EDISON

Locate Bio

Valuation report

A portfolio of novel orthobiologics

Healthcare equipment & services

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Locate Bio is a developer of next-generation orthobiologic products for use in orthopaedic surgery. The company's historical expertise is in drug delivery, which it is using to solve some of the issues with existing competitor products, such as the delivery of growth factor for its bone morphogenetic protein 2 (BMP-2) eluting graft substitute LDGraft. The company has three bone graft products and one cartilage product in development, with the first (CertOss) expected to have regulatory clearance in 2022. We value the company's portfolio of products at £113.1m.

Multiple solutions for a complex market

Orthobiologics are biologically active products such as graft substitutes designed to induce the regrowth of bone or cartilage. The historical benchmark these products have been compared to is autologous bone transplant, but modern graft substitutes have the capacity to deliver comparable fusion rates without the side effects of extracting a bone graft. Locate Bio is targeting multiple market segments with its products. CertOss is a growth factor-free graft substitute designed to compete with more expensive biologics such as demineralised bone matrix (DBM). CognitOss is a similar product that slowly elutes antibiotics for the treatment of osteomyelitis (bone infection). We value these products at £10.9m and £24.7m, respectively.

LDGraft: Going for best in class

The highest value product in our valuation is LDGraft (£53.6m), a BMP-2 eluting graft substitute designed to address some of the limitations of the BMP-2 eluting Infuse graft marketed by Medtronic (c $800m peak sales). These issues include poor handling characteristics and risks associated with how BMP-2 is delivered. LDGraft is a mouldable putty that delivers BMP-2 over a prolonged period, allowing for comparable performance at a fraction of the dose in model systems.

Chondro3: Bridging the gap

The company's last product in development is Chondro3, a cartilage graft that incorporates three layers to promote the regrowth of hyaline cartilage as well as the underlying bone substrate and the calcified cartilage layer connecting the two. It is the only product to our knowledge to adopt this three-layer approach and the only product that incorporates type II collagen, an essential component of hyaline cartilage. We value the product at £23.9m.

Valuation: £113.1m based on risk-adjusted DCF

Our valuation of £113.1m is based on a risk-adjusted DCF model, which includes cash flows from each of the above products. We consider LDGraft the highest risk product (10% success probability assessment) because of its early stage and the need for multiple in human studies. We expect Locate Bio to generate its first revenue in 2022 with the marketing clearance for CertOss. Our valuation does not include current cash or future operational financing needs.

Business description

Locate Bio is an orthobiologics company developing new graft substitutes for bone and cartilage. Its products are CertOss, a next-generation semi-synthetic graft, CognitOss, an antibiotic-eluting version of CertOss for osteomyelitis, LDGraft, a high-performance BMP-2 eluting graft, and Chondro3, a multi-layered cartilage graft substitute.

Next events

LDGraft large animal study complete	2021
CertOss 510(k) submission	2022

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Investment summary

Company description: Innovation in orthobiologics

Locate Bio is a healthcare company developing novel orthobiologic products for the orthopaedic medical industry. These products (to be regulated as medical devices) include CertOss, a semi-synthetic graft substitute (510(k) submission planned in 2022); CognitOss, the same graft substrate as CertOss but designed to elute antibiotics for the treatment of osteomyelitis (first in human studies projected in 2022); LDGraft, a BMP-2 eluting graft designed to improve on the handling profile of existing BMP-2 grafts (large animal preclinical study expected to complete in 2021); and Chondro3, a three-layer cartilage graft (first in human in planning stages).

Valuation: £113.1m, half from LDGraft

We arrive at a valuation of £113.1m, of which approximately half is associated with the LDGraft programme (£53.6m). All of our valuations are based on risk-adjusted DCF models. We model LDGraft with an initial approval in lumbar interbody fusion and include a follow-on indication of lumbar posterolateral fusion (PLF). The programme is high risk, with a 10% risk adjustment for the lead indication, based on its early development stage (entering the clinic in 2023). The remaining programmes are lower risk (20–40% risk adjustment for their primary indications), but have a lower peak sales potential. Not included in this valuation are company assets (such as cash) or company cashflows outside of these products.

Exhibit 1: Valuation of Locate Bio

Product	Indication	Launch	Peak sales ($m)	Risk adjustment	Value (£m)
LD Graft	Lumbar interbody fusion	2027	270	10%	30.6
	Lumbar PLF	2029	390	5%	23.0
CertOss	Spinal fusion indications	2022	50	40%	10.9
CognitOss	Osteomyelitis	2024	60	20%	9.0
	Revision Arthroplasty	2025	100	10%	15.7
Chondro3	Knee osteoarthritis	2025	130	20%	23.9
Total					113.1

Source: Edison Investment Research

Sensitivities: A combination of clinical and commercial risks

Locate will face a series of risks common to the development of medical products, as well as some risks specific to the orthobiologic space. The company's products all face different degrees of clinical and regulatory risk, depending primarily on their market authorisation pathway. For example, CertOss will require relatively little additional development and is expected to receive marketing clearance through the less stringent 510(k) pathway, whereas LDGraft will require multiple in-human clinical studies and a rigorous PMA approval approach. However, the degree of regulatory risk is inversely proportional to the commercial risk associate with each product. CertOss may be on the market as soon as 2022, but it will be face hundreds of competing products with which it will need to differentiate itself. LDGraft may be face more hurdles to gain approval but this acts as a barrier to competition. This being said, LDGraft will still need to compete with the well-established Infuse product from Medtronic. CognitOss and Chondro3 will be entering underdeveloped markets where similar products are not in routine use. Finally, each of these markets and the orthopaedic space in general is dominated by a small number of well-established incumbent companies that command a strong market power, making it challenging for smaller entrants to have commercial success.

Company description: Building better bones

Locate Bio is a healthcare company focused on the development of novel orthobiologics to promote the regrowth of bone and cartilage. Orthobiologics are products either derived from tissue or containing other active biologic substances such as growth factors or cells that are used to promote the regrowth of bone and/or cartilage, and the company has a portfolio of three bone-graft substitute products and one product to promote the healing of cartilage.

The company was originally spun out of University of Nottingham in 2001 and subsequently operated as a contract research organisation focusing on drug delivery technology. In 2018 following a venture investment from Mercia Asset Management, the company initiated its own internal development programmes in the orthobiologic space. This led to the development of LDGraft, a graft product with a controlled release of BMP-2 intended for lumbar fusion surgeries. This product is designed to address some of the existing limitations of BMP-2 products by improving safety and handling. We believe LDGraft has the greatest market potential of the company's products, but also has the longest expected timeline to commercialisation, with a launch not expected until 2027.

