EDISON

Pluristem Therapeutics

Initiation of coverage

First product to enter market

Pharma & biotech

We are initiating coverage on Pluristem Therapeutics, a company developing allogenic cell therapies derived from donated placental tissue. The company has two products, PLX-PAD for the treatment of vascular disorders and PLX-R18 for hematologic disorders. The lead program is for critical limb ischemia (CLI), with a Phase III expected to start in 2017. Based on feedback from both the FDA and EMA, a single pivotal 250-patient study will be required for approval. Our valuation is $182m.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
06/15	0.4	(24.7)	(0.35)	0.0	N/A	N/A
06/16	2.8	(23.2)	(0.29)	0.0	N/A	N/A
06/17e	0.0	(31.8)	(0.32)	0.0	N/A	N/A
06/18e	0.0	(39.3)	(0.38)	0.0	N/A	N/A

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

The appeal of placenta

Pluristem isolates mesenchymal stromal cells from placenta that are partially undifferentiated. The cells are not immortal or pluripotent like stem cells, reducing the risk of neoplasms, but they do secrete a large number of biologic molecules associated with growth and development. Additionally, they are inherently resistant to immune detection and can be used off the shelf without tissue typing.

Targeting revascularization

CLI is a disorder caused by occluded arteries in the leg that progress from pain to eventual amputation or death. As 50% of patients with CLI are not fit for revascularization surgery, there is a clear unmet need. PLX-PAD has been the subject of two Phase I trials (total n=27) with combined amputation-free survival (AFS) of 86% at one year compared to historical controls of 67%.

Radiation treatment a free option

The NIH is currently studying PLX-R18 for acute radiation syndrome with the aim of Emergency Use Authorization (EUA). These agents are stockpiled the by US government in case of radiological emergencies, and the last contract, for Neupogen (which only addresses low white cell counts while PLX-R18 addresses all three blood cell lineages), was for $155m in 2013. The company is currently not expected to spend any cash developing the product as the trials are fully supported by the NIH, and a stockpile agreement could be reached as soon as 2019.

Valuation: $182m (NIS683m)

We have arrived at an initial valuation of $182m (NIS683m), or $1.87 (NIS7.01) per basic share, based on a risk-adjusted NPV. We model the CLI program with the highest value at $56.8m. The development programs are high risk, given limited clinical data, partially mitigated by a large number of programs and limited competition. We expect it to require $50m in addition to current cash ($59m) to reach profitability in FY20.

23 November 2016

Price*	**US$1.56/ NIS5.91**
Market cap	**US$126m/ NIS478m**
	NIS3.75/$

*Priced as at 22 November 2016

Net cash ($m) at end September 2016	29.31
Shares in issue	80.8m
Free float	94%
Code	PSTI
Primary exchange	NASDAQ
Secondary exchange	TASE

Share price performance

%	1m	3m	12m
Abs	1.9	(6.6)	6.8
Rel (local)	(0.3)	(9.1)	1.5
52-week high/low		$1.85	$0.76

Business description

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

Next events

CLI Phase III initiation	Early to mid-2017
FNF Phase III initiation	Pending FDA meeting
IC Phase II top line results	YE17

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Investment summary

Company description: Off the shelf placenta cells

Pluristem is a biotech company developing cell-based therapies based on tissue derived from human placenta. The company was incorporated in 2001 and has accumulated $198m in paid in capital. 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 a 250-person Phase III trial expected to initiate in 2017. The company is also investigating the cells for the treatment of intermittent claudication (IC), femoral neck fracture (FNF), acute radiation syndrome (ARS), and hematopoietic cell transplant (HCT) support.

Valuation: $182m (NIS683m), or $1.87 (NIS7.01)

We value Pluristem at $182m (NIS683m), or $1.87 (NIS7.01) per basic share based on a risk-adjusted NPV analysis. Our highest value program is CLI at $57m with an estimated peak sales potential of $557m, followed by IC at $33m and peak sales of over $1bn. We assume probabilities of success for all development programs of between 7.5% and 20% due to small patient numbers and the absence of Phase II data for any program. We forecast the earliest profit potential from the ARS program of $155m in 2020, for a US stockpile contract. We expect the remaining programs to reach the market in 2020 through 2023, and for generic entrants in 2036.

