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Collagen Solutions

Engineering cartilage repairs

Collagen Solutions is a biomaterials company developing and manufacturing medical grade collagen components for use in medical devices, research, and regenerative medicine. A number of investment initiatives have been introduced over the last year to accelerate the rate of growth, including global commercial infrastructure and the development of a pipeline of finished medical devices. ChondroMimetic will be the first of these products and is expected to enhance significantly the value of the company which is not being reflected in the current share price. The recent capital raise and loan facility has resolved funding issues.

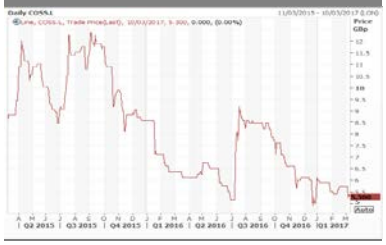
- **Strategy**: Management has embarked on an investment strategy through a series of initiatives to increase the growth opportunities. This strategy to move COS from a reliable collagen supplier to one that also has proprietary products will move it into profitability and cash generative at a faster pace.
- **ChondroMimetic:** Best described as a clever bi-layered and easy to use sponge that allows the regeneration of cartilage where cartilage is supposed to be, and bone where bone is supposed to be. ChondroMimetic is for surgeons to repair knee cartilage damage thereby delaying the need for joint replacement.
- **Forecasts:** The growth strategy is dependent on investment in R&D, sales & marketing, and corporate infrastructure. Management has not shied away from making this investment even though it is detrimental to short-term profitability; the benefits are clearly visible in medium to long-term sales forecasts.
- **Risks:** Modest investment is required in order to regain CE Mark in the EU for ChondroMimetic. Much greater investment will be needed for US approval, for which COS will seek a development partner. There is no precedent for the FDA approving a cartilage repair product with regenerative claims.
- **Investment summary:** ChondroMimetic fulfils management's stated strategy to move further up the value added chain. For relatively little up-front cost and modest investment, COS has obtained a largely de-risked proposition. Longer-term, ChondroMimetic has the potential to be the first regenerative cartilage product to be approved in the US, but this will require external investment.

Financial summary and valuation

Year end March (£000)	2014	2015	2016	2017E	2018E	2019E
Sales	24	973	3,130	4,085	5,290	7,270
Underlying EBITDA	-364	-663	-374	-1,277	-1,059	5
Underlying EBIT	-381	-793	-721	-1,724	-1,585	-542
Underlying PBT	-381	-920	-983	-1,826	-1,750	-673
Statutory PBT	-480	-1,102	-866	-2,171	-1,850	-773
Underlying EPS (p)	-0.87	-0.98	-0.64	-1.08	-0.61	-0.28
Statutory EPS (p)	-1.10	-1.17	-0.57	-1.26	-0.64	-0.31
Net (debt)/cash	1,492	3,282	2,384	8,303	4,899	1,772
Capital increase	3,374	5,422	207	9,027	1,000	0
P/E (x)	-6.2	-5.5	-8.4	-5.0	-8.8	-19.1
EV/sales (x)	-	7.0	2.2	1.7	1.3	0.9
EV/EBITDA (x)	-	-	-	-	-	-

Source: Hardman & Co Life Sciences Research

Healthcare Equipment & Supply



Source: Fidessa

Market data

EPIC/TKR	COS
Price (p)	5.4
12m High (p)	10.3
12m Low (p)	4.5
Shares (m)	316.3
Mkt Cap (£m)	17.0
EV (£m)	15.4
Free Float*	67%
Market	AIM

**As defined by AIM Rule 26*

Description

COS develops, manufactures and supplies medical grade collagen biomaterials, tissues and devices. Its products are used in research, *in vitro* diagnostics, medical devices and regenerative medicine. The company provides R&D and contract services to a global and diverse customer base.

Company information

CEO	Jamal Rushdy
CFO	Gill Black
CSO	Stewart White
Chairman	David Evans

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www.collagensolutions.co.uk

Key shareholders

Directors + management	19.7%
Seneca	13.6%
Calculus Capital	9.7%
Livingbridge	4.7%
Helium Rising Stars	4.1%

Next event

Jly-17	Finals
Aug-17	AGM
3Q-17	CM CE Mark filing

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Executive summary

Corporate strategy

In May 2016, the Board announced a change in the leadership of the group with the aim of increasing its growth opportunities. The new team re-focused group strategy and introduced several initiatives designed to improve and accelerate its core business performance and, in doing so, to create shareholdeer value.

Corporate strategy

Source: Collagen Solutions

One of the key components of this new strategy focuses on accelerating growth through the development and commercialisation of proprietary products. Specifically, management's target is to achieve a five-fold increase in sales by 2021. New products will come from the company's own internal R&D programmes or they could be acquired from external sources when suitable opportunities arise. The latter was exemplified by the acquisition of the assets and an exclusive worldwide licence to the IP of ChondroMimetic and related products in September 2015 and fulfils the goal of developing novel finished devices and moving up the value chain.

Orthomimetics Limited

Targeting the regenerative medicine and sports medicine markets

Orthomimetics (OM) was the first spin-out from the Cambridge-MIT Institute (CMI) and was incorporated in March 2005 to commercialise a family of surgical implants for the repair of cartilage, ligaments and tendons – tissues commonly damaged through accidents and sports – developed during a four-year programme supported by ca.£4.0m of CMI funding.

History of Orthomimetics Limited

Date	Event
2001-05	The Cambridge-MIT Institute (CMI) invest £4.0m/$6.5m into an R&D programme for surgical implants
2005	First spin-out from CMI – Incorporation of Orthomimetics (OM) Limited
2006	OM £5.4m/$10.0m Series A funding for R&D
2008	CE Mark for ChondroMimetic cartilage repair
2009	TiGenix BV acquires Orthomimetics for £14.8m/$26.9m
2012-13	OM founder + Cambridge Enterprise Ltd re-acquire assets and IP for ChondroMimetic and associated tissue repair products
2015	COS acquires the assets and an exclusive worldwide licence to ChondroMimetic and related products

Source: Company reports; Hardman & Co Life Sciences Research

OM successfully completed two large-animal (goat) trials with its lead product, ChondroMimetic, which assists the repair of articular cartilage. In 2008, OM obtained CE Mark for ChondroMimetic and commenced a small confirmatory trial in humans undertaken by a key opinion leader in surgical cartilage repair.

At this point, Orthomimetics was acquired by the Belgian biotech company, TiGenix BV, for £14.8m/$26.9m. However, a subsequent change in management and strategy led to a restructuring of TiGenix and its interest in ChondroMimetic and other orthopaedic technologies subsided. In 2012, the founder of OM, Dr Andrew Lynn, and Cambridge Enterprise re-acquired the assets of ChondroMimetic and associated IP. Collagen Solutions purchased these assets and obtained an exclusive worldwide licence for the IP in September 2015 for £200k + a single digit royalty.

ChondroMimetic

Cost of joint replacement: estimated at $36bn annually

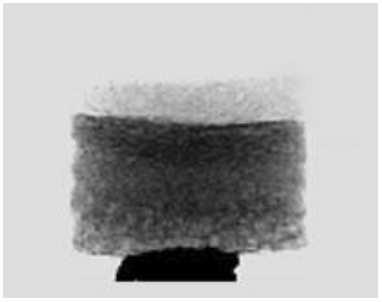
Repair of articular cartilage is an unresolved global challenge. Because articular cartilage does not have a blood supply, damaged tissue rarely heals or regenerates spontaneously. Patients with articular cartilage lesions/damage typically receive conservative treatment that does not restore full function and does not prevent progression to osteoarthritis. The ultimate goal is to delay as far as possible the total joint replacement, which is estimated to cost a staggering $36bn p.a. worldwide.

The market for bone and cartilage repair is still in need of a 'really good' product

Despite several attempts, the market for bone and cartilage repair is still in need of an effective product that is well tolerated by patients offering prompt post-surgical improvement with very low-to-no pain sensation during recovery. Chondro-Mimetic can be described as an off-the-shelf clever bi-layer sponge made from resorbable natural elements that can be readily implanted into small osteochondral defects of cartilage and bone during a standard surgical procedure, which singles it out in the field of reconstructive medicine. By treating younger patients more effectively when they first suffer injuries to soft tissues such as articular cartilage, meniscus and ligaments, products such as ChondroMimetic hold the potential to slow the pathological degeneration that ultimately leads to joint replacement.

ChondroMimetic – A bi-layer implant

Top layer: chondral (cartilage like)
Bottom layer: Osseous (bone-like)



X-ray of product

Source: Orthomimetics Limited; Collagen Solutions

The ability to heal both cartilage and subchondral bone provides a major advantage for the treatment of patients treated only several months after articular cartilage injury. Such injury is a permanent damage leading to pain, catching/clicking/locking, instability and effusion. Due to the very poor blood supply to cartilage, there is no healing potential. Only the underlying bone has that healing potential due to its vascularisation and the presence of stem cells.

Previous CE Mark approval

Clinical trial results: 100% of patients were favourable towards ChondroMimetic

On the back of positive pre-clinical results in large-animal trials, ChondroMimetic, together with its single-use procedure pack, received CE Mark regulatory approval for repair of bone and cartilage in late 2008. This was followed by a successful clinical trial in 17 humans conducted by a world renowned orthopaedic surgeon during 2009-2010. Having demonstrated marked clinical improvements compared to existing methods, this gave genuine hope that a long-term solution had been found.

ChondroMimetic was launched in September 2010 through TiGenix's salesforce and distributor network – including Greece, Italy, Spain, Poland, Turkey, South Korea and Mexico – and was used in over 300 procedures, generating sales of ca.£200k/$340k. However, a change in strategy at TiGenix to focus on its cell-therapy product portfolio lost the early momentum and management took the decision in 2011 to write-off its Orthomimetics' investment. Although only limited commercial access was garnered, the relationship with, and feedback from, surgeons and distributors was understood to have been generally positive.

ChondroMimetic was very well tolerated and gave a lower level of post-surgery complications compared to other methods. Moreover, ChondroMimetic received an overwhelming acclamation with 94% of the subjects giving a "very good or excellent" global rating of the outcome. The fact that ChondroMimetic could also be used in combination with other existing technologies adds a very strong commercial opportunity.

Commercialisation process

The first step in the commercialisation of ChondroMimetic will be to re-establish CE Mark for European markets. In the near-term, Collagen Solutions is in the process of re-establishing and re-validating the manufacture of the product in its existing GMP facility in Glasgow. Concomitantly, it has engaged with consultants regarding the collation of all the information required for the submission of its dossier to a Notified Body. While COS is on course to have everything ready for submission in about six months' time, the workload of Notified Bodies is extensive at the present time with approvals generally taking longer than seen historically. COS has a significant advantage in that ChondroMimetic has already received CE Mark in its current form.

For the medium term, COS will additionally be seeking approval from countries that recognise CE Mark but need extra information – usually of a bureaucratic nature. For the longer-term, COS will need to invest in clinical trials in the US in order to gain FDA approval – via Pre-Marketing Authorisation (PMA) as a Class III medical device in regenerative orthopaedics. COS is likely to seek a commercial partner to help fund the US approval process. To save time and get ChondroMimetic onto the market as quickly as possible, we believe that some aspects of these three steps will be performed in series. The table below sums up the steps and estimated costs needed to access the market in the different territories.

ChondroMimetic – Access to the market

Territory	What is needed	Time	Cost
Europe	Equipment purchase Technology transfer validation Getting ISO certificates Engagement of the notified bodies to get the CE Mark Engagement of distributors and/or commercial partner	6-9 months	$500,000
Countries recognising CE Mark (Australia, Korea, Malaysia, Jordan, Turkey, Thailand, Mexico)	Engagement of consultants for Korea Reviewing of protocol, certificate and validation documents Review of the clinical trial safety data Engagement of distributors and/or commercial partner	6-9 months	$300,000
US	Review of all previous documents Engagement of consultants Multicentre clinical trial 12-24 months follow up PMA application Engagement of distributors and/or commercial partner	48-60 months	$15-20m

Source: Hardman & Co Life Sciences Research

Commercialisation strategy

Collagen Solutions has re-engaged with Professor Hangody in Hungary, the leading orthopaedic surgeon who performed the original surgeries, implanting Chondro-Mimetic into 17 patients back in 2009/10. Over the last few months, approvals have been received from the relevant ethics committees to recall these patients for an MRI scan to provide clinical evidence of the quality of repair six years after surgery. It is anticipated that re-scanning of patients will commence early in 2Q 2017 and the expectation is that a majority will return. This will provide highly valuable 6+ year clinical outcome data – a rarity in the cartilage regeneration field as most other products have 1-2 years' results only – to support the company's marketing strategy, along with:

- Partnering with key distributors and/or commercial partners that have access and knowledge of local markets
- Re-engaging with key opinion leaders (KOL) in orthopaedic centres
- KOL advocacy and more data being presented at orthopaedic symposia

Impact on Collagen Solutions

Pulling all these assumptions together, the costs and sales to fund this programme are shown in the following table (note: all numbers in USD) and have been included in our full company forecasts at the back of this report (page 36).