The company expanded its pipeline in September 2020 through the licensing of three new products from the Royal College of Surgeons in Ireland (RCSI) University of Medicine and Health Sciences (terms undisclosed). The first is CertOss, a synthetic graft product for lumbar fusion. The goal with this product is to provide a next-generation, animal-derived graft capable of competing with DBM. The goal is that if this can be achieved, it will be more attractive due to problems of variability in DBM preparations. CognitOss is a similar product to CertOss but designed to elute antibiotics from the matrix. This product is intended to fill the voids formed after surgical treatment of osteomyelitis (bone infection) to promote the regrowth of bone while treating any residual disease. Finally, the company is developing Chondro3 as a treatment of cartilage lesions, typically a result of knee osteoarthritis (KOA). It is an animal-derived graft that includes subchondral bone to improve fusion with existing bone and cartilage growth.

These products are intended to be regulated as medical devices and the company will be seeking marketing authorisation through multiple pathways (Exhibit 2). CertOss is expected to be the first product cleared for marketing (targeting 2022) because it will require a relatively simple 510(k) clearance and is unlikely to need in-human studies. All of the company's other products under development will need additional clinical and preclinical studies and have planned launch dates between 2024 and 2027.

Exhibit 2: Locate Bio pipeline

Product	Indication	Pathway	Target approval	Stage
Bone				
CertOss	Spinal fusion	510(k)	2022	12-week GLP rabbit study planned, 510(k) submission planned for 2022
CognitOss	Osteomyelitis void filling	De Novo	2024	IDE submission planned for 2022, human study in 2022
LDGraft	Spinal fusion	PMA	2027	GLP large-animal study planned to complete in 2021, first in human 2023
Cartilage				
Chondro3	Knee osteoarthritis	PMA	2025	Human pilot study planned with IDE filing in 2022

Source: Locate Bio. Note: GLP=good laboratory practice.

Promoting the regrowth of bone

There are many different instances in modern orthopaedic medicine in which a physician needs to promote the growth of bone to restore function to a patient. Historically, this was done by removing bone tissue from another region of the body (often the iliac crest of the hip) and transplanting it.

These are referred to as autologous bone transplants ('autograft') and are excellent at promoting bone growth, but entail an additional invasive procedure with its own risks and sequelae to obtain the bone tissue.[1] Therefore, significant effort has been made to develop alternative products to achieve similar results. These include orthobiologics such as allografts and DBM and synthetic materials such as ceramics.

The performance of bone grafts can be evaluated along three different axes: osteoconduction, osteoinduction and osteogenesis. Osteoconduction is the ability of a graft to support the migration of bone cells into the graft from the patient's body. The cells can enter the graft and then proceed to use it as a template for more bone deposition. The key to achieving osteoconduction is the presence of a scaffold the cells can traverse, which can either be extracellular matrix extracted in the preparation of an orthobiologic or a synthetic substance such as a ceramic.

Osteoinduction is the ability of a graft to induce the body to produce more bone forming osteoblast cells. Osteoinduction can be the result of either the direct interaction of osteoprogenitor cells with the graft or more commonly, the result of growth factors and other proteins present in the graft. Products comprised primarily of BMP-2 or other growth factors operate primarily on the principle of osteoinduction. However, the presence of growth factors is a major contributor to the performance of other graft technologies such as allograft and DBM. Allograft refers to piece of bone harvested typically from cadavers for transplantation, whereas DBM is a similar tissue product made from demineralised human bone and used as a putty. Although allograft and DBM are processed, some portion of the growth factors from the donor's tissue remains intact and can improve performance. However, there can be significant variation in the concentration of growth factors between preparations due to underlying variation in the donors.[2] This is a potential causative factor for the variation outcome when using these products.

The last axis for the promotion of bone growth is osteogenesis. Osteogenesis is the capacity of a graft product to directly induce the regrowth of bone without the participation of the recipient's cell population. This property of grafts is limited to products that supply their own cell populations capable of secreting bone, either osteoblasts or various progenitors that can differentiate into osteoblasts. In this case osteoblasts from the graft itself contribute to bone regrowth. Because osteogenesis relies on the transplantation of intact cells, it is limited to grafts that can provide them, such as autografts and bone marrow aspirate. Allografts, although they are intact tissue, require a sterilisation step in their preparation, which kills these cells.

Exhibit 3: Properties of different bone grafts

Graft	Osteoconduction	Osteoinduction	Osteogenesis
Autologous bone	+++	++/+	+++
BMP/Growth factors	-	+++	-
Bone marrow aspirate	-	+/-	++
DBM	+	+/-	-
Allograft	+	+/-	-
Ceramics	+++	-	-

Source: Adapted from D'Souza et al.,[3] Whang et al.[4]

The market for bone graft substitutes is especially complex given there are a very large number of products, each with their different advantages and disadvantages, that are collectively being used for a wide range of procedures. However, they can be roughly organised by technology and price

1 Anderson DG, et al. (2003) Donor Site Morbidity After Anterior Iliac Crest Bone Harvest for Single-Level Anterior Cervical Discectomy and Fusion. *Spine* 28, 134-9.

2 Bae H, et al. (2010) Variability Across Ten Production Lots of a Single Demineralized Bone Matrix Product. *J Bone Joint Surg* 92, 427-435.

3 D'Souza M, et al. (2019) Graft Materials and Biologics for Spinal Interbody Fusion. *Biomedicines* 7, 75.

4 Whang PG and JC Wang (2003) Bone graft substitutes for spinal fusion. *Spine J* 3, 155-165.

point (Exhibit 4). Locate Bio has obtained some market research on this segment that is useful for framing the current technology, which we have summarised in Exhibit 4.

Exhibit 4: Graft substitute market segments

Technology	Average selling price	Market size	Advantages	Disadvantages
Autograft	Variable		High fusion rates	Damage to site of tissue extraction
BMP, other growth factors	$4,000–5,000	$1bn	High fusion rates	Side effects, poor handling characteristics
DBM	$1,800–2,800	$700m	Easy handling, good fusion rates	Variability
Stem cells	$1,800–2,800	$500m	Easy handling, good fusion rates	Variability
Allograft	$200–1,000	$200m	Inexpensive, rigid	Variability, poor fusion rates
Older synthetic	$200–1,000	$1.1bn	Inexpensive	Undifferentiated

Source: Locate Bio

The entire bone graft substitute market is positioned as an alternative to autologous graft and all these products are measured against this gold standard. Despite the downsides of requiring a second procedure (which involves a donor site), approximately half of all graft procedures use autograft.

The highest-performing and most expensive products are growth factor based, with the Infuse graft from Medtronic being the dominant product in this category (more information below). The market becomes increasingly fragmented with lower tier products: a review from 2017 listed 38 different DBM products,[5] whereas synthetic products are measured in the hundreds with little differentiation.

Spinal fusion

The lead indication for CertOss and LDGraft will be lumbar spinal fusion, a surgical procedure where two or more vertebrae of the lower back are fused to alleviate pain and other symptoms of degenerative back disease. Spinal fusion can also be performed at the thoracic or cervical vertebrae, with a similar technique. Spinal fusions are one of the most common non-maternal surgical procedures performed with over 460,000 procedures performed in the US per year,[6] with the majority (52%) in the lumbar region.[7]

There is a wide degree of variability in spinal fusion techniques and the medical devices employed, but all fusion procedures use a bone graft to encourage the formation of bone between the vertebrae. The general spinal fusion technique is as follows:

- The patient's spine is exposed via incision and dilating the surrounding tissue.
- Portions of the vertebra and disc that are damaged or causing pain are removed.
- A bone graft is then either placed between the transverse processes (PLF) and/or in the space formed by removing the disc in an interbody device (interbody fusion).
- Fixation hardware is installed to support the spine while the new bone forms.