Financials: $90m needed before profit

Pluristem ended Q117 on 30 September 2016 with $29.31m in cash and investments, which was subsequently increased by a $30m private placement in November with Innovative Medical Management. The company's current operational cash spending was $18.5m in FY16, which we expect to expand to $38.5m by FY18 because of increased spending on development with the advancement of the pipeline into late-stage trials. We currently forecast the company will need $50m ($20m in FY18 and $30m in FY19) in additional financing to reach profitability in 2020.

Sensitivities: Development risk predominates

The risks associated with Pluristem are predominantly associated with the current clinical development program. Historically, cell therapies have been less successful in the clinic than other forms of therapeutics. Despite advancing into late stage trials, the company has only limited early stage and preclinical data to support the efficacy of its technology. The CLI program has advanced on the basis of two open-label Phase I clinical trials that were not placebo controlled or powered for statistical significance with a total of 27 patients. The FNF clinical program is planned to advance to Phase III pending meetings with the FDA and is based on a Phase I/II study with 20 patients for a slightly different indication (total hip replacement). The remaining development programs are based on animal data, although this is not necessarily a limitation for the ARS program being developed via the animal rule. Commercial risks include the competition in the CLI market with advancing medical devices. We expect payer pushback for IC, which is treatable with exercise in many cases, and FNF, which has high degrees of patient and doctor satisfaction with the current standard of care. These risks aside, the indications that are being entered are largely unaddressed pharmacologically. There exists a financial risk associated with the additional $50m needed to complete development, which may result in dilution if sought on the equity markets.

The potent properties of placental products

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 that 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. The precise sub-lineage can be controlled by varying the culture conditions. However, the company has provided limited data on the precise cell population used used in their preparations. The placental expanded (PLX) cells are then cryogenically preserved and can been stored for a number of years (currently validated up to 3) 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 of 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)	Large animal study	PLX-R18
Hematopoietic cell transplant (HCT)	Phase I	PLX-R18

Source: Pluristem Therapeutics

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, similar to what is seen in the developing placenta. The product is currently being investigated for 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

[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.

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.

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. Globally, they have 76 granted patents and around 135 patent applications.

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%.[2] 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, 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.[3]

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.[3] 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 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.[4] 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

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

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

[4] 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.

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" criteria) 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. Currently the only other company with a Phase III development plan is Cesca Therapeutics, which intends to initiate a Phase III study using the bone marrow stem cell isolation device SurgWerks-CLI by the end of 2016.

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	Cesca	Phase III	Autologous	Bone marrow derived mononuclear cells	Stem cell isolation device. Enrolment begins in late 2016
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	Seeking Japanese approval on Phase II
Alecmestencel-T	apceth	Phase I/II	Autologous	Mesenchymal stem cells	
Biochymal	Taiwan Bio	Phase I/II	Allogenic	Mesenchymal stem cells	
ALO212	Arteriocyte	Phase I	Allogenic	Cord blood derived 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.[5] The largest trial to date examining AFS in CLI patients (the TAMARIS gene therapy trial) showed an AFS of 67% in the control arm.

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[5]

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

[5] 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.

were relatively mild in terms of CLI: before the start of the trial, patients had transcutaneous partial oxygen ($TcPO_2$) concentrations of 45.5 mmHg, with is on the low end of the normal range (depending on location of measurement the low end is 45-55 mmHg).[6] 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 has met with the FDA regarding a plan for a Phase III program. The company has also been accepted for an Adaptive pathway from the EMA, one of only six such programs today. The plan will include a single 250-person pivotal trial for both FDA and EMA approval. The primary endpoint of the trials will be mean time to amputation or death. This endpoint allows for survival analysis and the use of data from every enrolled patient, regardless of the duration of follow-up, allowing for an efficient trial design. Additionally, a large portion of the safety database will be provided by the ongoing intermittent claudication trial. The company has also received $8m in grant funding from the EU Horizon 2020 initiative to support the investigation of PLX-PAD for CLI. The company plans to initiate this program in early to mid-2017. 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 company also has approval for a 75-person pivotal Phase II trial in Japan from the PMDA via the accelerated pathway. The agency has a regenerative medicine initiative that allows for approval of new therapeutics of this class on the basis of significant safety, allowing for much smaller trial designs. The company has stated that it is seeking a Japanese development and commercialization partner.