ChondroMimetic – Cost and sales forecasts

Year end March ($000)	2017E	2018E	2019E	2020E	2021E
Europe CE Mark					
Cap-ex			-250		
R&D spend	-200	-300			
CE Mark recognition					
R&D spend		-200	-100		
Total development costs	**-200**	**-500**	**-350**		
Sales					
Europe		100	900	1,720	3,950
CE Recognition			200	750	1,275
Total sales ($000)	**0**	**200**	**1,100**	**2,470**	**5,231**

Source: Hardman & Co Life Sciences Research

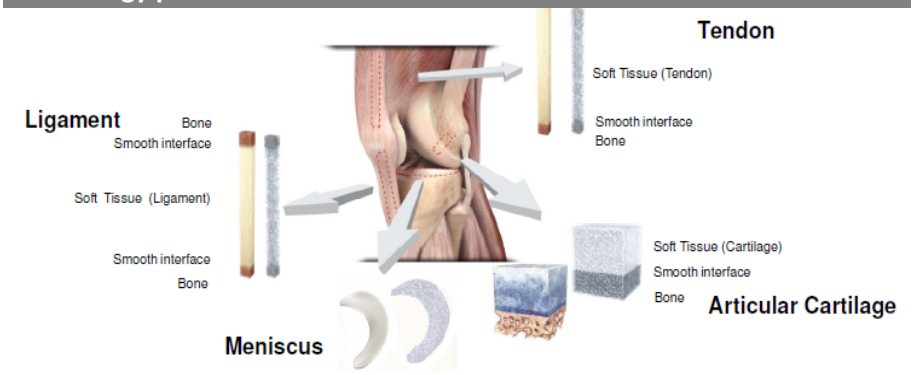
- Forecasts assume that COS will use its existing freeze-dryer initially and then to buy a large state-of-the-art (long-term view) freeze drier in 2019, est at $250k
- In total, medium-term R&D spend has been increased by $800k spread over a three year period, $300k of this is for CE Mark recognition work and will be dependent on receipt of CE Mark. Longer-term R&D spend for the US has not been included forecasts

Related products

The technology platform enables the cost-efficient, commercial-scale production of porous, bioresorbable tissue regeneration scaffolds that mimic, to an unprecedented degree, the composition and structure of complex anatomical locations that comprise a hard tissue (such as bone), a soft tissue (such as cartilage, ligament or tendon) and – most significantly – the smooth stable interface in between these two tissues. These novel medical devices support and separate the simultaneous regeneration of (1) cartilage, ligaments and tendons and (2) the bone to which they are attached.

Uniquely, the technology platform enables these devices to be manufactured using three safe, natural biomaterials that are already found in the body: collagen, glycosaminoglycans (GAGs), and calcium phosphate.

Technology platform for various sites



Source: Orthomimetics Limited; Collagen Solutions

ChondroMimetic is the first in a series of tissue repair products derived from this technology, although further investment in trials would be required in order to obtain regulatory approval and marketing support.

- LigaMimetic – repair of ligaments
- MeniscoMimetic – meniscus repair
- TenoMimetic – repair of tendon

Addressable market

On average there are 600,000 procedures performed in the US each year for the repair of articular cartilage. Therefore, by extrapolation, the number performed worldwide is estimated to be in the range 1.0 to 1.5 million. An estimated 50% these repairs are thought to be small defects that could be addressed by ChondroMimetic.

Articular cartilage repair market

	Europe	US	Global
Number of surgical cases per annum	350,000	600,000	1,250,000
Number suitable for ChondroMimetic	175.000	300,000	625,000
Price per implant	€1,000	$1,200	$1,000
1.75 implants/procedure packs/patient	2	2	2
Addressable market	€350m	$720m	$1,250m
Distributor margin	50%	50%	50%
Market potential	**€175m**	**$360m**	**$625m**

Source: Hardman & Co Life Sciences Research

These figures are forecast to show significant growth in the future, based on increases in:

- Life expectancy
- Knee damage due to obesity/being overweight
- People participating in sport
- Improved healthcare in developing countries

Based on these simple figures the addressable market equates to $625m globally after allowing for distributor margins, with $360m (58%) from the US. This assumes an average end-selling price of $1,000 and that two procedure packs per patient will be required – based on the experience in Europe that, an average of 1.75 implants per patient were used when ChondroMimetic was available commercially. Even a small share of this market (e.g. 10%) and taking account of the distributor margin would imply sales to Collagen Solutions of ca.$6.25m/£4.8m p.a.

Within the overall Orthomimetics stable, there are a number of other products each addressing significant potential markets which will be developed when COS has the necessary financial resource in place. To date, most development work has been undertaken with LigaMimetic a product for the repair and regeneration of ligaments.

Products and addressable markets

Product	Procedures (Worldwide)	Price Per Patient $	Addressable Market (growth)
ChondroMimetic	~625,000	$1,000	$625m (10%)
MeniscoMimetic	~850,000	$500	$400m (5%)
LigaMimetic	~1,000,000	$1,200	$1,200m (5%)
TenoMimetic	~96,000	$1,200	$115m (5%)

Source: www.hampshireknee.co.uk, Hardman & Co Life Sciences Research

Moving up the value chain

Collagen Solutions enters the medical device sector…

With ChondroMimetic, Collagen Solutions will be entering the medical device sector with an innovative product that has an application in the sports medicine, orthobiologics and regenerative medicine market. The device has already been largely de-risked by the historic achievement of CE Mark (needs to be re-registered), has Key Opinion Leader endorsement, and has demonstrated some sales traction.

Once ChondroMimetic is allowed back on to the market, acquisition of the assets and IP of Orthomimetics will have achieved one of Collagen Solutions stated key objective of moving up the value chain by retaining greater share of the end product's value together with control of the whole chain of production. ChondroMimetic is such an end-product, capturing a greater share of value not only through in-house production but also retaining a greater proportion of the end product's gross margin.

Moving up the value chain

Source: Hardman & Co Life Sciences Research

… with a complementary end-user product…

… and the capacity to capture greater share of end-user margin

Moreover, the acquisition is bringing IP and 'know-how' for programmes in ligament, tendon and meniscal repair where there is still the need for improved surgical methods. These applications range from rotator cuff tendons to digital flexor and extensor tendons in the hand. All development activities within these programmes aim to develop products comprising both implants and delivery devices to produce off-the-shelf procedure packs in the vein of ChondroMimetic. All these products embrace a market we estimate to be worth more than $2.3bn and still growing for to the reasons shown earlier.

The following clearly sets the main points and establishes the advantages ChondroMimetic and its IP bring to Collagen Solutions.

Checklist	
Criteria	**Comment**
Disruptive technology	Orthobiologics lead product and platform for sport medicine
Strong intellectual property	Proprietary biomaterials patent in multiple key territories
Large market potential	Market size $625m; $360m in the US
Implant manufacture	Efficient automatic manufacture in place
Iconic branding	University of Cambridge and MIT
Regulatory	CE Mark obtained for ChondroMimetic
Scientific support	Key Opinion Leader support
Clear route to market	Key distributor relationships established in multiple ex-US territories
Strong product pipeline	Products for application in other similar tissues
Defined technical challenges	Clear and achievable steps to establish product traction

Source: Hardman & Co Life Sciences Research

Key next steps

As a result of the lack of attention given to ChondroMimetic since TiGenix's decision to divest it in 2011, the CE Mark has lapsed. Consequently, Collagen Solutions will need to regain CE Mark certification. The key steps to commercialisation will involve:

Route to commercialisation to be elucidated but likely to involve…

- Appointment of a project leader to execute the exploitation of ChondroMimetic and the associated technologies –already done
- Developing in-house production capability, the costs of which are expected to be minimal given Collagen's ability to source and functionalise relevant collagen and the existing clean room facilities
- Re-applying for CE Mark, the cost of which is expected to be minimal and within the company's current cash balances
- Appointing an industry partner and/or distributor network (some of whom are likely to have previously sold ChondroMimetic) to focus on those markets where CE Mark is accepted. Initial focus is expected to be targeted on territories in which revenues can be achieved relatively quickly with a CE Mark.

Due to the previous experience of Orthomimetics, all these steps will be achieved without any major difficulties. We expect the US and Japanese markets to be exploited via partnerships given the specific regulatory and registration uncertainty and the associated high clinical trial investment required. Pursuing such a route, therefore, reduces the financial risk for Collagen Solutions.

Investment conclusion

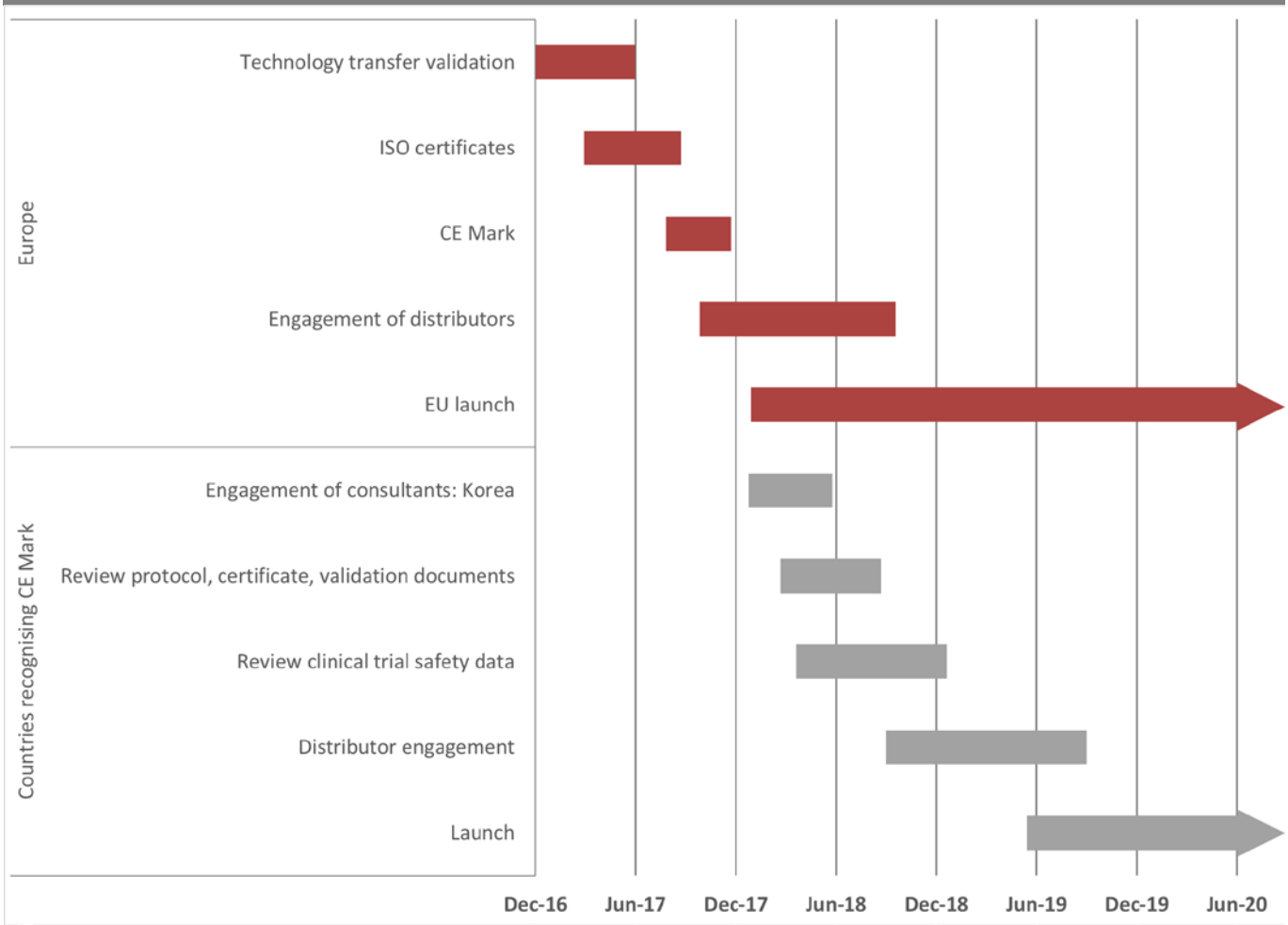
The acquisition of ChondroMimetic and its related IP fulfils the long-term goal of Collagen Solutions to move up the value chain. COS will get a greater share of the end product's value with control of the whole chain of production. ChondroMimetic is an end-product, capturing a greater share of value not only through in-house production but also retaining a greater proportion of the end product's gross margin.

In order to get EU regulatory approval and re-enter the European market, COS will need to regain the lapsed CE Mark. We believe this will be achieved around the end of calendar 2017 and with minimal cost. A Notified body was engaged early in the process and detailed discussions regarding the requirements for CE Mark have taken place. COS is also in the process of identifying/considering distribution partners throughout Europe for ChondroMimetic, so that it will be all set to commercialise as soon as CE Mark is received.

Amongst many others, Australia, Korea, Malaysia, Jordan, Turkey, Thailand and Mexico are countries that recognise the CE Mark but which would need additional information for marketing authorisation to be granted. The required material is predominantly bureaucratic and concerns the protocol, validation and safety data from the clinical trial. Engagement of consultants and distributors will also be needed but this could be overlapped during the CE Mark work.

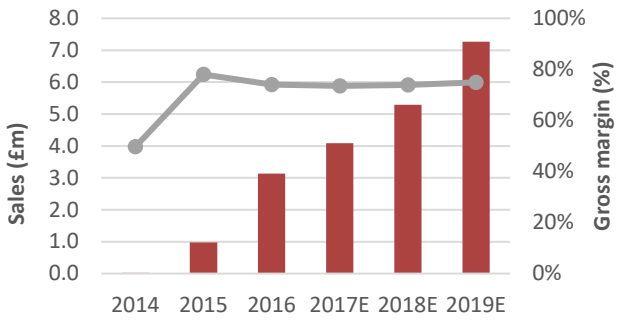
Access to the US market will be costly and is the longest step. The FDA does not provide any guidelines regarding the necessary procedures to get a PMA with claims of regenerative properties. There is no precedent, no regenerative cartilage repair product with regenerative claims has ever been approved by the FDA. Two options are available for COS: (1) application for a Bone Void Filler 510(k) or (2) application for a PMA with regenerative claims which will take much longer and will be considerably more expensive, but which would bring far greater long-term returns. In our opinion, if the six year patient follow-up data from the European trial is strong or compelling, COS should take the more value added route in the US.