PLF is an older but very common technique that uses relatively large grafts placed on the exterior of the spinal column. Interbody fusion, by comparison, uses a bone graft placed into a rigid body or cage placed in between the vertebrae where the disk has been removed. Interbody procedures require less graft material generally, and the graft is put under less strain (because it is protected by a cage that bears the weight along the spinal column), which makes these generally more

[5] Shehadi JA and Elzein SM (2017) Review of commercially available demineralized bone matrix products for spinal fusions: A selection paradigm. *Surg Neurol Int*

[6] McDermott KW, et al. (2017) Overview of Operating Room Procedures During Inpatient Stays in U.S. Hospitals, 2014. Healthcare Cost and Utilization Project; Agency for Healthcare Research and Quality.

[7] Rajaee SS, et al. (2012) Spinal Fusion in the United States: Analysis of Trends From 1998 to 2008. *Spine* 37, 67-76.

amenable to advanced graft substitutes. The Infuse bone graft product, for instance, is only indicated for use in interbody devices. The rate of interbody fusion procedures has been growing but remains a minority (~40%) of all fusions.[8]

LDGraft

LDGraft is designed to address some of the limitations with growth factor-based bone graft substitutes. These are the only products able to produce fusion rates similar to autograft but are difficult to handle and associated with significant side effects. These products can achieve fusion rates similar to autograft,[9] and combined they have an estimated market share of approximately $1bn. The dominant product in this category has historically been the Infuse Graft from Medtronic, which is a collagen sponge that is loaded with recombinant BMP-2. Medtronic does not consistently report sales of the product, but its biologics division (which is driven predominantly by Infuse) had peak sales of $884m in fiscal year 2011. Around that time, the product was involved some controversy as Medtronic was accused in multiple reports of concealing major side effects of the treatment, including cancer, male infertility and ectopic bone formation.[10] It was even implicated in some deaths when used off label for cervical procedures. Medtronic had also developed a different BMP-2 containing product, Amplify, intended for PLF. The product contained a different, more compression-resistant matrix and a higher dose of BMP-2 (40mg total compared to 6mg or 12mg for Infuse). This product was rejected by the FDA due to higher rates of cancer in the Amplify arm in clinical trials.

The high initial dose of BMP-2 has been postulated to be a significant factor contributing to the adverse effects of this molecule[11] and significant effort has been made into developing alternative carriers with improved release profiles. One review from 2017 catalogued 48 separate papers published from studies of new carriers for BMP-2.[12] There have also been complaints that the product was difficult to handle in practice, potentially leading to the release of BMP-2 outside the targeted area and subsequent problematic ectopic bone growth, such as around nerves. To apply Infuse, a surgeon must saturate a sponge made of collagen with the reconstituted BMP-2 solution, which must be placed into the void where growth is desired. If this sponge drips or is squeezed accidentally when being placed, it could lead to the release of concentrated liquid BMP-2.

LDGraft is a recombinant BMP-2 eluting product that aims to address these limitations through a series of design features. First, instead of a collagen sponge reconstituted with BMP-2, the product is provided as a putty already infused with BMP-2. This improves the handling of the product and reduces the risk of spills. Next, the BMP-2 is provided in a microencapsulated formulation. This limits the initial exposure to the growth factor, avoiding the high initial peak concentrations, while providing more sustained concentration at longer time points. The microencapsulation uses poly lactic-co-glycolic acid (PLGA) capsules, which have been widely used in controlled delivery systems. The objective is that this will improve the safety and tolerability profile of the treatment and reduce complications such as ectopic bone formation. Finally, although PLGA itself is

[8] Saifi C, et al. (2019) Utilization and Economic Impact of Posterolateral Fusion and Posterior/Transforaminal Lumbar Interbody Fusion Surgeries in the United States

[9] Infuse clinical data package

[10] Hustedt JW and Blizzard DJ (2014) The Controversy Surrounding Bone Morphogenetic Proteins in the Spine: A Review of Current Research. *Yale J Biol Med* 87, 549-561.

[11] Mroz TE, et al. (2010) Complications related to Osteobiologics use in spine surgery a systematic review. *Spine* 35, S86–S104.

[12] Bialy I, et al. (2017) Formulation, Delivery and Stability of Bone Morphogenetic Proteins for Effective Bone Regeneration. *Phar Res* 34, 1152-1170.

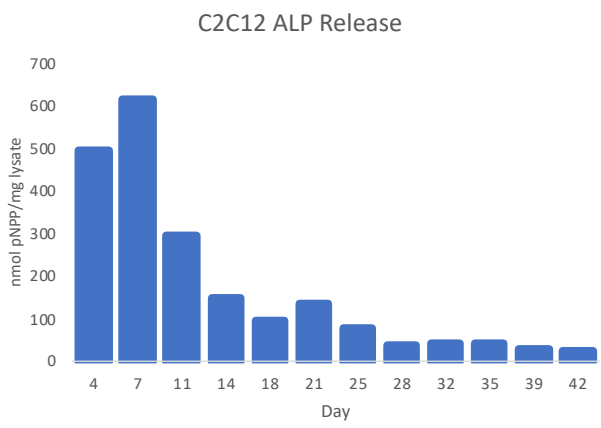
osteoconductive, the remainder of the graft material is composed of the synthetic bone scaffold β-tricalcium phosphate (β-TCP), which should further improve the graft's osteoconductive properties.

Preclinical evidence and development pathway

LDGraft is still in the relatively early phases of preclinical testing, so it is difficult to evaluate if these design elements will be effective. The results from some earlier versions of the technology using animal models have been published in the literature and one early conclusion is that these prototypes are effective at encouraging the regrowth of bone. To our knowledge these reports only examined PLGA-based grafts without β-TCP. One such study in a mouse calavaria-defect model found the scaffold itself improved bone growth in the defect by 31%, and the addition of BMP improved bone growth by 55% (over the empty defect) after six weeks, compared to empty defect.[13] In a similar rat calavaria-defect model, BMP-2 eluting PLGA graft was found to be able to achieve up to 80% repair of the defect in 12 weeks.[14]