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 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.[7] 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.[3]

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 the long period for its completion is indicative of enrolment difficulties. The trial had 150 patients enrolled as of May 2016, and the company reported an increase of 50 patients in the previous six months. Based on these enrolment rates, we expect it to be fully enrolled by the end of 2016, and top-line results should therefore be available near YE17.

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

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

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, but the current clinical pathway is focused more broadly on aiding recovery following 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 100k have FNF.[8]

FNF is most commonly treated surgically with either fixation and repair of the fracture with implants, or with hip replacement. The advancement of surgical techniques for hip replacement that are muscle sparing is likely to have led to the orientation of the company away from purely this indication. However, fixation with screws and other techniques still require an approach through muscle that must subsequently heal, and the new indication encompasses all of these techniques. The goal of the use of PLX-PAD is to improve the rate of recovery for these patients, which typically requires both inpatient and outpatient rehabilitative services. 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. It is unclear at this time the degree of medical need for such a therapy. Patients who have had a total hip replacement have lower levels of functionality than intact individuals, but exceptionally high levels of satisfaction with the results of the surgery (96%).[9] 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 THR, which reported results in January 2014. 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 muscle volume was measured via MRI as a secondary endpoint. The 20 patients in the 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 for both of these metrics was not reported. Although there was a trend toward 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.

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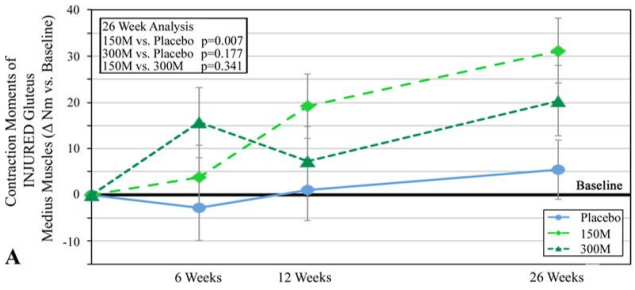
[8] Koval KJ and Zuckerman JD (1994) Overview and evaluation and treatment of femoral-neck fractures. *J. Am. Acad. Orthop. Surg.* 2(3), 141-149.

[9] Mariconda M, et at. (2011) Quality of life and functionality after total hip arthroplasty: a long-term follow-up study. *Brit. Med. J. Musculoskel. Dis.* 12(222).

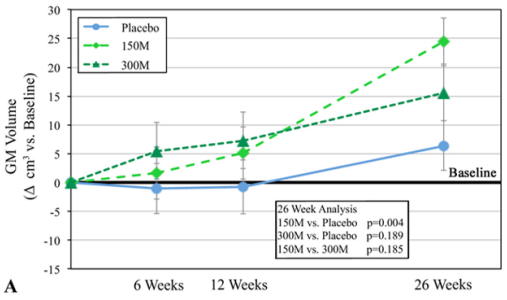
[10] Bhandari M, et al (2003) Internal Fixation Compared with Arthroplasty for Displaced Fractures of the Femoral Neck. *J. Bone Joiunt Surg.* 85(9) 1673-1681.

Exhibit 4: Muscle contractile force following THP



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

Exhibit 5: Muscle volume following THP



Source: Pluristem Therapeutics

The company has stated that it intends to initiate a Phase III study for patients after FNF following approval of the trial protocol by the FDA and EMA. We expect further studies to require functional assessments of mobility such as walking tests. We consider the strategy to move directly into Phase III trials without a confirmatory Phase II study with a functional endpoint to be aggressive and high risk.

Radiation exposure

The company is investigating using PLX-R18 cells for the treatment of individuals following severe radiation exposure. Acute radiation syndrome (ARS) is cluster of health effects following exposure to high doses of ionising 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 of 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 case of a nuclear event. The most recent acquisition contract was for $155m in 2013. 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. 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