ChondroMimetic – Development and launch timelines



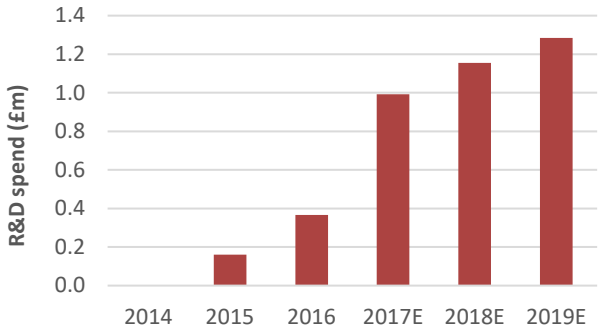
Source: Hardman & Co Life Sciences Research

Sales & Gross margin



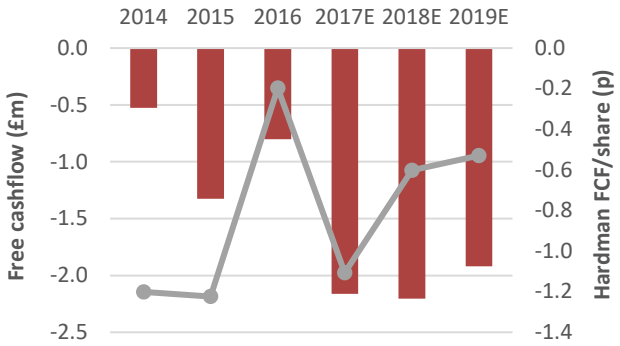
- Sales are expected to grow substantially as customers receive regulatory approvals and commercial investments realise new business
- Numerous new opportunities, but timing of their contribution is complex and, therefore, not included in our conservative forecasts
- The gross margin is dependent on the mix of business – contract manufacturing commands lower margins
- Gross margin is stable, but is likely to go higher as COS moves up the value chain

R&D spend



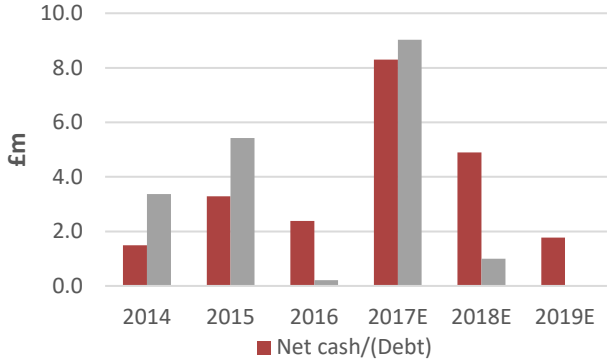
- The accelerated growth strategy necessitates higher investment in R&D and is included in forecasts
- Investment will deliver the strategy of developing more 'owned products'
- COS adds value through development of customer formulations
- ChondroMimetic development is additional to the company's ongoing R&D programmes

Free cashflow



- Accelerated spend on R&D, China JV and increasing the commercial team to drive medium to long term revenues affects short term cash flow
- Cash position is affected by deferred consideration in 2018 and 2019
- Modest cap-ex is required to support the manufacturing of ChondroMimetic

Net cash



- Accelerated R&D and marketing spend is utilising cash that would otherwise be used for deferred considerations
- Deferred considerations – Southern Lights and CS (US) – will push net cash into a net debt position from 2018
- Capital increases also include the deferred consideration for acquisition in shares
- Forecasts suggest that the recent capital increase and loan facility will be sufficient to get COS to a cash generative position

Source: Company data; Hardman & Co Life Sciences Research

ChondroMimetic

History

Originating from MIT and the University of Cambridge…

Incorporation of Orthomimetics (OM) was the result of a fruitful collaboration between the University of Cambridge (UK) and the Massachusetts Institute (US), known as Cambridge MIT Institute (CMI). The business was focused on the development and sale of regenerative medical devices for orthopaedics and sports medicine. After successfully securing £5.6m ($9.6m) Series A funding in December 2006, OM achieved all its key objectives in three years for its lead product, ChondroMimetic, culminating with CE mark for a Class III medical device, first human implantation, and first commercial distribution deal.

…TiGenix paid a handsome price in 2009

In November 2009, OM was acquired by the Belgium biotech company, TiGenix, for £14.8m ($23.9m), which constituted one of best returns worldwide for a small company biotech. Unfortunately, few clinical and marketing developments were carried out during the following three years and, coupled with a shift in strategy at TiGenix, led to the sale of the assets and IP of OM back to its founders, Dr Andrew Lynn and Cambridge Enterprise Ltd, in 2012 for a modest sum, despite the huge potential of its pipeline.

History of Orthomimetics Limited

Date	Event
2001-05	The Cambridge-MIT Institute (CMI) invest £4.0m/$6.5m into an R&D programme for surgical implants
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2012-13	OM founder + Cambridge Enterprise Ltd re-acquire assets and IP for ChondroMimetic and associated tissue repair products
2015	COS acquires the assets and an exclusive worldwide licence to ChondroMimetic and related products

Source: Company reports; Hardman & Co Life Sciences Research

Collagen Solutions already knew Orthomimetics and has now acquired its IP

Collagen Solutions knew Orthomimetics, being the supplier of medical grade collagen to the company, and has been opportunistic in acquiring all of the assets and an exclusive licence for the associated IP to ChondroMimetic and related products from Orthomimetics Limited in return for £100k in COS shares and a low single digit royalty. In order to commercialise these assets globally, COS must:

- Re-establish and re-validate the manufacturing of ChondroMimetic
- Re-apply and re-gain CE Mark
- Perform clinical trials in readiness for PMA regulatory submission in the US (expected to be with a partner)

Recent clinical trial results…

…and early market adoption

This innovative technology compares favourably with competitors' products, is supported by excellent clinical results and has been used in over 300 procedures to date. Although only limited commercial access was garnered by TiGenix, the relationship with and feedback from orthopaedic surgeons and distributors was understood to have been generally positive. Therefore, ChondroMimetic and its related products place Collagen Solutions in an ideal position in the field of regenerative bone and cartilage repair.

The technology

ChondroMimetic: a clever bi-layer resorbable implant…

ChondroMimetic is an off-the-shelf, bi-layer resorbable implant for the treatment of small osteochondral (cartilage and underlying bone) defects based on a biomaterials technology platform. It is best described as a "clever bi-layered sponge" that helps the regeneration of cartilage where cartilage is supposed to be, and bone where bone is supposed to be.

- **Chondral layer** (cartilage-like): Approximately 2mm thick and made from naturally occurring collagen and glycosaminoglycan (GAG)

Made of natural materials

- **Osseous layer** (bone-like): Scaffold approximately 10mm thick and made from a composite of naturally occurring collagen, calcium phosphate and GAG. Acts as an anchor to hold the chondral layer in exactly the right position

Natural product

Highly porous throughout and resembling styrofoam (polystyrene) to the touch when dry, this "sponge" has a bottom layer (ca.10mm thick) made of an advanced nanocomposite of collagen, calcium phosphate and glycosaminoglycan (GAG, mimicking natural bone) and a top layer (ca.2mm thick) made of a collagen and glycosaminoglycan (mimicking articular cartilage).

Materials in OM products and resulting therapeutic benefits

Material	Therapeutic advantage	Technical challenge overcome
Collagen	Fundamental building block of most mammalian tissues Ideal material for supporting healthy cell function Resorbs into the body without acidic by-products	Notoriously difficult to shape into porous forms that are mechanically stable when hydrated
Glycosaminoglycan (GAG)	Important constituent of articular cartilage Main constituent of many treatments for articular joints Toughens and strengthens collagen	GAGs are sub-optimal material for supporting healthy cell function
Calcium phosphate	Main constituent of bone Bonds directly to bone Adds stiffness to composite biomaterials	Calcium phosphates are sub-optimal material for supporting cell function and are very brittle

Source: Collagen Solutions; Hardman & Co Life Sciences Research

Bonding swiftly and seamlessly to the underlying bone, the osseous layer (bone scaffold) supports bone regeneration and simultaneously anchors the entire implant in place. In contrast to synthetic polymer scaffolds which are known to release acidic by-products when biodegraded, natural scaffolds do not, therefore ChondroMimetic is more likely to result in a better implant.

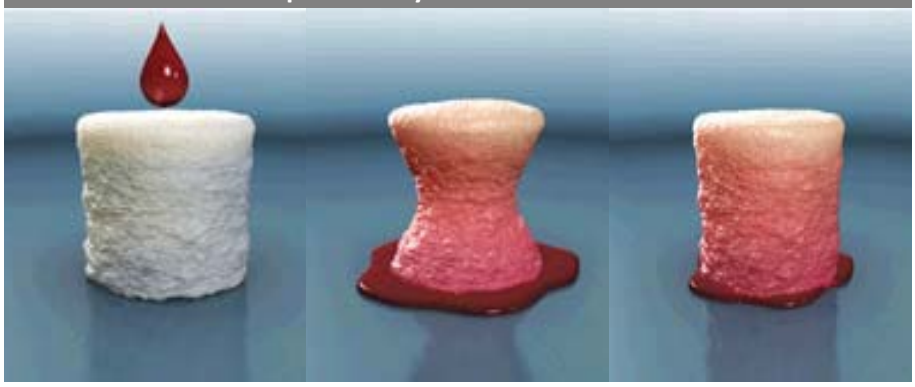
ChondroMimetic has innovative features

The most significant feature of ChondroMimetic, however, is the smooth, seamless interface between its two layers. This mechanically stable interface allows the soft, collagen/glycosaminoglycan (collagen/GAG) layer to remain firmly anchored in place, leaving it free to conform to the contour of the joint surface with no risk of potentially harmful hard edges protruding. This direct-bonding capacity avoids a significant drawback of treatments that seek to repair or replace cartilage using single-layered constructs, namely: the risk of implant detachment and/or damage to the surrounding healthy cartilage associated with suturing, gluing or screwing to the surface of articular joints.

Exceptional properties

Further development work has highlighted some of the exceptional properties of the product. Another exciting feature of ChondroMimetic is, when wet, it can be compressed to about 20% of its original volume and, once the compression is removed, it simply reverts to its original shape. This property will facilitate minimally invasive implantation and ensure a good press-fit into the defect site.

ChondroMimetic – shape memory

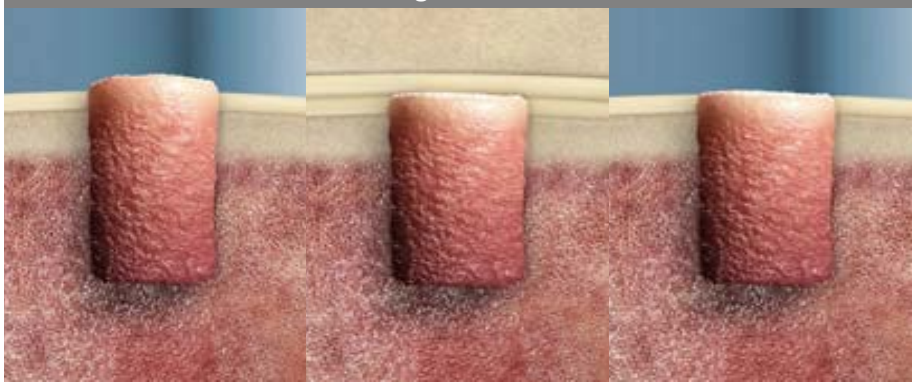


ChondroMimetic, when hydrated, can… | *…be compressed to 20% of its size…* | *…and instantly regain its original shape*

Source: Orthomimetics; Collagen Solutions

Furthermore, once inserted into the defect site, these properties allow the product to interact with the surrounding tissues to automatically conform to match the size and shape of the defect. This property avoids the need to either cut the cartilage and bone into the required product shape or hammering it into place, steps made necessary by more rigid implants, which can damage both the product and the surrounding healthy cartilage.

ChondroMimetic – self-contouring



When implanted proud…. | *… and subsequently contacted by the opposing articular surface …* | *…CM conforms to the shape, size and height of the defect*

Source: Orthomimetics; Collagen Solutions

Easily implanted

Given that ChondroMimetic can be easily cut and shaped with a scalpel, the original plan was for the orthopaedic surgeon to implant the product by simply pressing it into place with a blunt-instrument during the course of the surgical procedure. However, after consultations with surgeons, OM decided that the product would be positioned preferably using a delivery device, thereby taking advantage of the product's unique characteristics.

ChondroMimetic – procedure pack

Packaged product

Step 1: *Site is prepared using precision site preparation tool*

Step 2: *Preloaded implant is hydrated with any sterile fluid via the hydration porta*

Step 3: *Implant is delivered to the site with a simple finger or thumb actuated trigger*

Source: Orthomimetics; Collagen Solutions

This single-use delivery device initially punctures the sub-chondral bone plate to recruit bone marrow-derived stem cells, allowing ChondroMimetic to draw in blood containing cells, signalling factors and nutrients throughout its two-layered structure. Through this "wicking" process, ChondroMimetic ensures not only that all key molecules are distributed evenly throughout the entire site, but also that these essential precursors to cartilage and bone regeneration remain within the implant. The combined action of these recruited cells, nutrients and signalling factors then converts ChondroMimetic's tissue-like scaffolds into healthy new bone and cartilage, before ChondroMimetic is resorbed safely and naturally into the body.