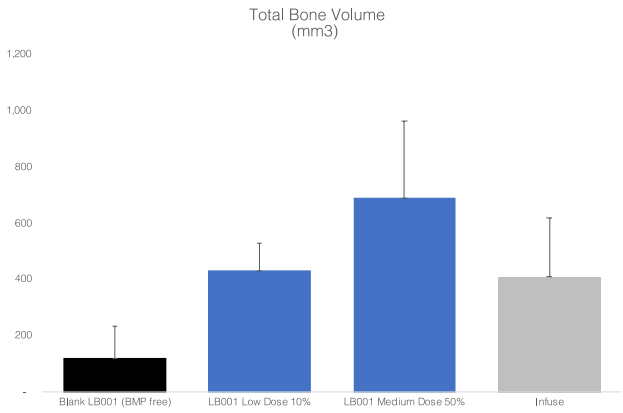
To truly differentiate LDGraft, the product must not only promote the regrowth of bone but improve the release profile of the molecule and translate this into improved outcomes. The product shows a slow BMP release profile in vitro, with peak release kinetics up to seven days after implantation (Exhibit 5). By comparison, the majority of BMP-2 from collagen sponge is lost in a day in vitro.[15] In addition to improvements in safety and tolerability, the prolonged release profile may improve the effectiveness of the product in regrowing bone. Brown et al. found the greatest potentiation in bone growth when the BMP-2 release profile was controlled, but the majority of protein was still delivered in the first week.[15] This appears roughly analogous to the kinetics of LDGraft, and indeed, when the product is examined in a rabbit model of PLF, similar bone regrowth is seen with only 10% of the concentration of BMP-2 compared to Infuse at 12 weeks (Exhibit 6).

Exhibit 5: Kinetics of BMP-2 release from LDGraft



Source: Locate Bio. Note: BMP-2 activity measured as alkaline phosphatase (ALP) release from C2C12 cell line.

Exhibit 6: LDGraft bone growth compared to Infuse



Source: Locate Bio. Note: In a rabbit model of PLF, measured at 12 weeks.

It is worth noting, when evaluating the data in Exhibit 6, that Infuse is not approved for any PLF procedure (let alone in rabbits), so the performance in this model may not represent the intended use for Infuse, but we believe that this highlights an important point. The Infuse product likely benefits from the local confinement of BMP-2 in the interbody space, which improves its

[13] Rahman CV, et al. (2012) Controlled release of BMP-2 from a sintered polymer scaffold enhances bone repair in a mouse calvarial defect model. *J Tis Eng Regen Med* 8, 59-66.

[14] Rosario C, et al. (2015) Evaluation of nanostructure and microstructure of bone regenerated by BMP-2-porous scaffolds. *J Biomed Mat Res Part A* 103, 2998-3011.

[15] Brown KV, et al. (2011) Improving Bone Formation in a Rat Femur Segmental Defect by Controlling Bone Morphogenetic Protein-2 Release. *Tiss Eng A* 17, 1735-1746.

effectiveness, and the loss of this local confinement is why such a larger amount of BMP-2 was needed for the Amplify product (in addition to other changes). However, a controlled release product such as LDGraft is unlikely to have this limitation (as supported by Exhibit 6) and could potentially be used in either PLF or interbody procedures.

LDGraft is in testing in small animals and the next step towards testing it in the clinic will be a large animal study with good laboratory practice (GLP) protocols. The company is finalising the protocol for such a study that is planned to initiate in 2021. If successful, this study will form the basis for an IDE application in 2022, with a target of first-in-human studies in 2023. The product will be regulated as a Class 3 medical device requiring a PMA for marketing authorisation and the associated in human pivotal studies.

Other products on the market and in development

Despite the controversy surrounding Infuse, it remains the dominant product in this category of growth factor-eluting products. Stryker previously marketed OP-1 Putty, a BMP-7 eluting graft, but divested the product in 2010 to Olympus Biotech, which stopped marketing the product in 2014. Other growth factors have been employed in other graft replacements, including:

- The Augment graft from Wright uses combines a β-TCP scaffold with platelet-derived growth factor BB. The product boasts fusion rates comparable to autograft but is marketed primarily for orthopaedic procedures on the foot.
- The i-Factor product from Cerepedics also boasts fusion rates similar to autograft. Instead of using growth factor that elutes from the product, it uses a peptide chemically bound to the graft substrate to encourage the infiltration of osteoprogenitor cells and encourage their differentiation. I-Factor is the only other product besides Infuse with a class 3 (PMA) approval for spinal fusion.
- A new product in development worth paying attention to is Fibrin-PTH (KUR-113) at Kuros Biosciences. The product is a combination of fibrin, the clot-forming protein component of blood, and parathyroid hormone (PTH). PTH has a well-established role in promoting the growth of bone, albeit a much milder effect than is seen with BMP-2. A derivative of PTH (consisting of the first 34 amino acids) has been marketed for the treatment of osteoporosis as Forteo (teriparatide, Eli Lilly) since 2002. The PTH in the Fibrin-PTH product similarly uses the 1-34 amino acid fragment, and is engineered to be released as the fibrin network is broken down by infiltrating cells. Kuros claims the product has replicated fusion rates of BMP-2 in animals. It is in a Phase II clinical study in patients undergoing lumbar interbody fusion. The study has a target enrolment of 50 patients and a target completion date of December 2021. Unlike the products in development at Locate Bio, Fibrin-PTH is regulated as a drug and will be progressing through an NDA (as opposed to PMA) pathway.
- Finally, another technology in development is the NEL-like protein 1 (NELL-1) based graft from Bone Biologics. NELL-1 is a growth factor similar to BMP, but operates at a later phase of bone cell differentiation. It encourages the proliferation of pre-existing osteoblasts, so the intent is that this will only induce the formation of bone in the presence of bone, and limit problematic ectopic bone formation. However, this has yet to be tested in clinic as Bone Biologics has planned to initiate Phase I testing in 2021.

CertOss

CertOss is a bone graft product in development at Locate Bio, aiming to provide superior bone fusion rates in a growth factor-free and cell-free product. This was among the products (along with CognitOss and Chrondo3) licensed from RCSI University of Medicine and Health Sciences in September 2020. CertOss is what we would call an advanced semi-synthetic graft substitute. It

cannot truly be called a synthetic graft because it contains animal derived collagen, and moreover, the intent of the product is to compete with DBMs, stem cells, and other products that have historically outperformed synthetics. Operationally for Locate Bio, CertOss is likely to be the first product marketed by the company, as an application for 510(k) clearance is expected in 2022.

CertOss is composed primarily of a collagen matrix that is deposited over an ultrapure microcrystalline formulation of hydroxyapatite (HA). HA is the calcium-containing inorganic mineral that comprises the bulk of the mass of bone and is a common component of synthetic bone grafts. The formulation of CertOss is made to resemble bone, which is comprised in large part by collagen and HA. The collagen is deposited over the HA crystals using a freeze-drying technique that maximises the porosity of the product (reported at over 95%). The high porosity promotes osteoconduction and provides an increased surface area for migrating bone cells. Moreover, mineralised collagen has been shown to have some osteoinductive properties all on its own, in the absence of growth factors or other biologics.[16]

Preclinical experience

Preclinical studies of CertOss have confirmed it supports the regrowth of bone. It was initially investigated in some animal studies for use as a carrier for BMP-2 and other molecules, in a similar fashion to the collagen sponge in Infuse. However, it was found the collagen/HA substrate itself showed significant capacity to induce the growth of bone. In one study using the rabbit radial defect benchmark, CertOss showed a similar extent of regrowth of bone over 16 weeks compared to autograft (no statistical difference) and improved bone volume.[17] When combined with BMP-2 (albeit at 10% of the dose in Infuse), bone growth was further potentiated.