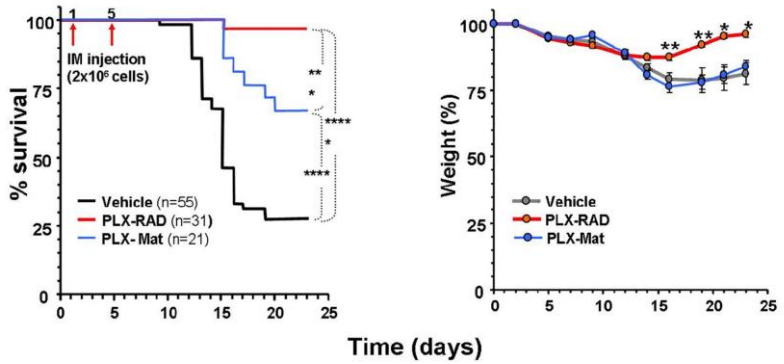
Product	Target	Company	Latest completed trials
Entolimod	TLR5 agonist	Cleveland BioLabs	Pivotal animal
HemaMax	Interleukin-12	Neumedicines	Large animal
Recilisib	DNA repair modulator	Onconova	Human safety, small animal

Source: Pluristem Therapeutics reports, Evaluate Pharma

Previous research

Unlike most other development plans, treatments for radiation exposure cannot be developed using human subjects, and the company is developing the therapy under the FDA animal rule. PLX-R18 has been tested in mice following exposure to potentially lethal doses of radiation. Mice were exposed to 7.7 Gy of radiation because this exposure level is lethal to approximately 70% of animals, but allows for sufficient number of survivors for follow up bloodwork. Animals were treated with PLX-R16 (called PLX-RAD in this study), PLX-Mat, a different placental cell fraction derived from maternal tissue, and placebo. The animals were injected with 2m cells 24 hours following irradiation and then again at five days.

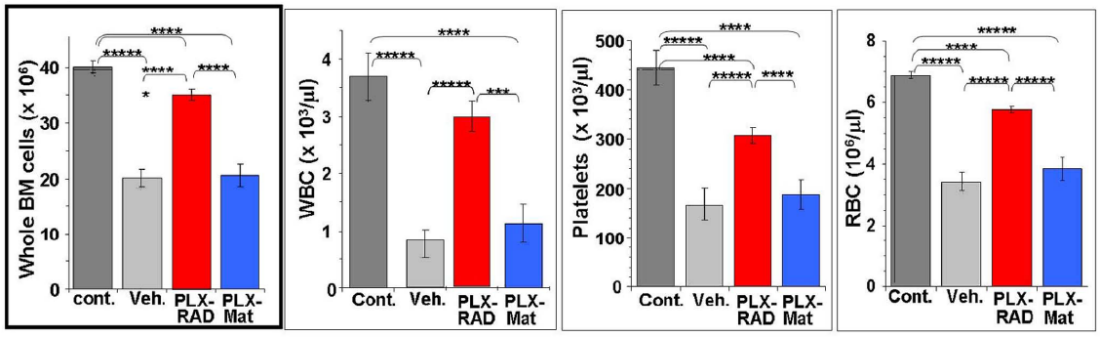
Exhibit 7: PLX-RAD effect on survival and weight following radiation exposure.



Source: PLoS One.[11] Note: PLX-RAD is the same as PLX-R18, * = p<0.05, ** = p<0.01,*** = p<0.005, **** = p<0.001, ***** = p<0.0001.

After 23 days, 97% of mice treated with PLX-R18 survived compared to 27% of those treated with placebo vehicle (p<0.0001; Exhibit 7). The mice treated with PLX-R18 had returned to approximately the same weight as before the radiological insult. When the hematologic cell counts of these mice were measured, the PLX-R18 arm showed significant improvement across all measured compared to vehicle and the PLX-Mat cell fraction (Exhibit 8).

Exhibit 8: Hematologic parameters following radiation exposure



Source: PLoS One.[11] Note: PLX-RAD is the same as PLX-R18, * = p<0.05, ** = p<0.01,*** = p<0.005, **** = p<0.001, ***** = p<0.0001.

PLX-R18 is being further developed in a dose selection study performed by the NIH. At this time, the development program is being fully funded by institute. The ongoing study will examine the

[11] Gaberman E, et al (2013) Mitigation of Lethal Radiation Syndrome in Mice by Intramuscular Injection of 3D Cultured Adherent Human Placental Stromal Cells, *PLoS One*, 8(6), e66549.

dosing in large animals and will proceed to a pivotal animal study to support an Emergency Use Application (EUA). Data on the large animal study is expected around YE16. One of the benefits of this program is that this research is fully funded with government resources, and we expect this to continue, although the company does not have control over the trial proceedings and timeline as a result. The company has also signed an agreement with Fukushima Medical University to collaborate on developing PLX-R18 for the treatment of the side effects of radiation therapy for cancer.