This device forms part of the overall CE Mark for the product and will continue to be sourced from the original supplier. It is designed for single use and will be disposed of at the end of surgery.

Manufacturing

Manufacturing process already established…

In the original commercial plan, Orthomimetics established a full commercial-scale GMP production capability at an outsourced cleanroom manufacturer (BioUetikon Ltd; Dublin, Ireland), together with a back-up. The outsourced packaging, sterilisation and shipping procedures all passed notified body requirements and were compliant, as verified by a notified body audit, with Medical Device Directive (ISO 13485). The company's internal design and documentation procedures passed this audit with observations that it was "of the highest quality". A full suite of toxicity, carcinogenicity and other safety tests had also been conducted on ChondroMimetic material composition, which had received ISO10993 (EU) and 21CFR820 (US) certifications, further confirming the high standards of the company's internal practices.

…and technology transfer proven

In addition, all raw materials suppliers together with manufacturers and subcontractors used by Orthomimetics were selected, approved and audited annually to ensure maintenance of these standards. The new plan will involve Collagen Solutions bringing all this work in-house to be undertaken at its regulatory approved manufacturing facility in Glasgow, thereby retaining more of the gross margin. The technology transfer and manufacturing process is in the throes of being re-validated in preparation for COS re-applying for CE Mark.

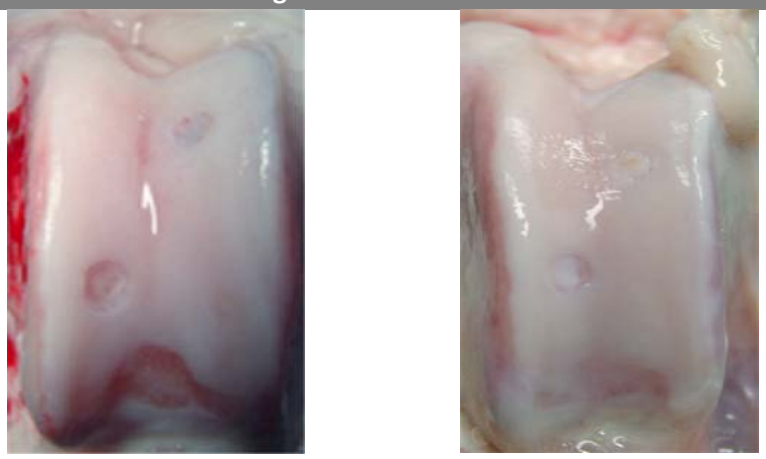
Pre-clinical results

Pre-clinical trials on goats…

Three different trials on strong large animals (goats) were performed. After an initial successful study of an early 6-week pre-clinical trial in 2005, carried out at the University of Cambridge, a second was conducted in 2007 over 16 weeks with six goats, two implants per goat, at Harvard Medical School – one of the world's premier centres for pre-clinical cartilage research. The following pictures show the repair surfaces treated with standard (unfilled) marrow stimulation alone and marrow stimulation with ChondroMimetic.

16-week outcome data using ChondroMimetic

…show excellent defect filling…



Control:	**ChondroMimetic**
Unfilled microfracture defect – 16 weeks	16 weeks

Source: Hardman & Co Life Sciences Research

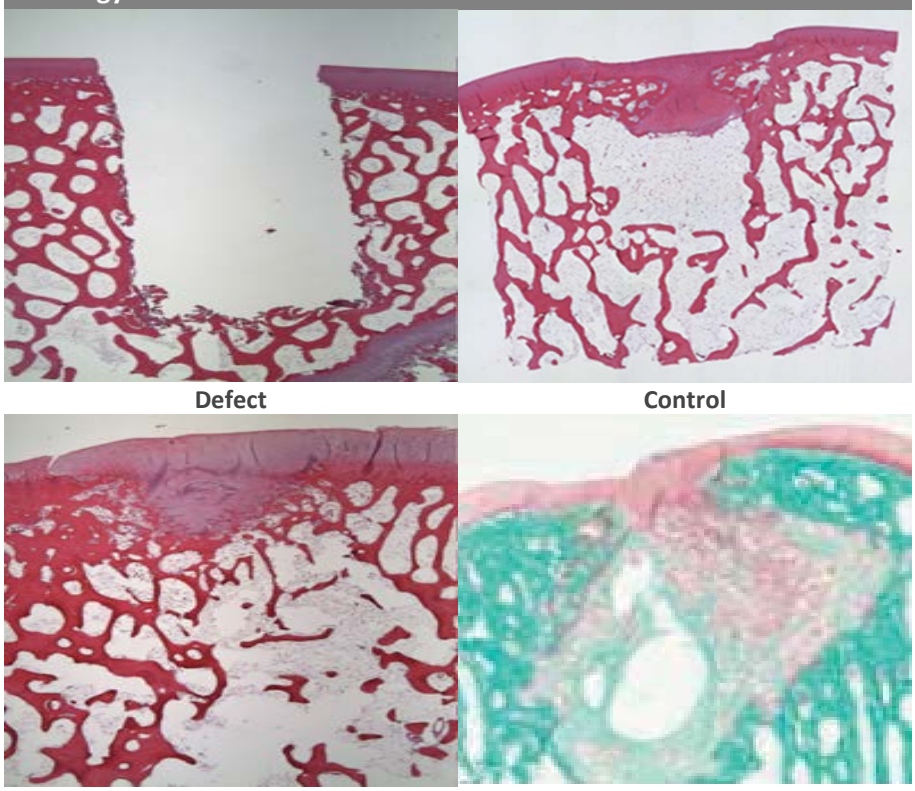
In the control animals, although there is some filling of the defect, the surface is clearly not flush with the existing cartilage which, given that this area of the knee is high use and weight bearing, is likely to result in further damage to the surrounding cartilage and pain. In contrast, in animals which received the ChondroMimetic implant, the newly formed cartilage – largely hyaline – is barely distinguishable from the healthy cartilage surrounding it.

ChondroMimetic versus TruFit

…and better than TruFit

After resorption of the device, a clear filling of the defect with healthy bone marrow as well as cartilage is seen compared to a control. Based on preliminary histological examination, the treatment outcome at 16 weeks using ChondroMimetic looked superior to that produced at 26 weeks using TruFit-CB (Smith & Nephew) in the same defect model and the same goat species. Note the smooth surface of regenerated cartilage obtained with ChondroMimetic's technology, and how it conforms to the curvature of the joint (unlike the inconsistent repair achieved with TruFit-CB).

Histology of ChondroMimetic versus TruFit



Defect | Control

ChondroMimetic – 16 weeks | TruFit – 26 weeks

Source: Orthomimetics; Collagen Solutions

Also note the evolution of replacement bone throughout the area/space formerly occupied by the bottom osseous layer of ChondroMimetic, as opposed to the empty space (white hole) and residual material (pink regions in the bone) present in the TruFit-CB images.

Human trial

Clinical trial ran by a leading orthopaedic and trauma surgeon…

… giving total recovery six months post-surgery…

… and very well tolerated…

… toward the complete filling of the defect

Following the exceptional results obtained on goats, a 20 month clinical trial was conducted in 2009/10 by Professor Laszlo Hangody – a leading orthopaedic and trauma surgeon – at the Sándor Károlyi Hospital, Budapest in Hungary. The open trial enrolled 17 subjects with bone and/or cartilage defects less than 2cm^2, caused by trauma or surgical intervention that required surgical treatment.

- **Primary objective:** to confirm the safety and explore the performance of ChondroMimetic in osteochondral defects of the knee
- **Secondary objective:** to evaluate the surgical technique for implantation of ChondroMimetic

In 15/17 patients ChondroMimetic was used to fill mosaicplasty donor sites, with mosaicplasty being performed in the knee or ankle, whereas in two cases it served to treat primary osteochondral defects of the medial femoral condyle.

Overall, after a slight initial worsening after one month, signs, symptoms and disability had improved relative to baseline after three months and almost disappeared after six months. One month post-surgery the knee was still healing and there was still inflammation, swelling and pain in the joint.

Adverse events – low incidence

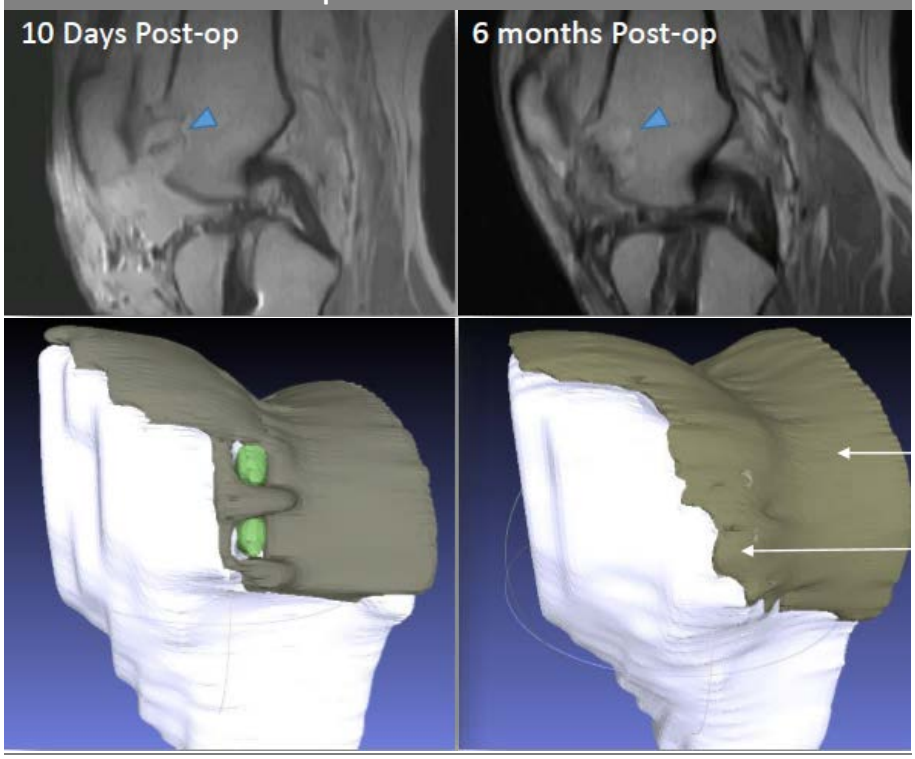
In total three adverse events (AEs) were reported during the study and all three were considered to be 'not unexpected'. Two AEs (moderate 'fistulae synoviae' and severe 'arthritis purulenta' associated with positive *Staphylococcus aureus* culture) occurred in the same patient and were rated as serious. The 'arthritis purulenta' and the non-serious adverse event 'synovitis' of moderate intensity were classified as possibly related to the device. All the adverse events recovered over time. The occurrence of an infection after arthroscopic surgery is not unexpected. Overall, the incidence of adverse events reported in these 17 subjects over a 6-month period is low compare to existing procedures and would indicate that ChondroMimetic is safe for use in the first 6 months after implantation.

Results

One month post-surgery, the increase of the Visual Analogue Scale scores – a psychometric response scale – and the decrease of the Cincinnati scores – measure of disability – show an increase in pain and disability for the patients. But this is due to the normal inflammation and swelling expected after surgery. The same scores noticeably change for the good after 3 and 6 month post-surgery, showing a clear recovery and a diminished pain level of the knee for all the patients. The Bandi scores – measure of the pain level – after 6 month post-surgery shows that 10 patients had no pain and the 7 remaining subjects had occasional pain and/or had pain with strenuous activity. The global assessment was 'good' for all 17 subjects. These all show that ChondroMimetic is being effective and performing as required.

The physical examination of the knee showed an expected quadriceps muscle atrophy in all patients at 1 month post-surgery. However, this all returned to normal after 6 months of normal post-surgery re-education. The following shows the MRI scan and computer analysis 10 days and six months post-surgery in a typical patient.

ChondroMimetic – Post-operative MRI scans

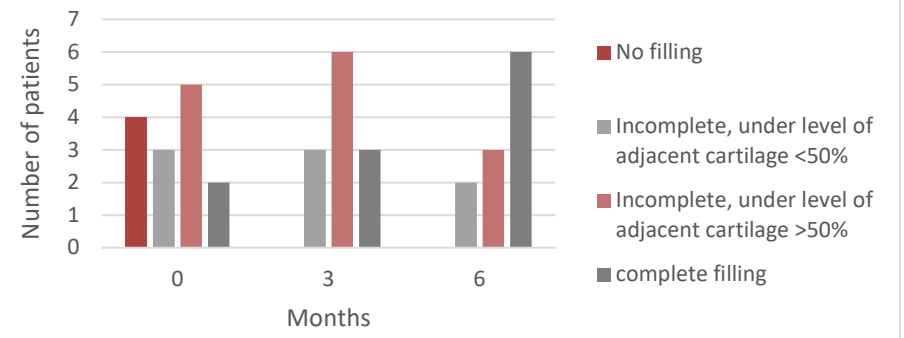


Source: Courtesy of Professor Hangody; Orthomimetics; Collagen Solutions

The degree of defect repair and filling was assessed for 14 subjects by MRI using the magnetic resonance observation of cartilage repair tissue (MOCART). The following photographs illustrate outcomes in a single patient receiving two implants 10-days and six-months post-surgery. Although difficult to visualise by the untrained eye, after 10 days, boundaries between the implants and the bone are clearly defined and there is no cartilage repair. However, six months after surgery, there is little differentiation between the implant and the bone and the scaffold has been filled with new 'bone'. But, more importantly the cartilage scaffold has been filled by cartilaginous repair.