In a separate study, the CertOss substrate was again tested as a carrier for BMP and the osteogenic drug, zoledronic acid. The benchmark in this case was the ability to form ectopic bone (in a rat hind limb) and it was found CertOss was capable for induce the growth of bone without any additional factors.[18] Ectopic bone growth is undesirable for an orthopaedic procedure but the ability to induce it in a model system is a benchmark for the bone forming activity of a product. Ectopic bone has historically been difficult to achieve for products without growth factors or cells, but is becoming a criteria for next-generation products.

Locate Bio will be pursuing marketing clearance through the 510(k) pathway for this product and it does not expect to need in human clinical data to complete the application. The product is considered substantially lower risk than LDGraft, and therefore will not require a PMA application. It has a small amount of preclinical animal work to complete (a GLP rabbit study) but anticipates that it should submit its 510(k) in H122 with a target of marketing clearance in 2022. The initial indication for the product is expected to be lumbar fusion.

The company also has two follow-on programmes for CertOss with the names HC002 and ZN001. Both products are slight formulation changes intended to improve the product for specific applications: HC002 is intended to improve the product for PLF, and ZN001 is intended to improve performance in higher risk groups. However, it has not shared any further specifics save that additional clearances for these formulations are expected in 2022 and 2023, respectively. We await more details on these programmes, as the product progresses through the regulatory process.

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16 Xu SJ, et al. (2015) Osteogenic Differentiation Gene Expression Profiling of hMSCs on Hydroxyapatite and Mineralized Collagen. *Tis Eng A* 22, 170-181.

17 Lyons FG, et al. (2014) Novel Microhydroxyapatite Particles in a Collagen Scaffold: A Bioactive Bone Void Filler? *Clin Orthop Relat Res* 472, 1318-1328.

18 Murphy CM, et al. (2014) A collagen–hydroxyapatite scaffold allows for binding and co-delivery of recombinant bone morphogenetic proteins and bisphosphonates. *Acta Biomat* 10, 2250-2258.

Market and competition

Unlike the market for growth factor-eluting grafts, which is dominated by a single product, the broader market for graft substitutes is highly fragmented, with even advanced products commanding small market shares. However, there are a small number of other high-performance products.

The product MagnitOs from Kuros is aiming to fill a similar niche to CertOss. It is a synthetic graft made of biphasic calcium phosphate designed to have a submicron topology more amenable to bone formation. Indeed the product is capable of inducing the formation of ectopic bone without the need for growth factors or stem cells.[19] The product was fully launched in September 2019 (after an initial soft launch) and Kuros had CHF1.3m in sales from the product in H120.

The AttraX series of products from Nuvasive are similar products advertising improved bone formation through improved surface chemistry. AttraX is a formulation of β-TCP and HA in either synthetic polymer (for the putty or granule product) or collagen (for the scaffold product) similar to CertOss. This product is one of the few to demonstrate fusion rates comparable to autograft in a human clinical study.[20] The company does not break out sales of this product, so it is difficult to draw conclusions about its market share.

CognitOss

CognitOss is a formulation of bone graft substitute in development at Locate Bio designed for the treatment of osteomyelitis and related indications. Osteomyelitis is very tenacious and difficult to treat. It is typically treated by surgically excising the infected or dead bone tissue (potentially using a bone graft) followed by four or more weeks of systemic antibiotics. Despite intense antibiotic regimens, relapse rates are high: one retrospective study of patients receiving four weeks of parenteral antimicrobial therapy found relapse rates of 31%.[21] Moreover, the condition can develop into a chronic disease if it is unable to be treated.

In addition to osteomyelitis, CognitOss could potentially also be used in other procedures where high local doses of antibiotics need to be delivered to the bones, such as reversion arthroplasty or trauma.

The goal of CognitOss is to provide a drug-eluting bone graft substitute that can be used as a void-filler and delivers antibiotics directly to the site of infection. The intent is that this can improve the outcomes in osteomyelitis patients by delivering higher, localised doses of drug. We expect the product to likely be used in combination with systemic antibiotics. If the product can improve the resolution of the infection, there is the potential it could also improve the subsequent graft uptake. The bulk of the material that makes up CognitOss is the same as CertOss, a microcrystalline HA in a collagen matrix. However, this matrix can be impregnated with antimicrobials and potentially other drugs. Studies of the drug-loaded composite show it has two phases of drug release: an initial burst followed by a slow-eluting phase.[22] Additionally the company has stated the release of drug during the slow-eluting phase is sensitive to the presence of pathogen, releasing more drug presumably due to localised inflammation or other processes.

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19 Yuan HP, et al. (2020) Ectopic bone formation by submicron structured calcium phosphates: role of the innate immune system. *Spine J* 20, S116-S117.

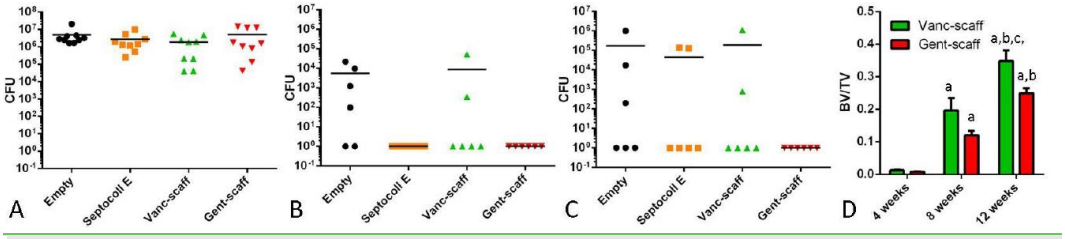
20 Lehr AM, et al. (2020) Efficacy of a Standalone Microporous Ceramic Versus Autograft in Instrumented Posterolateral Spinal Fusion. *Spine* 45, 944-951.

21 Tice AD, et al. (2003) Outcomes of Osteomyelitis among Patients Treated with Outpatient Parenteral Antimicrobial Therapy. *Am J Med* 114, 723-728.

22 Sheehy EJ, et al. (2018) Evaluation of the capacity of an antibiotic-eluting scaffold to treat infection in a rabbit model of chronic osteomyelitis. *Orthop Proc* 100-B Supp 14.

CognitOss is still in development and to our knowledge a decision has not yet been made over which antibiotic drug to pair the product with. An account was previously published in which vancomycin and gentamicin-eluting grafts were both tested in a rabbit model of chronic osteomyelitis and compared to gentamicin eluting fleece (Septocol E, Zimmer Biomet). After eight weeks of treatment only, the gentamicin CognitOss reduced the infection to below the limits of detection for six out of six of the animals tested (Exhibit 7).[23] Moreover, both the vancomycin and gentamicin eluting grafts encouraged the regrowth of bone.