Stem cell transplant

Pluristem is also investigating 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 over 19k hematopoietic cell transplants (HCTs) reported in 2013.[12] Over half of these (57%) were autologous transplants of the patient's own cells, with the vast majority of remaining transplants from HLA matched donors or cord blood.

The company has reported only preliminary preclinical data regarding the efficacy of PLX-R18 for HCT. 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 armed ($p<0.05$). The company initiated a 30-person Phase I clinical study of PLX-R18 to treat incomplete recovery following HCT in the US.

Sensitivities

Pluristem faces a series of hurdles that pose risk to the future success of the company. The clinical programs being investigated by the company are uniformly high risk. Historically, cell therapies have had one of the lowest success ratios of any class of therapeutic. 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 Phase I clinical trials, and the total number of patients that 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. The basis of the company pursuing CLI is from two open label trials, only one of which had patients with severe ischemia. Neither of the

[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.

clinical trials reached statistical significance. The previous FNF clinical experience was with only 20 patients, and the metrics used in the study (muscle strength and MRI of muscle volume) are not functional assays like a walking test, which would be needed in later studies. Moreover, the higher dose in the trial showed reduced efficacy, which may be indicative of dosing limitations. The only data we have on the efficacy of PLX-R18 for ARS and HCT is from mice, which have historically responded much more strongly to cell based therapies than larger animals or humans.

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 low rate of complications and high quality of life and satisfaction of patients following hip surgery may present issues with adoption and payer support. 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 need at least $50m in additional financing before profitability in FY20, and this is attached to the typical financing and dilution risks.

Valuation

We value Pluristem at $182m (NIS683m), or $1.87 (NIS7.01) per basic share based on a risk-adjusted NPV analysis. This valuation is dependent on a series of assumptions about the company's development programs and eventual commercialization. For all programs, we assume generic entry in 2037 based on the expiration of the composition of matter patent (2031 with five-year Hatch-Waxman extension). All pricing assumptions assume a 40% lower price in Europe compared to the US and a gross/net pricing at 70%. We assume reimbursement in Japan at parity with the US, unlike other therapeutics, on the basis of the regenerative medicine initiatives in that country. We also arrive at a higher probability of approval in Japan because regenerative medicine products only require demonstration of safety for approval. Commercialization in Japan for PLX-PAD assumes an out-licensing for 20% of sales. COGS are based on a cost per dose of $700 ($1,400 per course), which is low for cell based therapies, on account of the company's efficient manufacturing process and the negligible cost of sourcing placenta. However, we believe that the sourcing of tissue from mixed donors will require a degree of manufacturing control overhead to ensure the safety of donated tissue, link donors and cell batches and track HLA types in the case of potential adverse reactions. Selling costs assume an overhead of $5m per program and local and 10% variable selling costs. We assume that the company will take advantage of its status under the Israeli Encouragement Law, which will provide tax exemptions until 2023 and a reduced rate (10-25%) for five to eight years thereafter (modeled as 15% for five years). We are not including the PAH program in our estimates at this time due to the lack of data and the recent termination of the development agreement with United Therapeutics.

We forecast an initial pricing of PLX-PAD of approximately $22.5k per treatment course (two injections) for CLI. This pricing is a significant discount to the cost of amputation ($54k as reported in 2005-07).[15] We model a peak 10% penetration of patients that are unfit for revascularization, but we expect the fraction of patients that are inoperable to decline (from 50% to 33% by 2036), based on the advancement of surgical interventions. Our probability of success for this program is 10% because of the lack of statistically significant efficacy data from a randomized controlled trial.

Our pricing assumptions for FNF assume parity with the CLI program ($22.5k at launch). Our probability of success for the program is 15% on the basis of the single Phase I trial. We expect that

[15] Peacock JM, et al. (2009) The Incidence and Health Economic Burden of Critical Limb Ischemia and Ischemic Amputation in Minnesota: 2005–2007. *Circulation* 120(S18).

further studies will require a functional assessment such as a walking test or quality of life measures, which were not examined. Our predicted peak penetration is low at 2%, because of the high reported satisfaction of patients and doctors with the current standard of care and the lack of a clear unmet medical need.