Analysis has indicated that all patients in the trail showed some improvement and repair after six months, and 55% of patients had a complete filling of the defect.

MOCART – Degree of defect repair and filling of the defect over time



Source: Orthomimetics, Hardman & Co Life Sciences Research

Acclaimed by 100% of the subjects

It is worth mentioning the opinion of the 17 patients six-month post-surgery. The table below presents the answers to a few of the questions that have been asked in a patient survey. The overall impression is very positive. All patients were pleased with the outcome of the surgical treatment as it at least met their expectations. ChondroMimetic was very well tolerated by all, and they were keen to have the same treatment again in future, if needed. These clearly show real improvements, the increase in well-being, and tolerability that ChondroMimetic brought to all the subjects in the trial.

Patients' opinion

Question	Answer	Score
Did the treatment meet the subject expectation?	Yes, almost totally:	5 (29.4%)
	Definitively yes:	12 (70.6%)
Would you have the same treatment again?	Probably yes:	3 (17.6%)
	Definitively yes:	14 (82.4%)
Rating of the overall success?	Good:	1 (5.9%)
	Very good:	6 (35.3%)
	Excellent:	10 (58.8%)
Global rating	Good:	17 (100%)

Source: Collagen Solutions; Hardman & Co Life Sciences Research

In order to assess the resorbable property of ChondroMimetic, biopsy is needed. Only five patients consented to have an arthroscopy and this small number does not allow any conclusion to be drawn regarding integrity of the implant and histological repair tissue evaluation. But the data indicated that ChondroMimetic performed well in the treatment of osteochondral defects of the knee, supporting the MRI scan evidence shown earlier.

Regulatory requirements

Europe

Work towards resubmission of ChondroMimetic for CE Mark is well advanced. The key requirement is to finalise the development of an in-house manufacturing capability. Given that there was an existing technology transfer to BioUetikon, all the protocols are well established. There is some essential 'know-how' in the manufacturing process, but COS' existing expertise, coupled with the fact that the company is using Orthmimetics' founder as a consultant and appointed him onto its SAB, should ensure that this transfer is relatively straightforward. Once this has been achieved, COS will liaise further with its Notified Body to re-apply for CE Mark.

United States

The situation regarding regulatory approval in the US is much more complex. On the one hand, COS could simply apply for a 510(k) for ChondoMimetic to be used as a back-fill bone filler. The main questions that would need to be addressed would be:

1) Does the bone scaffold stay in place once implanted?
2) Is there any pain subsequent to the surgery?

This would be a straight-forward procedure and would not involve too much work, as these hurdles are relatively low. However, such a process would not allow COS to make any claims about ChondroMimetic having regenerative capacity and the capability of the device being used as a therapeutic, which is where all the value added resides. As such, COS would not be able to command a premium price.

In order to realise the full potential of ChondroMimetic in the US, COS will need to apply to the FDA for Pre-Marketing Authorisation (PMA) as a Class III medical device – the most stringent regulatory category for evaluating the safety and effectiveness of a device. To achieve this, the company will need to commission one 200-patient multi-centre trial (or two x 100 patient trials).

Cartiva sets a precedent

Although not directly in competition with ChondroMimetic, COS has been able to watch the progress and pitfalls that have been encountered by Cartiva, which had an Advisory Committee at the FDA for its synthetic cartilage toe implant (Cartiva SCI) earlier in 2016. Although the committee had concerns about the data, it voted overwhelmingly to recommend approval of the product, which was endorsed by the FDA giving PMA approval in July 2016. This is important, as it sets a precedent about what is likely to be required by the FDA for the approval of ChondroMimetic in the US.

Cartiva SCI

Source: Cartiva

In its FDA PMA submission, Cartiva presented data from a single clinical trial ('MOTION') involving 236 patients in 12 centres in Canada and the UK, where the product has already been approved. Patients were randomised to receive either the Cartiva implant (about 65%) or bone fusion (35%), where the toes are permanently fused together, and were followed up after two-years. The primary end-point was a 15% non-inferiority margin compared to bone fusion, which had previously been agreed with the FDA. The study investigators concluded that Cartiva was almost as effective (ie within the non-inferiority margin) as fusing the toes together, with both arms of the trial having similar failure rates requiring follow-up surgery in about 10% of patients.

Cartiva SCI toe implant was approved by FDA in July 2016…

…on the basis of being non-inferior to toe fusion

Interestingly, as part of the discussion, Cartiva also involved some patients, getting them to speak about their experience with the product/surgery. Despite this, several committee members were sceptical that the device was as effective as toe fusion. Panel members were also concerned that a significant number of the patients implanted with Cartiva needed secondary subsequent interventions due to pain or because the implant was not placed properly the first time. Criticism was also voiced by an occupational medicine specialist, who was the non-voting consumer representative, that the data was only subjective and that the FDA should be considering products that are superior to standard-of-care, not simply aiming to prove non-inferiority.

Despite all the objections, the product was considered safe and the committee voted to recommended the device as another option available to physicians and patients.

Intellectual Property

Over the years, the IP surrounding ChondroMimetic has been consolidated from eight patent families down to four, covering:

- The know-how of the production line for cartilage and ligament repair
- The composition of the scaffold
- The manufacture methods

The patent families are sets of either patent applications or publications taken in multiple countries by the company to protect ChondroMimetic. A first application is made in one country – the priority – and is then extended to other countries.

All families are being prosecuted in all developed-country territories, as well as in India, China, and a number of other key emerging territories.

ChondroMimetic – Details of patent families

Patent family	Title	Reference	Priority date
P001:	Composite biomaterials comprising calcium phosphate materials, collagen and glycosaminoglycans	WO2005/051447	28-Oct-2003
P002:	Biomaterials layered scaffold comprising porous layers of collagen, calcium phosphate and GAG	WO2006/095154	07-Mar-2005
P003:	Biomaterials layered scaffold produced by solid co-synthesis and solid-liquid co-synthesis	WO2008/017858	11-Aug-2006
P004:	Fabrication process	WO2011/107807	05-Mar-2010

Source: Hardman & Co Life Sciences Research

Existing procedures

The two main goals of all procedures for articular-cartilage repair are to (1) remove loose particles and smooth jagged edges that could cause further damage and (2) induce, when required, the formation of repair tissue that is sufficiently durable to prevent further defect growth and stop the bones on either side of the joint from rubbing together. The primary use of ChondroMimetic is for the repair of articular cartilage – not of the meniscus, which is composed of a different type of cartilage (fibrocartilage). Four main procedures are used for repairing articular cartilage:

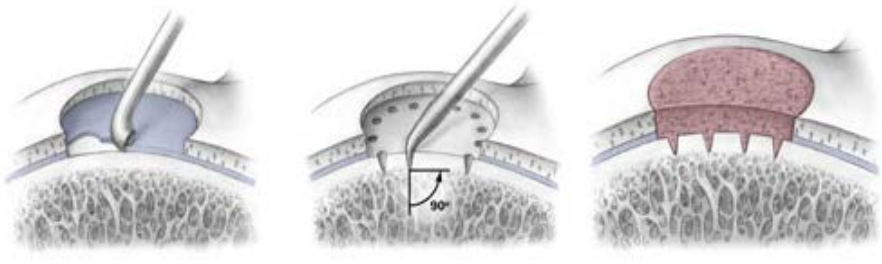
Chondroplasty (arthroscopic debridement)

Chondroplasty is the most common surgical procedure that involves the simple removal of loose cartilage and the smoothing of any rough edges remaining on the articular joint surface. This technique does not induce the formation of repair tissue, and is thus unsuitable for defects that are deep or larger than a few square millimetres in size. But it does have the advantage of being widely available and allows further surgical options to be tried if chondroplasty alone fails to reduce pain and restore mobility. While short-term results from this type of treatment are generally positive, eventual growth of the defect often makes further surgical treatment necessary.

Microfracture (Marrow stimulation; abrasion arthroplasty; subchondral drilling)

Microfracture promotes cartilage repair by recruiting marrow-derived stem cells to the site of the injury through puncturing or removing part of the subchondral bone plate to induce blood and repair cells to enter the defect from the marrow cavity. Marrow stimulation is widely available, can be performed arthroscopically, and leaves room for further treatment options to be performed in the future. It is suitable for defects of any depth and up to 2cm^2 in surface area. The repair tissue formed after marrow stimulation is a type of fibrocartilage, which is less durable than healthy articular cartilage.

Microfracture

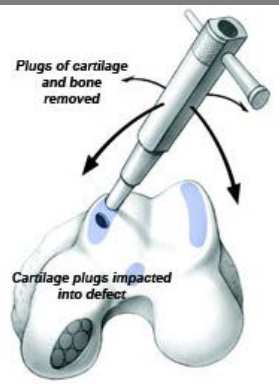


Step 1: Damaged cartilage removed	Step 2: Awl makes holes in sub-chondral bone	Step 3: Healthy response

Source: Mithoefer at al, 2006

Results in high performance athletes have been disappointing and the average length of time until patients (with average levels of activity) need further treatment is roughly 5 years. The ability of the blood clot, which forms within the defect site, to support the action of repair cells is a source of concern, with irregular (concave) shape and poor durability being the most commonly observed deficiencies of repair tissue formed via marrow stimulation. In order to improve the technique, in 2011 a new study suggested that injection of autologous peripheral blood progenitor cells and hyaluronic acid would help greatly cartilage regeneration for difficult to treat grade IV or kissing lesion in the knee.

Osteochondral autograft



Source: Hangody et al, 2004

Osteochondral autograft (autologous osteochondral transfer; mosaicplasty)

Osteochondral autograft involves the harvest of cylindrical plugs of healthy, mature bone and cartilage from a non-load-bearing portion of the joint, which are then inserted into the site of injury in a mosaic pattern. Plugs of different diameters are used to fill the site as thoroughly as possible. Due to the high degree of surgical precision involved, osteochondral autograft is generally available only at specialist clinics, but has the advantage of being able to treat defects slightly larger (up to 4cm^2) compared to marrow stimulation. Concerns regarding this technique include adverse consequences (sensitivity, pain, restricted range of motion) linked to damage and tissue death at the donor site, and the high variability of outcomes believed to result from the complexity of the procedure.

Autologous chondrocyte implantation/transplantation (ACI/ACT)

ACI is a double intervention procedure based on the removal and culture of a patient's own cells, followed by re-implantation. During the first procedure, a biopsy sample of cartilage is removed from a healthy, non-load-bearing portion of the joint, and then sent to a cell-culture facility. Cartilage cells (chondrocytes) are isolated from the sample and cultured over several weeks before being sent back to the original site for re-implantation. Ten years ago, there were high hopes for this procedure, however, the costs were prohibitive and the outcomes extremely variable – largely because the new tissue was anchored into place with multiple sutures that damaged the existing healthy tissue. Not viable commercially.

Other treatments

Osteochondral allograft transplantation: Where a cartilage defect is too large for an aoutograft, an allograft might be considered, whereby the tissue graft is taken from a cadaver donor. It is sterilised in the laboratory, prepared and tested for disease. Rarely used.

Viscosupplementation (intra-articular injection)**:** Involves the introduction of highly viscous substances, such as hyaluronan, to provide additional lubrication and allow joints to articulate with less discomfort. Provides only temporary, symptomatic relief and does not induce regeneration of new tissue.

ChondroMimetic – Small addition for improved outcomes

ChondroMimetic could be used in conjunction with existing procedures

ChondroMimetic offers a way of improving the standard of treatment for cartilage lesions by working with existing techniques, as opposed to replacing them. Plugs can be tailored to match the defect, used without altering materially the methods that surgeons already employ, while overcoming many of the inadequacies of these same methods. This was borne out in Key Opinion Leader and surgeon surveys undertaken when the product was available commercially.

ChondroMimetic – A simple addition to existing procedures

Source: Orthomimetics; Collagen Solutions

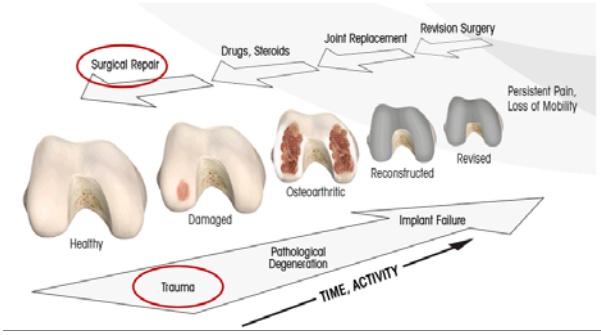
Commercial opportunity

$36bn spent in total joint replacement…

Each year, an estimated $36bn is spent on total joint replacement surgeries worldwide. Although joint replacement is an effective means of restoring mobility and alleviating pain, the clinical reality is that patients can expect, on average, no more than 17 years before their joint replacements fail. Revision procedures that repair or replace failed implants are painful for the patient, last for an even shorter period of time compared to the primary implants, and place a burden of over $4.5bn on governments and healthcare insurers worldwide. Thus, there is a real and pressing need for treatments that prevent or delay the need for total joint replacement. The orthobiologics market is a rapidly evolving area of regenerative medicine. With a market driven by the need to reduce healthcare expenditure as well as improving the standard of living, new and innovative technologies are necessary. The ultimate aim is to delay the as far as possible the need for total joint replacement.