Exhibit 7: Bacteriological and osteogenic response to CognitOss prototypes



Source: Locate Bio, Sheehy et al. 2019.[23] (A) bacterial load beginning of treatment. CFU, colony forming unit. (B) bacterial load in the site of the defect at eight weeks. (C) bacterial load in the surrounding bone at eight weeks. (D) BV/TV, bone volume to tissue volume ratio, showing bone regrowth.

To market CognitOss, Locate Bio will need to establish that the product can provide a benefit to osteomyelitis patients and we expect the company will need to do a clinical study to support this conclusion. We expect Locate Bio will file for an IDE in 2022 to support running such a study in 2022. It has stated that it intends to seek approval though the de novo 510(k) pathway at the FDA, which has the comparatively lower regulatory bar of a 'reasonable assurance of safety and effectiveness', compared to a PMA.

Market landscape

The product will initially seek clearance in the US for osteomyelitis, with a potential expansion to other indications after the initial approval. In Europe the product will be seeking a CE mark and is planned to be available for a range of uses from the start. However, we expect initial European marketing efforts to focus on osteomyelitis (as there will be clinical support for that indication).

Osteomyelitis has an estimated incidence of 24.4 per 100,000 person-years in the US.[24] The incidence has been increasing in more recent decades due in part to the increased prevalence of diabetes in the US, which is a major comorbidity. Diabetes is cited as etiology of the disease in 27% of cases, whereas 19% are caused by a blood infection and 19% are related to trauma. The infection itself is commonly caused by *Staphylococcus aureus* (44% of cases), which raises concerns from epidemiologists due to the increasing prevalence of methicillin-resistant *S. aureus*.

Following initial traction in this market, we expect the company to initiate follow-on studies to expand the market, with revision arthroplasty as our speculative next indication of choice. In the US there are over 700,000 knee replacements and over 500,000 hip replacements per year. Although complications are rare, many of these patients will need revision surgery at some point to correct issues with their prosthesis, such as instability or damage due to an accident. The 10-year revision rate on both procedures is 12%.[25] The revision arthroplasty procedure carries a high risk of infection because the prostheses are prone to biofilm formation and given large bone voids are formed during the procedure, it is a good fit for the product. We believe it may also be possible to

[23] Sheehy EJ, et al. (2019) Antibiotic-Eluting Collagen-Hydroxyapatite Scaffolds Eradicate Infection and Facilitate Bone Healing in a Rabbit Model of Osteomyelitis. ORS 2019 Annual Meeting Paper No. 0033

[24] Kremers HM, et al. (2015) Trends in the epidemiology of osteomyelitis: a population-based study, 1969 to 2009. *J Bone Joint Surg* 97, 837-845.

[25] Labek G, et al. (2011) Revision rates after total joint replacement; Cumulative results from worldwide joint register datasets. *Bone Joint J*, 93-B, 293-297.

seek marketing clearance for this indication via a 510(k) pathway, which we assume for our models will be pursued following the initial osteomyelitis clearance.

Competitive analysis

The notion of using an antibiotic eluting device to improve outcomes in osteomyelitis is not new. Bone cement (polymethylmethacrylate) can be loaded with antibiotic and has an attractive release profile, but is non-resorbable. This makes it less than ideal as a void filler, because the cement will need to be removed with a surgical procedure. This cement-based approach is the current standard of care for revision arthroplasty, a so-called two-stage revision, in which a drug-eluting spacer made of cement is used to fix the joint and treat the infection, followed by surgical removal and replacement of the prosthesis. Palacos G (Zimmer Biomet) is an example of such a cement product used for this purpose.

The products with the most similarities to CognitOss are Cerament G and Cerament V in development by the company Bonesupport. Both Cerament G and V are formulations of Bonesupport's marketed Cerament synthetic graft that elute gentamicin and vancomycin, respectively. Cerament G is the more advanced of the two products and an application was submitted for clearance (via the De novo pathway) in April 2020. Both of the products are CE marked and commercially available in Europe and make up the vast majority of the company's sales in that region (SEK19.8m Q320).

Wright Medial also makes a drug-eluting graft product Osteoset-T, which is composed of tobramycin-eluting calcium sulfate pellets. PerOssal (Osartis) is a similar pellet product designed to be loaded with different antibiotics by the physician. Other products that could potentially compete with CognitOss include other antibiotic-eluting substrates that could be used in combination with a bone graft, although not part of the same product. These include resorbable scaffolds and fleeces, such as the Septocoll E fleece from Zimmer Biomet.

Chondro3

Chondro3 is the company's product designed as a treatment for cartilage defects resulting from KOA. Cartilage growth is substantially more difficult to achieve than bone growth for a number of reasons, including that functional cartilage is a heterogeneous tissue and regeneration requires the simultaneous growth of multiple tissue types. Similar to the company's other products, Chrondro3 is a semi-synthetic graft substitute, but unlike the other products it contains three distinct graft layers to encourage the regrowth of three types of tissue important for the regeneration of cartilage:

- A layer with the same composition as CertOss, type I collagen and HA microcrystals, designed to improve fusion with the underlying bone.
- An intermediate layer with type I collagen and hyaluronic acid (HyA) intended to encourage the formation of calcified cartilage.
- A cartilaginous layer composed of type I and type II collagen and HyA.

HyA is a natural polysaccharide that is a major component of synovial fluid and is responsible for its lubricating properties. It is also an essential component of cartilage where it becomes cross-linked into a rigid matrix that provides structural support to the tissue. In patients with OA, HyA is depolymerised and reduced in concentration, significantly reducing its joint protecting properties. One feature specific to Chondro3 is the presence of type II collagen in the third layer of the product. Type II collagen is specific to cartilage and the basis for the formation of hyaline cartilage, the glassy interarticular cartilage. All of these biologic materials are easily obtained from animal sources.

Each layer is deposited using freeze drying to provide a high porosity scaffold for the patient's regenerative cells. The product is intended to be used in connection with a microfracture procedure, in which small fractures are induced in the subchondral bone to encourage the migration of chondrocytes and other progenitor cells into the lesion. Microfracture alone is a routine treatment for KOA (see below) with established utility and the intent is that by providing a functionalised scaffold to be used as part of the procedure that the product can enhance this regenerative capacity.

In one animal case study, the product was used in a 15-month-old horse following the development of osteochondritis dissecans, a condition when cartilage becomes damaged due to lack of blood flow that is common in children.[26] Following debridement and microfracture, the graft was implanted in both left and right rear knee joints. After five months, the horse showed the formation of immature cartilage over the top surface of the graft, which was contiguous with the surrounding tissue. Both lesions were scored at 10/12 on the International Cartilage Regeneration Scale, which puts them in the 'nearly normal' category. By 22 months, the horse had resumed its full athletic regimen and the joint was confirmed radiographically to have filled the subchondral bone defect and restored the integrity of the joint surface.