We expect that the IC program will need to develop a separate product and pricing ($11.5k) based on PLX-PAD compared to CLI, because the disease can be controlled in many cases though low cost interventions such as exercise, and we expect payer resistance. For the same reasons, we predict low penetration (0.5%), but coupled with the much higher prevalence of the disease (approximately 2% of the general population), we forecast the highest peak sales for this indication of over $1bn. We consider this the highest risk program at the company (7.5% probability of success) because it relies on the same non-significant, unblended data as the CLI program, but the IC indication, which has pain as the primary symptom, was not investigated.

The ARS program with PLX-R18 assumes two potential awards from the US government of $155m in FY2020 and 2025. This award is based on the size of the award reported by Amgen for Neupogen in 2013. We assign a 20% and 10% probability of obtaining these awards respectively. The program is current supported entirely by government grants and we expect this to continue if it shows promise and we have therefore not assigned any development costs.

Finally, the HCT program is assigned a launch pricing of $29.3k, due to the fact that it can potentially avoid high cost re-transplantation ($96k to $204k in 2012)[16] following graft failure. We model 50% penetration of allogenic stem cell transplants by 2036. We assume a risk of 5% for the program because of the lack of clinical data for this indication, although we regard the animal data presented for this and the ARS program as promising.

Exhibit 9: Pluristem valuation

Development Program	Prior data	Clinical stage	Prob. of success	Launch year	Launch Pricing ($)	Peak sales ($m)	Patent/ Exclusivity Protection	Royalty/ Margin	rNPV ($m)
CLI, US	2x Phase I	Phase III	10%	2021	22,500	235	2036	63%	39.92
CLI, Europe	2x Phase I	Phase III	10%	2021	13,500	247	2036	59%	37.85
CLI, Japan	2x Phase I	Phase I/II	20%	2021	22,500	76	2036	20%	6.90
CLI, development costs									-23.22
FNF (US and Europe)	Phase I for THR	Phase III ready	15%	2020	22,100	172	2036	56%	17.80
Radiation treatment	Mouse Studies	Large Animal Study	10%-20%	2020	N/A	155/contract	2036	77%	22.17
IC, US	N/A	Phase II	7.5%	2022	11,500	443	2036	57%	33.89
IC, Europe	N/A	Phase II	7.5%	2022	6,900	466	2036	50%	30.03
IC, Japan	N/A	Phase II	15%	2022	11,500	144	2036	20%	6.31
IC, development costs									-37.08
HCT (US and Europe)	Mouse Studies	Phase I ready	5%	2023	29,300	239	2036	61%	7.48
Unallocated costs									-19.01
Total									123.03
Net cash and equivalents (Q117 + Offering) ($m)									59.31
Total firm value ($m)									182.34
Total basic shares (m,Q117 + Offering)									97.67
Value per basic share ($)									1.87

Source: Pluristem Therapeutics reports, Edison Investment Research

[16] Khera N, et al. (2012) Economics of hematopoietic cell transplantation. *Blood*, 120, 1545-1551.

Financials

The company's fiscal Q1 ended on 30 September 2016. The company ended the period with $29.31m in cash and investments. The company recently completed (November 2016) a private placement with Innovative Medical Management, a China-based subsidiary of Zheshang Venture Capital Co, for $30m. The offering includes 16.89m shares at $1.77 and 4.42m warrants exercisable at $2.50. The majority of operational spending for the period ($6.56m) was devoted to R&D ($5.00m). We expect the R&D spending to increase to $25.3m for FY17 and $30.8 for FY18 to fund the recently started Phase III clinical trial for CLI and new trails for FNF and HCT. The clinical trial costs are partially offset by an $8m research grant as part of the EU horizon 2020 initiative. We forecast that the company will need $50m in additional financing before it is cash flow positive in 2020. We have recorded this as illustrative debt ($20m in FY18 and $30m in FY19). The forecast for positive cash flow in FY20 depends on the successful negotiation of a government contract for ARS (modelled as $155m in FY20), but we expect the $50m to provide sufficient resources to reach sustainable profitability in FY21 from the sales of PLX-PAD for CLI. This financing will also provide the $14m in CAPEX we expect to be required to prepare for commercial operations.