…That costs the healthcare system $4.5bn

Driving orthobiologic demand



Key Statistics – Worldwide	
Annual expenditure on total joint replacement	$36bn
Annual expenditure on revision joint replacement	$4.5bn (12.5%)
Average life of a total joint replacement for a 65-year-old patient	17 years
Average life of a total joint replacement for a 45-year-old patient	10 years

Source: Orthomimetics, Hardman & Co Life Sciences Research

New techniques are needed in orthobiologics

While a vast majority of surgeons agree that existing first-line surgical procedures for the repair of cartilage, ligament, and tendon injuries do not adequately delay the need for joint replacement, existing commercial products are failing to overcome four main barriers to market growth. ChondroMimetic addresses the market for small lesions in articular cartilage, where key factors determining product competiveness are shown in the table below.

With its remarkable ability to heal both cartilage and subchondral bone, Collagen Solutions would have the possibility to play an important role in saving the healthcare system $4.5bn per year worldwide.

Competiveness

	Existing products	ChondroMimetic
Therapeutic benefit	Existing products are failing to demonstrate clear therapeutic benefit over existing surgical treatment	ChondroMimetic improves the efficacy of existing surgical procedures, providing a clear path to therapeutic benefit
Cost of conversion	The need for specialised training limits surgeon acceptance of current products	Compatibility with existing surgical techniques eliminates the need for specialised training
Price / benefit	High product pricing (despite low margins) has led insurers to limit reimbursement for autologous-cell products	High gross margins offer the flexibility to accommodate insurer pricing concerns
Speed to market	Tightening of EU and US regulatory policy have resulted in stricter regulatory requirements for new cell and biologics based products.	Classification as medical device in both the US and EU reduces regulatory requirements, shortens time to market

Source: Hardman & Co Life Sciences Research

Addressable market

600,000 surgical procedures performed in US only per year…

There is an average of 600,000 procedures performed in the US each year for the repair of articular cartilage. Therefore, by extrapolation, the number performed worldwide is estimated to be in the range 1.0 to 1.5 million. Approximately 50% these repairs are thought to be small defects that could be addressed by ChondroMimetic.

Articular cartilage repair market

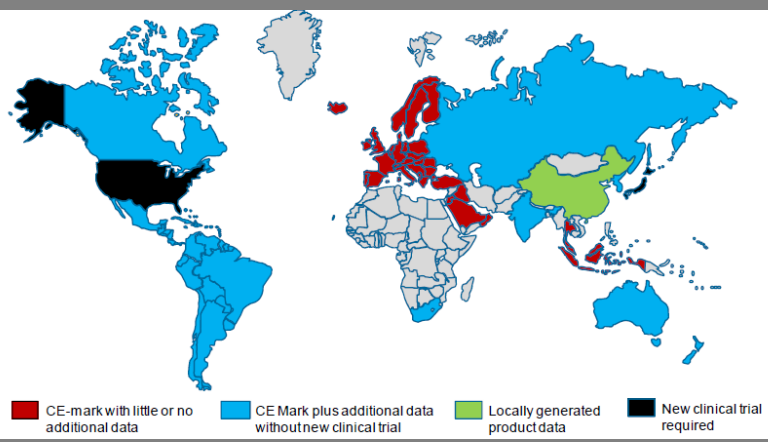
	Europe	US	Global
Number of surgical cases per annum	350,000	600,000	1,250,000
Number suitable for ChondroMimetic	175.000	300,000	625,000
Price per implant	€1,000	$1,200	$1,000
1.75 implants/procedure packs/patient	2	2	2
Addressable market	€350m	$720m	$1,250m
Distributor margin	50%	50%	50%
Market potential	**€175m**	**$360m**	**$625m**

Source: Hardman & Co Life Sciences Research

…with an addressable market of $1,250m…

Based on these simple figures the addressable market equates to $625m globally after allowing for distributor margins, with $360m (58%) from the US. This assumes an average end-selling price of ca.$1,000 and that two procedure packs per patient will be required – based on the experience in Europe that, an average of 1.75 implants per patient were used when ChondroMimetic was available commercially.

Addressable market access



Source: Collagen Solutions

ChondroMimetic will enter the European and ex-US territory…

Initially, Collagen Solutions will be focusing on markets which recognise CE mark, such as Europe and some territories in SE Asia, or an estimated 350,000 repairs annually. With an end-selling price of €1,000, this would give rise to an addressable market of €350m/£275m. Even a 10% share ($35.0m/£27.5m ex-factory) of this market over time would have a significant positive impact on a company the size of Collagen Solutions.

The second stage of COS' commercialisation programme would be to obtain approval in those markets that recognise CE mark, but which require additional, non-clinical, data. These countries are shown in blue in the graphic above. This would probably open ChondroMimetic up to a further 300,000 case per annum, making the opportunity, even in the absence of US regulatory approval, substantial with 10% market share equal to $30.0m/£21.0m ex-factory sales.

…With the aim to enter the more challenging US market

In order to access the US market, the FDA will require COS to undertake two clinical trials involving an estimated 120-200 patients in several centres in order to apply for a PMA. This will cost an estimated $20m-$40m and could be done in partnership if the company sees early success in Europe. However, the rewards for a successful PMA would be substantial, opening ChondroMimetic up to an unsatisfied market of $720m.

Competitive landscape

It is a competitive market

The orthobiologics market is a very active sector where new technologies are needed to delay the requirement for joint replacement surgery. The worldwide broad orthobiologics market was estimated at $2bn in sales in 2009, with bone graft subset encompassing nearly 1 million procedures and generating $1.5bn in revenue. It is widely believed that this sub-segment of orthopaedic industry would give the highest growth rate.

Most of the techniques address the market of large defects (>2cm^2) and osteoarthritis and not the small lesions (<2cm^2) where ChondroMimetics sits. The main competitors in the small lesion market are described below. Some caution needs to be exerted as some of these products have been included to demonstrate the different approaches taken by companies, but have subsequently been withdrawn from the market for various reasons. A non-exhaustive list of approaches is described below.

TruFit-CB

Withdrawn from market in 2013
Source: Smith & Nephew

TruFit-CB® – Smith & Nephew

Smith & Nephew obtained TruFit Bone Graft Substitute (TruFit-CB) through its acquisition of Osteobiologics for $72.3m cash in 2006. TruFit works in a similar manner to ChondroMimetic, but is totally being made from polygraft material (a blend of poly DL-lactide-co-glycolide, calcium sulfate, polyglycolide fibers and surfactant). The material degrades over 4-8 months following implant, but in doing so is known to release acid into the bone space which is reported to cause considerable discomfort. On the basis of non-availability in the US market, weak sales and poor patient feedback, S&N withdrew TruFit from the all markets in 2013.

In 2014, Gelber[1] described results from a clinical trial conducted on 57 subjects. The authors concluded that TruFit failed to restore the normal MRI aspect of the subchondreal bone and lamina. Moreover, a comparative study between Chondro-Mimetic and TruFit in goats was also performed by Hangody and showed the same results (see page 17). ChondroMimetic showed a better healing defect with a better smooth surface cartilage. The main differences are that ChondroMimetics is made of natural biomaterial, which decreases the risk of any immune response, and is very flexible, especially when wet, resulting in a tight and smooth fit into the defect.

BST-Cargel® – Smith & Nephew

On January the 12th 2016, Smith & Nephew acquired BST-Cargel from Piramal for an undisclosed price. BST-CarGel is a chitosan-based liquid scaffold, which is a natural polymer. It is mixed with autologous blood before implantation into a debrided cartilage lesion prepared with bone marrow stimulation. Some of the downsides that have been noticed from the technology is that BST-Cargel will not give a full and smooth cartilage surface. Also BST-Cargel addresses only the repair or cartilage and not the underlying bone. BST-Cargel is not available in the US.

[1] Gelber PE, et al "Magnetic resonance evaluation of TruFit plugs for the treatment of osteochondral lesions of the knee shows the poor characteristics of the repair tissue", *Knee*, **2014,** 21, 4, 827-832.

MaioRegen® – Finceramica

MaioRegen is probably the biggest threat to ChondroMimetic. It is a three-layered scaffold:

- **Top** – De-antigenated type 1 equine collagen to mimic cartilage tissue
- **Middle** – Composed of magnesium enriched Hydroxyapatite (Mg-HA)
- **Bottom –** Mostly constituted of Mg-HA, aimed to simulate the sub-chondral bone structure, which are 50% (volume) mineralised hydroxyapatite

It acts like ChondroMimetic, can also be shaped to match the defect, and can be used on a larger surface. However, the device is fixed into place using fibrin sealant. During the healing process, the cells proliferate and differentiate according to the matrix. An initial clinical trial comparing MaioRegen with established surgical techniques (microfractures and subchondral drilling) with 1 year follow up on 30 subjects showed excellent results and good resorption of the device.

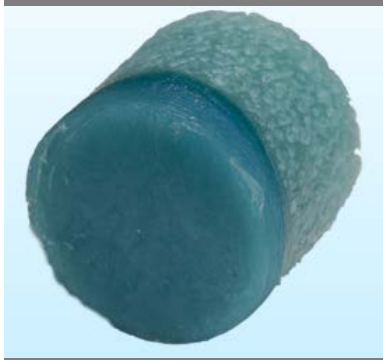
However, another trial originally in 10 subjects with osteochondral lesions of the knee (n = 6) or the ankle (n = 4) has produced less convincing results at up to three years' post-surgery[2]. Two patients needed to be re-operated on and were excluded from follow up. After 2.5 years, six (ex-8) subjects were reported to have none to very limited (<10%) bone formation in the defects with the other two subjects having 50-75% bone formation. MRI scans did not show improvement in the three-dimensional magnetic resonance observation of cartilage repair tissue (MOCART) score at any time point. The study concluded that use of the MaioRegen scaffold resulted in incomplete cartilage repair and poor subchondral bone repair at 1- and 2.5-year follow-up. Although clinical improvements were observed, the results raised serious concerns about the biological repair and that MaioRegen scaffold should be used with caution.

MaioRegen and MaioRegen Slim

Source: Finceramica; Hardman & Co Life Sciences Research

[2] Christensen, B.B., Foldager, C.B., Jensen, J. et al. Knee Surg Sports Traumatol Arthrosc (2016) 24: 2380. doi:10.1007/s00167-015-3538-3

Chondrofix



Source: Zimmer

Chondrofix® – ZimmerBiomet

Chondrofix is an osteochondral allograft – cleaned bone and cartilage tissue recovered from a donor (allograft). After extraction, the tissue is cleaned of blood, fat and other living tissues – decellularized hyaline cartilage and cancellous bone. There is no need for anti-rejection drugs although there remains some potential to elicit an immune response. Zimmer was conducting a clinical trial with Chondrofix in 29 subjects, but this was terminated early due to inadequate enrolment and decreased need for clinical data to support the product. Other clinical trials with Chondrofix appear to have produced mixed outcomes[3][4].

DeNovo® NT – ZimmerBiomet

DeNovo NT natural tissue graft is an off-the-shelf human tissue juvenile hyaline cartilage implant that has been developed with ISTO technology. The graft is an FDA-approved tissue product used for knee, hip, ankle and shoulder cartilage restoration since 2007 with over 6,000 surgeries completed. It has proven to be well tolerated and it is intended for the repair of articular cartilage defects in a single-stage procedure. The DeNovo NT Graft surgical technique mitigates the need for harvesting and suturing of a periosteal flap, unlike autologous chondrocyte implantation (ACI), as it employs a fibrin sealant to secure the minced tissue pieces into the defect. It is often used as a primary treatment option for lesions larger than $1cm^2$ or as a secondary treatment option to previous cartilage repair treatments that have failed.

DeNovo NT

Source: Geistlich

[3] Farr, J, Gracitelli, G. & Gomoll, AH. Decellularized Osteochondral Allograft for the Treatment of Cartilage Lesions in the Knee. Orthopaedic Journal of Sports Medicine July 2015 3, no. 2 suppl 2325967115S00068

4 Long, WJ, Greene, JW & Cushner, FD. Early Clinical Outcomes Associated with a Novel Osteochondral Allograft Transplantation System in the Knee. Advances in Orthopedic Surgery, 2016, Article ID 1979348

Orthoss®-Collagen – Geistlich

Orthoss Collagen is a thick malleable and resorbable monolayer implant made of natural bovine nanocrystalline carbonated hydroxyapatite and porcine collagen. The reported advantage of the device is its bimodal pore structure: the nanosize pores ensure the capillary action and liquid storage capacity, while the macrosize pores allow the entry of all the regenerative cells. The surgical procedure consists to clean and realise microfractures technique to the defect. The implant is then shaped, placed into the defect and impregnated with autologous blood. Finally, the chondral defect can be covered with a Chondro-Gide membrane using fibrin as a sealant. It is worth noting that Orthoss, the substance used to manufacture Orthoss-collagen, has been used successfully in more than 3 million patients over 25 years, showing its high tolerability as a bone graft substitute.

Orthoss

Source: Geistlich

Chondro-Gide

Source: Geistlich

Chondro-Gide®– Geistlich

Chondro-Gide is a thin bilayer sheet of natural collagen used for large defects (from 2 to 8mm in diameter). The pack also includes an aluminium sheet that is used to create a template of the shape of the defect. The compact upper layer which has a smooth surface is cell occlusive, preventing cells from diffusing into the synovial fluid and also protecting them from mechanical impact. The inner layer consists of collagen fibres in a loose and porous arrangement that favours cell invasion and attachment. After a microfracture treatment, the implant is shaped and then glued and or sutured into the defect using fibrin. The main advantage of the device is that it can be used for larger defects where no real treatment exists so far. Chondro-Gide can also be used as a thin membrane covering repaired defects as used in the following product.