To expand on these findings, a study in goats was performed in which 19 adult female goats had cartilage defects induced in the trochlear ridge or medial femoral condyle.[27] The Chondro3 scaffold was compared against the synthetic bilayer scaffold Trufit (Smith & Nephew) and empty defect. Chondo3 achieved superior cartilage thickness at 6 months (213μm compared to 96μm for empty $p<0.01$ and 140μm for Trufit $p<0.05$) and this was maintained for up to 12 months (238μm vs 98μm $p<0.01$ and 66μm $p<0.05$ respectively). The cartilage thickness at this point was statistically insignificant from natural unperturbed tissue. One potential finding that helps explain this improved performance is that the Chondro3 graft showed dramatically superior formation of subchondral bone. Fusion to subchondral bone is essential to the performance of autologous cartilage graft (autograft cartilage). The empty defects and the Trufit defects saw negligible bone regrowth at six months, whereas Chondro3 saw nearly complete repair ($p<0.001$). No joint-related adverse events or complications were observed in the study. The company is in the planning stages for a human pilot study and anticipates filing an IDE in 2022.

The KOA market

OA is a degenerative bone disease caused by the progressive degradation of cartilage in joints. KOA is the most common form of the disease from an incidence perspective (240 per 100,000 person-years), although the prevalence in the knee is lower than in the hand due to age-related effects. The prevalence of KOA increases from 5% in adults over 25 to 19% of those over 45 in the US,[28] making the disorder one of the most common non-infectious diseases.

Approximately 15% of patients do not have improvement in pain with over-the-counter NSAIDs or COX-2 inhibitors and are candidates for more invasive treatment.[29] Intra-articular corticosteroids are highly effective treatments (effect size of 0.72) and have a better side-effect profile than oral steroids (which are not recommended for OA). However, the steroids only provide pain relief for a

[26] Stack JD, et al. (2015) Repair of large osteochondritis dissecans lesions using a novel multilayered tissue engineered construct in an equine athlete. *J Tiss Eng Regen Med* 11, 2785-2795.

[27] Levingstone TJ, et al. (2016) Cell-free multi-layered collagen-based scaffolds demonstrate layer specific regeneration of functional osteochondral tissue in caprine joints. *Biomaterials* 8, 69-81.

[28] Zhang Y and Jordan JM (2008) Epidemiology of Osteoarthritis. *Rheum. Dis. Clin. North Am.* 34, 515–529.

[29] Kamath CC, et al. (2003) The Cost-Effectiveness of Acetaminophen, NSAIDs, and Selective COX-2 Inhibitors in the Treatment of Symptomatic Knee Osteoarthritis. *Val. in Health* 6, 144-157.

matter of weeks and are therefore limited to the treatment of acute flares.[30] Intra-articular HyA (aka viscosupplementation) can also be effective in poorly controlled patients (effect size 0.32), and can provide improvement in KOA symptoms for six months or more. There are several brands of HyA for intra-articular injection available. Synvisc is produced by Sanofi and had peak sales of $493m in 2013, and the similar brand Artz (Kaken) peaked in 2011 with sales of $403m. It is worth noting, however, that despite the widespread use of intra-articular steroids and HyA, neither is recommended by the American Association of Orthopedic Surgeons, on the basis of lack of comprehensive efficacy data.

There are a number of surgical options for patients with severe deterioration of the knee cartilage that is inadequately addressed by other therapies. The first-line surgical intervention is often arthroscopy, in which the knee is debrided of loose fragments of cartilage. The procedure is performed on approximately 650,000 patients in the US per year.[31] However, there have been a number of recent studies that have questioned its effectiveness and improvement in arthritis symptoms is limited.[32] Microfracture surgery is another arthroscopic option, in which after debridement, numerous tiny fractures, are introduced into the bone plate underlying the knee cartilage. This process triggers a healing response in which the damaged bone is covered over with a layer of new cartilage. However, this procedure generally has better results in patients aged 45 years or younger due to the more limited healing response and worse prognosis in older patients. There are approximately 100,000 microfracture procedures performed in the US per year.[33] We expect the addressable market for Chondro3 to be similar to the market for microfracture, and for it to be potentially combined with the procedure. The most invasive treatment for KOA is partial or total knee replacement in which the joint is replaced with a prosthesis. Although this procedure is typically reserved for patients with debilitating disease and with few other options, there are approximately 700,000 total knee replacements carried out in the US per year.[34]

Cartilage transplant, either autologous or allogeneic, remains rare, making up around 2% of all KOA procedures (excluding knee replacement).[35] Cartilage grafting, when performed, is more likely to be used on larger defect sizes (>4cm^2), although for autograft, this may require the excision of tissue from multiple sites (a so called mosaicplasty). A limiting factor on the use of allograft is its expense at over $11,000 per tissue sample.[36] Additionally, unlike bone allograft, many cartilage allograft products are not sterilised prior to transplantation (in order to preserve the donor chondrocytes), which increases the potential risk of contamination and disease transmission in such cases. We believe the cartilage transplant market can become much bigger as more advanced cartilage graft substitutes are developed.

The market for cartilage graft substitutes is less developed than that for bone grafts and there are fewer approved and in development products (Exhibit 8). The market is similar to that of bone grafts in that products are stratified (as in Exhibit 3) with a range of technologies spanning the gap from fully synthetic substitutes to cell therapies, to allograft. The product we have the best commercial insight into is MACI from Vericel (because Vericel is the only company to report product-level sales

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30 Hepper CT, et al. (2009) The efficacy and duration of intra-articular corticosteroid injection for knee osteoarthritis: a systematic review of level I studies. *J. Am. Acad. Orthop. Surg.* 17, 638-646.

31 National Center for Health Statistics.

32 Kirkley A, et al. (2008) A Randomized Trial of Arthroscopic Surgery for Osteoarthritis of the Knee. *New Eng. J. Med.* 359, 1097-1107.

33 Cole BJ and Kercher JS (2010) Special Issue on Microfracture. *Cartilage* 1, 77.

34 Kurtz s, et al. (2007) Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J. Bone Joint Surg.* 89, 780-785.

35 Hancock KJ, et al. (2019) Trends in Knee Articular Cartilage Treatments: An American Board of Orthopaedic Surgery Database Study. *Knee Surg* 32, 85-90.

36 Familiari F, et al. (2018) Clinical Outcomes and Failure Rates of Osteochondral Allograft Transplantation in the Knee. *Am J Sports Med* 46, 3541-3549.

data we are aware of). MACI is a cell therapy product, in which a physician uses a kit to grow a patient's chondrocytes on collagen scaffold that is then implanted. MACI was approved in 2016 and had $91m in sales in 2019 and $25m in sales in the most recent quarter (Q320). MACI can provide improved outcomes (in pain and function) compared to microfracture, but the procedure for its use is involved, requiring an initial biopsy, cell culture and then an open implantation procedure. Chondro3 would require only a single procedure, which positions it more attractively as an add-on to an existing microfracture procedure. We expect Chondro3 to be marketed for mid-sized and smaller (<4cm^2) lesions, where options are currently limited.

