.2m, $2.4m and $600,000 respectively, and a large portion will go directly to manufacturing costs associated with the studies, although there may be other cost savings.

Exhibit 9: Financial summary

$'000s	2015	2016	2017	2018e	2019e
Year end 30 June	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP
PROFIT & LOSS					
Revenue	379	2,847	0	0	0
Cost of Sales	(13)	(100)	0	0	0
Gross Profit	366	2,747	0	0	0
Research and development	(19,173)	(19,580)	(21,092)	(33,754)	(35,267)
Selling, general & administrative	(6,460)	(6,486)	(6,927)	(7,151)	(7,508)
EBITDA	(27,341)	(25,469)	(30,196)	(42,443)	(44,032)
Operating Profit (before amort. and except.)	(25,267)	(23,319)	(28,019)	(40,905)	(42,775)
Intangible Amortisation	0	0	0	0	0
Exceptionals/Other	0	0	0	0	0
Operating Profit	(25,267)	(23,319)	(28,019)	(40,905)	(42,775)
Net Interest	590	73	205	(1,395)	(3,795)
Other (change in fair value of warrants)	0	0	0	0	0
Profit Before Tax (norm)	(24,677)	(23,246)	(27,814)	(42,300)	(46,570)
Profit Before Tax (IFRS)	(24,677)	(23,246)	(27,814)	(42,300)	(46,570)
Tax	0	0	0	0	0
Deferred tax	0	0	0	0	0
Profit After Tax (norm)	(24,677)	(23,246)	(27,814)	(42,300)	(46,570)
Profit After Tax (IFRS)	(24,677)	(23,246)	(27,814)	(42,300)	(46,570)
Average Number of Shares Outstanding (m)	70.3	79.5	87.4	106.2	113.6
EPS - normalised (c)	(35.11)	(29.22)	(31.81)	(39.82)	(40.99)
EPS - IFRS ($)	(0.35)	(0.29)	(0.32)	(0.40)	(0.41)
Dividend per share (c)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	11,287	10,345	8,518	7,209	11,170
Intangible Assets	0	0	0	0	0
Tangible Assets	10,173	9,216	7,277	5,947	9,908
Other	1,114	1,129	1,241	1,262	1,262
Current Assets	56,868	35,596	29,016	30,550	11,452
Stocks	0	0	0	0	0
Debtors	1,691	2,228	1,036	25	25
Cash	53,119	32,750	26,665	29,054	9,956
Other	2,058	618	1,315	1,471	1,471
Current Liabilities	(6,183)	(5,775)	(5,414)	(10,658)	(8,429)
Creditors	(6,183)	(5,775)	(5,414)	(10,658)	(8,429)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	(3,829)	(2,010)	(1,869)	(21,819)	(51,819)
Long term borrowings	0	0	0	(20,000)	(50,000)
Other long term liabilities	(3,829)	(2,010)	(1,869)	(1,819)	(1,819)
Net Assets	58,143	38,156	30,251	5,282	(37,626)
CASH FLOW					
Operating Cash Flow	(20,605)	(18,522)	(21,611)	(31,036)	(43,880)
Net Interest	0	0	0	0	0
Tax	0	0	0	0	0
Capex	(831)	(1,750)	(378)	(267)	(5,218)
Acquisitions/disposals	0	0	0	0	0
Financing	17,201	807	15,728	14,724	0
Dividends	0	0	0	0	0
Other	0	0	0	0	0
Net Cash Flow	(4,235)	(19,465)	(6,261)	(16,579)	(49,098)
Opening net debt/(cash)	(58,819)	(53,119)	(32,750)	(26,665)	(9,054)
HP finance leases initiated	5	0	0	0	0
Exchange rate movements	0	0	0	0	0
Other	(1,470)	(904)	176	(1,032)	0
Closing net debt/(cash)	(53,119)	(32,750)	(26,665)	(9,054)	40,044

Source: Edison Investment Research, Pluristem company reports

Contact details	Revenue by geography
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Management team

Chairman and co-CEO: Zami Aberman	President and co-CEO: Yaky Yanay
Mr Zami Aberman joined Pluristem in September 2005, and redirected the company's strategy towards cellular therapeutics. Prior to Pluristem, Mr Aberman had a 30-year career as a senior executive in the high-tech industry with multiple companies in Israel, the US, Europe, Japan and Korea. Previous roles include chairman of VLScom, a private company specializing in video compression for HDTV and video over IP.	Yaky Yanay was appointed as Pluristem's president and chief operating officer in February 2014 and prior to that served as Pluristem's chief financial officer and secretary since November 2006, and executive vice president since March 2013. Before joining Pluristem, Mr Yanay was the chief financial officer of Elbit Vision Systems, a public company. Prior to that Mr Yanay served as manager of audit groups of the technology sector at Ernst & Young Israel.
CFO: Erez Egozi	**VP of Clinical and Medical Affairs: Esther Lukasiewicz Hagai, MD, PhD**
Erez Egozi joined Pluristem in March 2015 as vice president of finance and became CFO in March 2017. Prior to joining Pluristem, Mr Egozi spent eight years with Verint Systems Inc (Nasdaq: VRNT), serving as senior director of finance – worldwide finance controller of Verint's Communications and Cyber Intelligence Solutions division. From 2003 to 2007 Erez was with Intel Corporation.	Dr Lukasiewicz-Hagai has 12 years' experience in drug development. She joins Pluristem from Teva Global R&D, where she was director, clinical program leader, leading the global clinical development of multiple biosimilars and innovative drugs in various oncologic and neuropsychiatric indications.

Principal shareholders	(%)
Zami Aberman	3.99%
Yaky Yanay	3.38%
Renaissance Technologies, LLC	1.46%
Menora Mivtachim Holdings	0.92%

Companies named in this report

Amgen (AMGN), Cesca Therapeutics (KOOL), Fate Therapeutics (FATE), Merck Serono (MRK.FWB), Otsuka (4578.TYO), Vericel (VCEL)

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