Carticel® – Vericel

In May 2014, Vericel purchased the Cell Therapy and Regenerative Medicine business from Sanofi for $6.6m. Included within this portfolio was Carticel. In 2013, Carticel, together with Epicel (cultured epidermal autografts) and MACI (matrix-induced autologous chondrocyte implant) were reported to have sales of $44m, suggesting that the purchase price, EV/sales of 0.15, was incredibly low. However, despite its early promise, Carticel has underperformed market expectations.

The low consideration for these assets might be explained by the fact only 22,000 implant procedures were performed between 1997 and 2014[5]. This might be associated with the very high price ($70,000) that was charged for the Carticel procedure. These two points have made Carticel commercially unviable and in subsequent reports, annual sales have fallen significantly from the level reported at the time of acquisition.

The Carticel technique consists of harvesting cartilage from a remote area of the knee where it is not needed. These cells are then sent to Vericel laboratories where a special cartilage cell growth technique is used. Six weeks later, the patient goes back for further surgery where, first, a small piece of cartilage is harvested from the tibia and placed over the defect being attached with tiny stiches and a biologic glue; and secondly, the cultured cartilage cells are then injected under the graft into the defect. We understand that the process of suturing the cartilage graft into place caused significant damage to a previously healthy area of cartilage. This could be the reason for the 24% failure rate noted in the STAR clinical trial – 37 patients failed treatment out of the 154 patients enrolled into the study STAR study.

Agili-C

Source: CartiHeal

Agili-C® – CartiHeal

Agili-C is also a new bi-layered product that is in the clinical stage and where the main constituent is aragonite, which is a high pressure polymorph crystal of calcium carbonate. The thin first layer is made of hyaluronate-impregnated aragonite and the bottom one calcium carbonate in the aragonite crystalline form. The pre-clinical results show that the resorbable implant has the ability to recruit cells from the surrounding tissues and the histological and immunohistochemical stainings indicated the presence of collagen type I only in the bone phase and type II in the cartilage layer. There is one case report describing the clinical use of this implant and the follow up after 24 months is very encouraging and clinical trials of >200 patients at 12 European sites is ongoing. A European launch of the implant is anticipated in 2017.

[5]Vericel report third-quarter 2015 financial results

Competitive landscape

Product	ChondroMimetic	TruFit-CB	BST-Cargel	ChondroFix	MaioRegen	Chondro-Gide	Orthoss-Collagen	Carticel	Agili-C
Manufacturer	Collagen Solutions	-	Smith & Nephew	Zimmer	Finceramica	Geistlich	Geistlich	Vericel	CartiHeal
Nature	Natural	Synthetic	chitosan, derived from chitin	Bone (allograft)	Natural/Mineral	Natural	Natural	Autologous	Synthetic
Type	Scaffold	Plug	Gel	Plug	Scaffold	Scaffold	Scaffold	Gel (?)	Scaffold
Property	Flexible	Hard	Injectable	Hard	Hard	Hard	Maleable	Injectable	Hard
Size of defect	<2cm2	<2cm2	<2cm2	<2cm2	1.5-6cm2	1-8cm2		No size restriction	<2cm2
Bone/Cartilage	Bone & cartilage	Bone & cartilage	Cartilage	Bone & cartilage	Bone & cartilage	Cartilage	Bone & cartilage	Cartilage	Bone & cartilage
Number of layers	Bilayer	Monolayer	N/A	N/A	Trilayer	Thin bilayer	Monolayer	N/A	Bilayer
How fixed in place	Expands to fit *in situ*	Different sizes 5 to 11mm	applied on the lesion after bone marrow stimulation	Different sizes 7 to 15mm	Cut to shape	Cut in shape and glued after microfracture	Cut to shape	Autologous cartilage cell growth and autologous cartilage	Exist in different sizes 6-18mm, mosaicplasty
Implant device	yes	yes	No	Yes	Not reported	No	No	No	Not reported
Price		Discontinued						$70,000	

Source: Company data, Hardman & Co Life Sciences Research

With a vast R&D pipeline

Potential in R&D?

At present, autografts and allografts are still considered the gold standard procedures for orthobiologics but the R&D pipeline presents promising and elegant technologies.

It is worth noting that most of these new technologies are addressed for spinal injury but with the vision to extend the therapy to broader bone injuries, which would compete directly with the potential market for ChondroMimetic. However, ChondroMimetic offers surgeons a uniquely flexible device, which is easy to use and gives faster and more flexible repair.

Competitors' R&D pipelines

Company	Products
Mesoblast	NeoFuse product comprising allogeneic Mesenchymal Precursor Cells for interbody lumbar fusion
BoneTherapeutics	Use of autologous osteoblastic cells (PREOB, in Phase III for osteonecrosis and none union fractures) and allogenic osteoblastic cells (ALLOB, Phase I/II for the treatment of delayed-union fracture, spinal fusion)
Kuros Bioscience	Bone graft substitute (natural healing matrix (fibrin) combined with a bone growth factor) for tibial fracture repair and spinal fusion
Cerapedic	i-FACTOR Bone Graft is the only biologic bone graft that utilises a synthetic small peptide (P-15) bound to an anorganic bone mineral
BioSet	Amplex bioresorbable ceramic granules scaffold used in combination with a peptide enhancing bone healer. Induce spinal fusion
BoneBiologics	Bone filler using demineralised human bone with Nell-1 recombinant protein for spinal fusion

Source: Hardman & Co Life Sciences Research

Tissues that are being targeted by orthobiologics are presented in the table below.

Tissues targeted by orthobiologics

Tissue	Target
Bone	Spine, ankle, knee
Cartilage	Ankle, knee
Tendon	Achilles, rotator cuff (600,00 repair per year in the US)
Ligament	Anterior cruciate ligament
Meniscus 5	Knee

Source: Hardman & Co Life Sciences Research

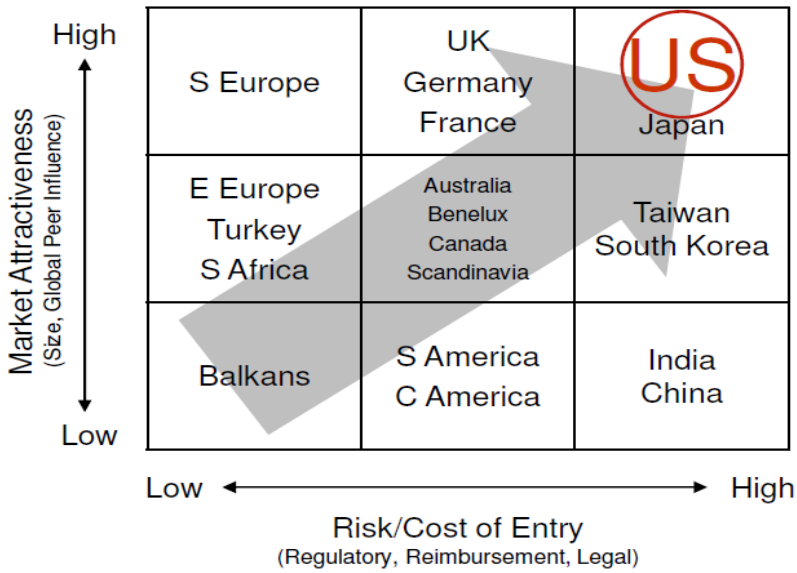
Impact on Collagen Solutions

Strategy

With an historic CE mark approval and compatibility with reimbursement codes in key territories, ChondroMimetic is well positioned in the European and emerging markets. Both are seeking cost-effective treatments due to the ongoing European crises and exploding population, respectively. Excluding the US market, this still represents 68% of the worldwide market.

ChondroMimetic was actively being sold during 2012 in five territories under the CE Mark (Spain, Italy, Greece, Poland and Turkey). Two distribution partners were identified and contracts and product registrations were under discussion. In another 15 countries, the distribution partners were also identified, but not yet contracted. The strategy put in place by Orthomimetics at that time was (1) to create first a strong high quality relationship with distributors and surgeons in territories where minimal extra documentation is required and (2) to refine performance of sales channels and focus on revenue growth, for example, by establishing bundling models.

Orthomimetics strategy to access the market



Source: Orthomimetics, Hardman & Co Life Sciences Research

A new commercial strategy is needed

ChondroMimetic is ideally suited to COS' accelerated growth strategy for which the company recently raised £6.8m of new capital and obtained a commitment from specialist healthcare strategic investor, Norgine Ventures, to subscribe for up to £4.0m of senior secured private bonds. This was important because competition in orthobiologics is growing fast, particularly in the US. Therefore, it will also be beneficial for COS to address soon the US market, which represents 32% of the global market opportunity for ChondroMimetic. Initiating pivotal clinical trials as soon as possible would be an advantage, given that no scaffold product to be used with regenerative claims has been put through the FDA as a PMA. Greater investment would be needed to run such trials, as illustrated by Cartiva which enrolled more than 200 patients into a trial programme to support its PMA for its polyvinyl alcohol hydrogel plug with no regenerative claims, Cartiva SCI (Synthetic Cartilage Implant). However, the strategy of COS is to get its regenerative ChondroMimetic device onto the market in countries with low risk and low cost entries, with the appropriate commercial partners.

The commercial strategy can be divided into three distinct areas:

Re-gaining the CE Mark

COS will use its own collagen supply for fabricating ChondroMimetic on equipment already installed in its GMP facilities in Scotland. Once optimised, the manufacturing process will need to be validated and gain ISO-13485 certification. Meanwhile COS is in active discussions with its Notified Body about the requirements for CE Mark and has opened dialogue with potential distribution partners. Submission to the Notified Body is anticipated during 3Q 2017. For the longer-term, COS will need to purchase a new state-of-the art freeze-drier, dedicated for use with ChondroMimetic and the related family of products.

Countries recognising the CE Mark

Amongst many others, Australia, Korea, Malaysia, Jordan, Turkey, Thailand and Mexico are countries that recognise CE Mark but would need additional information for marketing authorisation to be granted. The required material is predominantly bureaucratic and concerns the protocol, validation and safety data. Engagement of consultants and fully staffed distributors that can handle market access, contracts etc. will also be needed. We expect minimal cost of $300,000 spread over a 6-9 month period, with some overlap in timing towards the end of the CE Mark work.

United States

Access to the US market will be costly and the longest step. The decision for management is whether to take the easy approach short-term and pursue ChondroMimetic as a bone void filler via a 510(k), or to take the more costly decision to seek a PMA with regenerative claims. Given that the bone void space is competitive and lowly priced, in our opinion COS should pursue the PMA in order to generate high quality long-term returns.

Given the approach taken by Cartiva, we believe that COS would need to undertake 1 x 200 or 2 x 100 multicentre clinical trials with ChondroMimetic with a follow-up period of 12-24 months using MRI scans to assess the repair. Based on our view that the average cost per patient will be in the region of $100-200k, the total cost of this trial would be in the order of $20-40m, although this would likely be borne by a marketing/distribution partner. The table below sums up the steps needed to access the market in the different territories.

ChondroMimetic – Access to the market

Territory	What is needed	Time	Cost
Europe	Equipment purchase Technology transfer validation Getting ISO certificates Engagement of the notified bodies to get the CE Mark Engagement of distributors and/or commercial partner	9-12 months	$500,000
Countries recognising CE Mark (Australia, Korea, Malaysia, Jordan, Turkey, Thailand, Mexico)	Engagement of consultants for Korea Reviewing of protocol, certificate and validation documents Review of the clinical trial safety data Engagement of distributors for market access, contracts etc	6-9 months	$300,000
US	Review of all previous documents Engagement of consultants 2 clinical trials -multicentre 12-24 months follow up PMA application Engagement of distributors and/or commercial partner	48-60 months	$15-20m

Source: Hardman & Co Life Sciences Research

In our opinion, ChondroMimetic is a better product compared to competitors' products as it provides less post-surgery trauma, is associated with a quicker recovery period and generates improved clinical outcomes – regenerated cartilage is hyaline-like articular cartilage. When early sales traction information becomes available in Europe and RoW, COS should have no problem finding a large partner to license the product for the US market and fund/co-fund the US trials.

Changes to forecasts

Pulling all this together, the costs and sales to fund this programme are shown in the following table (all numbers in USD) and have been included in our full company forecasts.

ChondroMimetic – Cost and sales forecasts

Year end March ($000)	2017E	2018E	2019E	2020E	2021E
Europe CE Mark					
Cap-ex	-	-	-250		
R&D spend	-200	-300			
CE Mark recognition					
R&D spend	-	-200	-100		
Total development costs	**-200**	**-500**	**-350**		
Sales					
Europe	-	200	800	1,720	3,956
CE Recognition	-	-	200	750	1,275
Total sales ($000)	**0**	**200**	**1,000**	**2,470**	**5,231**

Source: Hardman & Co Life Sciences Research

- The key cap-ex requirement is a new freeze drier. Short-term, COS will use existing equipment to re-gain the various authorisations. While the company could purchase a relatively small freeze-dryer for the work which would be at lower cost, our preferred option is to take a longer-term view and put in a large, dedicated freeze-drier given that the company will always be the manufacturer of ChondroMimetic whoever becomes its partner/distributor. This will cost around $250k and has been included in forecasts for fiscal 2019
- Medium-term R&D spend has been increased by $800k spread over a three year period. Part of this will only be spend once the CE Mark has been regained. The longer-term R&D spend for the US does not currently show in forecasts and can be adjusted when management states its US strategy/out-licenses the product
- ChondroMimetic is expected to contribute to sales forecasts from the final quarter of fiscal 2018

Detailed analysis on the impact of incorporating these figures into our forecasts can be found in the following section.