Exhibit 8: Selection of knee cartilage graft substitutes

Product	Company	Status	Class	Details
DeNovo NT	Zimmer Biomet	Marketed	Allograft	Particles of juvenile cartilage
Cartiform	Arthrex	Marketed	Allograft	Expanded allograft
ProChondrix CR	AlloSource	Marketed	Allograft	Simple allograft
MACI	Vericel	Marketed	Cell therapy	Autologous chondrocytes on collagen
Novocart 3D	Aesculap	Pivotal study	Cell therapy	Autologous chondrocytes on collagen
Trufit	Smith & Nephew	Marketed	Synthetic graft	PLGA and calcium sulphate
Hyalofast	Anika	Pivotal study	Synthetic graft	HyA based polymer
Agili-C	CartiHeal	Pivotal study	Synthetic graft	Bi-phasic calcium carbonate (aragonite)

Source: Company websites

Sensitivities

Locate Bio, like many other companies developing medical products, will face the typical uncertainties over clinical development and regulatory approval. CertOss has the lowest clinical/regulatory risk because no human studies are likely to be needed to support 510(k) clearance, whereas LDGraft faces significant clinical risk because it has not yet been tested in humans and will need multiple clinical trials. Moreover, LDGraft will need marketing approval through the more stringent PMA pathway.

The company also faces a series of risks specific to the orthobiologics space. The market for orthobiologics is highly fragmented, with hundreds of products across multiple subcategories. CertOss will face the most competition because there are large number of poorly differentiated graft substitutes that fall into the similar category of growth-factor and cell-free products. We believe CertOss is likely to provide superior performance to earlier generation synthetic grafts, but this will need to be communicated to the market effectively. LDGraft by comparison is likely to see the majority of its competition from a single product, the Infuse graft from Medtronic. This being said, the Infuse graft is well established and marketed by one of the most resourceful companies in the space. CognitOss and Chondro3 will also face competition, but the biggest commercial hurdle for these products is that their markets are poorly developed. Establishing these products will require setting up a new treatment algorithm for osteomyelitis and KOA respectively. To further complicate the commercial hurdles, the market for orthopaedic products in general is dominated by a small number of well-established companies (Zimmer, Medtronic, Stryker, etc) with strong market influence, which may limit the commercial access available to smaller companies seeking to market competing products.

Finally, Locate Bio will face the financing risks common to pre-commercial companies. For the clinical development of LDGraft, we forecast $36m in R&D costs before approval in 2027. In our blue sky scenario in which all products are approved and perform well commercially, our models predict the company running a deficit until at least 2024, before accounting for any corporate overhead or development activity outside of what we have already outlined. The company may offset some future costs through partnering of its products, but this carries its own risks and uncertainties.

Valuation

We have determined a valuation for Locate Bio of £113.1m. Each product in the portfolio is valued on the basis of a risk-adjusted DCF analysis with a 12.5% discount rate, our standard for precommercial products. Our valuation is based solely on product cashflows and does not include any corporate assets, such as cash, or any unallocated costs such as corporate overhead or exploratory R&D.

Some of the parameters for our model are presented in Exhibit 9. Our market estimates are based on the epidemiology of each indication (presented above) in the US and Europe (EU + UK). We expect each product to have a period of market share growth following initial approval (seven years for LDGraft and Chondro3, five years for other products) followed by increased competition and market share decline as more advanced products enter the marketplace. We expect LDGraft and Chondro3 to resist competition longer because competitors will need to run clinical trials and seek PMA approval. Each model includes a terminal value with a negative 10% growth rate following peak sales.

Exhibit 9: Valuation parameters

Product	Indication	Base price (US$)	Addressable procedures/ year	Peak penetration	Launch	Market share decline	COGS	R&D costs	Marketing costs (per year after launch)
LDGraft	Lumbar interbody fusion	2500	260k	30%	2027	2034	15%	Phase 1–3: 360pts at $100k each	$10m overhead + 10%
	Lumbar PLF	2500	390k	30%	2029	2034	15%	Phase 3: 300pts at $100k each	$10m overhead + 10%
CertOss	Spinal fusion indications	1200	1.25m	5%	2022	2027	15%	$1m yearly costs until 2025	$5m overhead + 10%
CognitOss	Osteomyelitis	1800	210k	15%	2024	2029	15%	Pivotal studies:150pts at $50k each	$5m overhead + 10%
	Revision Arthroplasty	1800	400k	10%	2025	2029	15%	Pivotal studies:150pts at $50k each	$5m overhead + 10%
Chondro3	Knee osteoarthritis	2000	260k	20%	2025	2032	15%	Phase 2-3: 300pts at $50k each	$5m overhead + 10%

Source: Edison Investment Research. Note: Pts=patients.

Our pricing assumption assume each product will be priced competitively; for instance LD graft is priced ($2,500) at a discount to other BMP products (average selling price $4,000–5,000) and CertOss is priced ($1,200) at a discount to DBMs and other high performance graft products ($1,800–2,800). We include 2% annual price growth in our model from these base prices. We include COGS of 15% for each product, which includes the cost of production as well as any royalties payable as part of the academic licensing agreements for the products.

We assume LDGraft will initially be approved for lumbar interbody fusion and have included PLF fusion as a follow-on indication. Likewise, we have included revision arthroplasty as a follow-on indication for CognitOss. In both cases, we assume a higher risk for the follow-on indication because it will be gated by the primary indication. For CertOss, we assume Locate Bio will proceed with a series of 510(k) submission to progressively expand the indications on the label for the product and to provide new formulations for different use cases. This includes HC002 and ZN001 as well as additional future line extensions. We assume $1m in yearly R&D costs associated with seeking these marketing clearances. R&D costs for other products are presented in Exhibit 9, with costs per patient based on the cost of the underlying procedure. Likewise, our costs of selling are presented in Exhibit 9, which assume higher marketing costs for LDGraft.

Each product is risk adjusted based on a combination of clinical and commercial risks. The orthobiologics space is highly competitive and even if the company develops a superior product, this will not ensure it will be able to gain market share. LDGraft is the highest risk programme (10% probability of success for the initial approval in interbody fusion) because it is early in development, will need multiple clinical trials, to compete with an established product marketed by a major

company (Medtronic's Infuse), and to change perceptions over the safety of BMP-2. Despite this, it is the product we value the highest at £53.6m, or approximately half the total valuation. CertOss is the lowest risk (40% risk adjustment) because clinical and regulatory risks are expected to be much smaller than other programs, but commercial risks are substantial and the downside in this case represents the scenario in which the company is unable to market the product successfully.

Exhibit 10: Valuation of Locate Bio

Product	Indication	Launch	Peak sales ($m)	Risk adjustment	Value (£m)
LDGraft	Lumbar interbody fusion	2027	270	10%	30.6
	Lumbar PLF	2029	390	5%	23.0
CertOss	Spinal fusion indications	2022	50	40%	10.9
CognitOss	Osteomyelitis	2024	60	20%	9.0
	Revision arthroplasty	2025	100	10%	15.7
Chondro3	Knee osteoarthritis	2025	130	20%	23.9
Total					113.1

Source: Edison Investment Research

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