Exhibit 10: Financial summary

$'000s	2014	2015	2016	2017e	2018e
Year end 30 June	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP
PROFIT & LOSS					
Revenue	379	379	2,847	0	0
Cost of Sales	(11)	(13)	(100)	0	0
Gross Profit	368	366	2,747	0	0
Research and development	(19,542)	(19,173)	(19,580)	(25,265)	(30,813)
Selling, general & administrative	(8,676)	(6,460)	(6,486)	(6,810)	(7,151)
EBITDA	(29,752)	(27,341)	(25,469)	(34,023)	(39,863)
Operating Profit (before GW and except.)	(27,850)	(25,267)	(23,319)	(32,076)	(37,963)
Intangible Amortisation	0	0	0	0	0
Exceptionals/Other	0	0	0	0	0
Operating Profit	(27,850)	(25,267)	(23,319)	(32,076)	(37,963)
Net Interest	918	590	73	238	(1,362)
Other (change in fair value of warrants)	0	0	0	0	0
Profit Before Tax (norm)	(26,932)	(24,677)	(23,246)	(31,838)	(39,325)
Profit Before Tax (IFRS)	(26,932)	(24,677)	(23,246)	(31,838)	(39,325)
Tax	0	0	0	0	0
Deferred tax	0	0	0	0	0
Profit After Tax (norm)	(26,932)	(24,677)	(23,246)	(31,838)	(39,325)
Profit After Tax (IFRS)	(26,932)	(24,677)	(23,246)	(31,838)	(39,325)
Average Number of Shares Outstanding (m)	63.5	70.3	79.5	99.6	102.6
EPS - normalised ($)	(0.42)	(0.35)	(0.29)	(0.32)	(0.38)
EPS - IFRS ($)	(0.42)	(0.35)	(0.29)	(0.32)	(0.38)
Dividend per share ($)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	12,036	11,287	10,345	10,110	9,917
Intangible Assets	0	0	0	0	0
Tangible Assets	10,823	10,173	9,216	8,988	8,795
Other	1,213	1,114	1,129	1,122	1,122
Current Assets	61,987	56,868	35,596	43,291	23,121
Stocks	0	0	0	0	0
Debtors	2,263	1,691	2,228	2,765	2,765
Cash	58,819	53,119	32,750	39,976	19,806
Other	905	2,058	618	550	550
Current Liabilities	(7,397)	(6,183)	(5,775)	(11,432)	(7,321)
Creditors	(7,397)	(6,183)	(5,775)	(11,432)	(7,321)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	(4,503)	(3,829)	(2,010)	(1,992)	(21,992)
Long term borrowings	0	0	0	0	(20,000)
Other long term liabilities	(4,503)	(3,829)	(2,010)	(1,992)	(1,992)
Net Assets	62,123	58,143	38,156	39,977	3,725
CASH FLOW					
Operating Cash Flow	(19,121)	(20,605)	(18,522)	(21,647)	(38,464)
Net Interest	0	0	0	0	0
Tax	0	0	0	0	0
Capex	(1,573)	(831)	(1,750)	(1,750)	(1,707)
Acquisitions/disposals	0	0	0	0	0
Financing	12,624	17,201	807	30,004	0
Dividends	0	0	0	0	0
Other	0	0	0	0	0
Net Cash Flow	(8,070)	(4,235)	(19,465)	6,607	(40,170)
Opening net debt/(cash)	(54,213)	(58,819)	(53,119)	(32,750)	(39,976)
HP finance leases initiated	0	5	0	0	0
Exchange rate movements	0	0	0	0	0
Other	12,676	(1,470)	(904)	619	0
Closing net debt/(cash)	(58,819)	(53,119)	(32,750)	(39,976)	194

Source: Company accounts, Edison Investment Research

Contact details	Revenue by geography
Pluristem Therapeutics Inc. MATAM Advanced Technology Park Building #5 Haifa 31905, Israel www.pluristem.com	N/A

Management team

Chief Executive Officer: Zami Aberman	Chief Operating Officer: 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 Ltd., 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 Ltd., a public company. Prior to that Mr Yanay served as manager of audit groups of the technology sector at Ernst & Young Israel.
VP of Finance: 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. 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	2.6%
Yaky Yanay	1.8%
Renaissance Technologies, LLC	1.4%
Barclays PLC	0.9%
Mark Germain	0.5%
Isaac Braun	0.5%
Hava Meretzki	0.5%

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