Financial analysis

Profit & Loss

- Accelerated growth strategy as described in the FY 2016 annual report (previous reports have included some of the implications of this)
- The positive effect from the acquisition of the assets of Orthomimetics Limited once the CE Mark for ChondroMimetic has been regained. However, there will be some up-front R&D and consultancy associated with this
- The effect on translation of the weakness in sterling – positive on sales and negative on COS' overseas cost base
- The recent capital increase and concomitant venture debt facility

Profit & Loss account

Year end March (£000)	2014	2015	2016	2017E	2018E	2019E
GBP:USD	0.00	1.57	1.46	1.30	1.30	1.30
GBP:EUR	0.00	1.29	1.31	1.18	1.18	1.18
GBP:NZD	0.00	1.95	2.03	1.84	1.84	1.84
Sales	**24**	**973**	**3,130**	**4,085**	**5,290**	**7,270**
Cost of goods sold	-12	-214	-811	-1,079	-1,377	-1,819
Gross profit	**12**	**759**	**2,319**	**3,006**	**3,913**	**5,451**
Gross margin	49.7%	78.0%	74.1%	73.6%	74.0%	75.0%
Admin expenses	-304	-1,106	-2,107	-2,574	-2,909	-3,112
Selling & marketing	-72	-219	-333	-817	-1,058	-1,200
R&D	0	-160	-367	-992	-1,155	-1,285
Other income/grants	0	63	114	100	150	150
Underlying EBITDA	**-364**	**-726**	**-489**	**-1,277**	**-1,059**	**5**
Depreciation	-13	-75	-175	-255	-315	-315
Amortisation	-4	-55	-172	-192	-212	-232
Underlying EBIT	**-381**	**-793**	**-721**	**-1,724**	**-1,585**	**-542**
Share based costs	-25	-27	-36	-50	-100	-100
Exceptional items	-75	-155	152	-294	0	0
Statutory EBIT	**-480**	**-975**	**-605**	**-2,068**	**-1,685**	**-642**
Net financials	0	-128	-262	-103	-164	-131
Underlying pre-tax	-381	-920	-983	-1,826	-1,750	-673
Exceptional items	0	0	0	0	0	0
Reported pre-tax	**-480**	**-1,102**	**-867**	**-2,171**	**-1,850**	**-773**
Tax liability/credit	0	-21	-114	-148	-193	-241
Underlying net income	**-381**	**-942**	**-1,097**	**-1,976**	**-1,943**	**-914**
Statutory net income	-480	-1,123	-981	-2,320	-2,043	-1,014
Ordinary shares:						
Period-end (m)	63.8	171.0	171.4	316.3	324.5	324.5
Weighted average (m)	43.7	96.4	171.2	183.5	317.0	324.5
Fully diluted (m)	47.7	102.3	180.4	193.5	327.0	334.5
Underlying Basic EPS (p)	**-0.87**	**-0.98**	**-0.64**	**-1.08**	**-0.61**	**-0.28**
Statutory basic EPS (p)	-1.10	-1.17	-0.57	-1.26	-0.64	-0.31
U/l Fully-diluted EPS (p)	**-0.87**	**-0.98**	**-0.64**	**-1.08**	**-0.61**	**-0.28**
Stat. fully-diluted EPS (p)	-1.10	-1.17	-0.57	-1.26	-0.64	-0.31
DPS (p)	0.00	0.00	0.00	0.00	0.00	0.00

Source: Hardman & Co Life Sciences Research

Sales

- **Underlying growth rates** – For 2018, our underlying sales growth rate has been increased slightly from +27% to +29% to allow for ChondroMimetic sales in the last quarter of the year. Most of the growth is being derived from the investment in sales and marketing.
- **ChondroMimetic** – Regulatory approval via the regaining of CE Mark is expected in 4Q calendar 2017, with only modest sales – ca. $100k/£77k – in the last quarter of fiscal 2018. While a full year's contribution will be made in Europe in fiscal 2019, that from countries that recognise CE Mark is again only anticipated in 4Q 2019
- **Currency** – Weakness in sterling during calendar 2016 has a big impact on the group. For fiscal 2017, the average rate for GBP:USD is 1.30, which will be used for forecasts in subsequent years. Taking into consideration all the relevant currencies, forex is expected to have a beneficial effect of ca.£330k on 2017 sales.

Impact of ChondroMimetic on sales forecasts

Year end March (£000)	2016	2017E	2018E	2019E
Original forecast	3,130	3,755	4,190	4,800
Effect of ChondroMimetic	-	-	+1,100	+2,470
Effect of forex		+330	-	-
Revised forecast	**3,130**	**4,085**	**5,290**	**7,270**
Underlying growth rate	+74%	+20%	+29%	+37%

Source: Hardman & Co Life Sciences Research

Costs

Sales & marketing

One component of the accelerated growth strategy announced with FY 2016 results was to increase investment in sales & marketing in order to increase the number of cross-selling opportunities with existing clients, and also to boost the underlying rate of sales growth. This investment will continue in future years. It has added about -£200k to costs in 2017, which has a knock-on effect into 2018 and beyond.

General administration

In 2016, the corporate overhead was -£2.1m and whilst this was expected to increase with the appointment of some new senior staff, the joint venture in China has added further to this cost in 2017, with the establishment and staffing of a local office presence. Overall, it is thought to have added around -£100k in fiscal 2017 and a further -£200k in 2018 and beyond.

R&D spend

In line with the accelerated growth strategy, our original forecasts had allowed, to some extent, for the desire to invest in certain projects to bring them to market faster thereby taking COS further up the value chain. They did not, however, allow for the increased costs expected to get ChondroMimetic back onto European markets, given that the strategy and timetable were only in the early planning stages.

Now that there is a better understanding of full the development timetable for ChondroMimetic, we have been able to add the sales, as indicated above, and the costs, to our forecasts. However, given they will occur beyond the forecast period, and because COS is seeking a co-development and marketing partner, no allowance for the costs associated with the US PMA trial indicated earlier in this report have been included.

Collagen has also appointed some clinical and regulatory consultants that specialise in the field of orthopaedics. These additional costs (ca $100k) will be invoiced in USD and will, therefore, be currency sensitive.

Changes to R&D forecasts

Year end March (£000)	2016	2017E	2018E	2019E
Original forecast (Sept 2016)	-367	-575	-608	-800
R&D costs for ChondroMimetic	-	-200	-500	-100
Other new R&D costs	-	-185	-	-335
Effect of forex	-	-34	-47	-50
Total R&D spend	**-367**	**-992**	**-1,155**	**-1,285**

Source: Hardman & Co Life Sciences Research

Balance sheet

- Our balance sheet has been updated to reflect the recent capital increase and drawdown of the three-tranche venture debt facility from Norgine Ventures. These were all detailed in our reports dated 14th February 2017 – '*Capital increase to support accelerated growth*'.
- **Net cash/debt** – Following the capital increase, net cash is now forecast to be +£8.3m at 31st March 2017, comprised cash of £10.4m and debt of -£2.1m.

Balance sheet

@ 31st March (£000)	2014	2015	2016	2017E	2018E	2019E
Shareholders' funds	6,256	12,853	13,896	21,077	19,034	18,020
Cumulated goodwill	0	0	0	0	0	0
Total equity	6,256	12,853	13,896	21,077	19,034	18,020
Share capital	683	1,755	1,759	1,759	1,839	1,919
Reserves	5,573	11,099	12,137	19,317	17,195	16,101
Deferred tax	0	285	253	449	337	253
Long-term loans	0	88	63	2,063	3,943	2,723
Short-term debt	0	22	46	46	46	46
less: Cash	1,492	3,391	2,493	10,412	8,889	4,541
less: Deposits	0	0	0	0	0	0
less: Long-term invests.	0	0	0	0	0	0
Invested capital	**7,174**	**14,176**	**14,203**	**15,660**	**15,709**	**16,529**
Fixed assets	232	794	1,161	1,036	1,015	900
Intangible assets	6,894	12,919	12,971	12,780	12,568	12,336
Inventories	39	219	264	345	446	613
Trade debtors	*0*	*419*	*429*	*560*	*725*	*996*
Other debtors	*167*	*226*	*207*	*207*	*207*	*207*
Tax liability/credit	*0*	*-40*	*0*	*-114*	*-148*	*-193*
Trade creditors	*0*	*-215*	*-694*	*-757*	*-806*	*-1,066*
Other creditors	*-160*	*-144*	*-135*	*1,605*	*1,702*	*2,734*
Debtors less creditors	7	245	-193	1,500	1,680	2,679
Invested capital	**7,174**	**14,176**	**14,203**	**15,660**	**15,709**	**16,529**
Net cash/(debt)	**1,492**	**3,282**	**2,384**	**8,303**	**4,899**	**1,772**

Source: Hardman & Co Life Sciences Research

Cashflow

- Changes to our P&L account have a direct impact on cashflow forecasts, coupled with the translational effects of sterling weakness. Currencies used in our forecast are clearly stated at the top of the P&L account
- **Cap-ex** – At some point in the near future, COS will need to invest in a new freeze-dryer for the manufacture of ChondroMimetic and the related family of products. While management does have various (cheaper) options, we would expect it to take a long-term view and invest in a large top-end model. The costs of this would be around $250k. However, COS's existing equipment is more than adequate for the technology transfer and to re-gain CE Mark. Therefore, this expenditure is expected to be incurred in fiscal 2019
- **Loan facility** – Forecasts have been adjusted to reflect both the drawdown and repayment of the loan facility from Norgine Ventures. For each tranche, after an initial interest only period, COS will start capital repayments through equal monthly instalments, such that the whole tranche is paid off with 42 months of the date of drawdown. An additional line has been added into the following table to indicate clearly the cash outflow for these capital repayments.

Cashflow

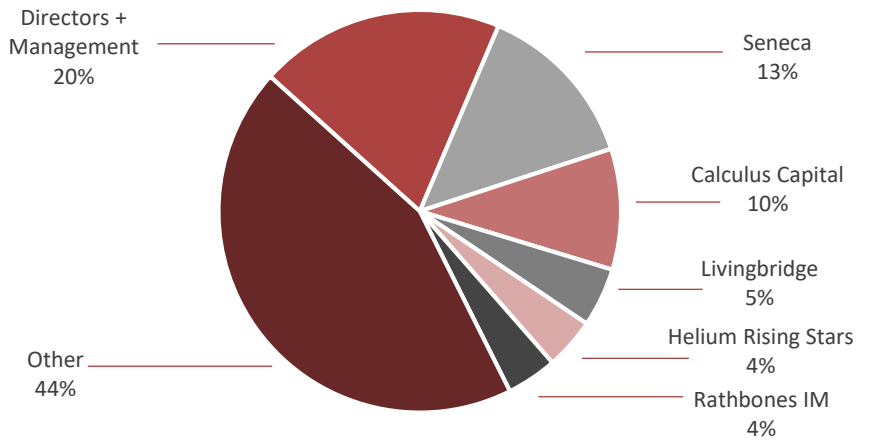
Year end March (£000)	2014	2015	2016	2017E	2018E	2019E
Operating profit	**-381**	**-793**	**-721**	**-1,724**	**-1,585**	**-542**
Depreciation	13	75	175	255	315	315
Amortisation	4	55	172	192	212	232
Inventories	*-13*	*-123*	*-48*	*-81*	*-102*	*-167*
Receivables	*-66*	*-195*	*-10*	*-431*	*-165*	*-271*
Payables	*-7*	*90*	*479*	*63*	*49*	*259*
Working capital	-72	-105	469	-448	-116	-12
Exceptionals/provisions	-75	-155	152	0	0	0
Other (Fx)	-1	-106	-346	-200	-200	0
Net cash used in ops.	**-525**	**-1,152**	**-147**	**-1,926**	**-1,477**	**-174**
Net interest	0	-2	2	8	-164	-131
Loan repayments	0	0	0	0	-120	-1,220
Tax paid/received	0	-26	-194	-114	-148	-193
Operational cashflow	**-525**	**-1,180**	**-338**	**-2,031**	**-1,909**	**-1,719**
Capital expenditure	0	-159	-464	-130	-294	-200
Sale of fixed assets	0	13	1	0	0	0
Free cashflow	**-525**	**-1,326**	**-802**	**-2,161**	**-2,203**	**-1,919**
Dividends	0	0	0	0	0	0
Acquisitions	-1,357	-2,192	-207	-1,027	-2,200	-1,209
Other investments	0	-127	-93	0	0	0
Cashflow after invests.	**-1,882**	**-3,645**	**-1,101**	**-3,189**	**-4,403**	**-3,128**
Share issues	3,374	5,422	207	9,027	1,000	0
Currency effect	0	12	-18	80	0	0
Change in net debt	**1,492**	**1,790**	**-898**	**5,919**	**-3,403**	**-3,128**
Hardman FCF/share (p)	-1.20	-1.22	-0.20	-1.11	-0.60	-0.53
Opening net cash	0	1,492	3,282	2,384	8,303	4,899
Closing net cash	**1,492**	**3,282**	**2,384**	**8,303**	**4,899**	**1,772**

Source: Hardman & Co Life Sciences Research

Shareholders

Following approval of the capital increase at the recent General Meeting for shareholders, the enlarged share capital consists of 316,299,077 Ordinary shares.

Key shareholders



Source: Company announcements

Glossary

FDA	The US Food & Drug Administration
MOCART	Three-dimensional magnetic resonance observation of cartilage repair tissue
PMA	Pre-Marketing Authorisation

Notes

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